Transition Metal-Catalyzed Redox Reactions

A Journey from Homogeneous Ruthenium
to Heterogeneous Palladium Catalysis

Oscar Verho
Life would be indeed easier if the experimentalists would only pause for a little while.
[Rudolph A. Marcus]
Abstract

The first part of the thesis covers the development and utilization of electronically modified (pentaarylcyclopentadienyl)Ru-complexes in the racemization of secondary alcohols. This study revealed that the electronic properties of the substrate were the main factors dictating whether $\beta$-hydride elimination or hydride re-addition becomes the rate-determining step of the racemization process. With this knowledge in hand, it proved to be possible to design more efficient racemization protocols by matching the electronic properties of catalyst and substrate.

The second part describes mechanistic work that aimed at elucidating the role of CO dissociation in the mechanism of secondary alcohol racemization catalyzed by a (pentaarylcyclopentadienyl)Ru-complex. From CO exchange studies, we demonstrated that CO dissociation occurred in the catalytically active tert-BuO-species as well as in the chloride precatalyst. Furthermore, an inhibition study showed that an increase of the partial pressure of CO had a negative influence on the racemization rate. Together, these two observations provide strong support for CO dissociation as a key step in the racemization of secondary alcohols.

The third part concerns the improved synthesis and characterization of a heterogeneous catalyst consisting of Pd nanoparticles immobilized on aminopropyl-functionalized siliceous mesocellular foam. The developed Pd nanocatalyst was found to be a highly efficient and recyclable catalyst for the aerobic oxidation of a wide range of primary and secondary alcohols to the corresponding aldehydes and ketones.

The fourth part deals with the successful application of the Pd nanocatalyst in chemically-induced H$_2$O oxidation, when using either ceric ammonium nitrate or [Ru(bpy)$_3$]$^{3+}$ as the terminal oxidant. Remarkably, the Pd nanocatalyst proved to catalyze this reaction with high efficiency and the measured TOF was found to greatly exceed those of current state-of-the-art metal oxide catalysts.

The fifth and final part describes the co-immobilization of Pd nanoparticles and the enzyme Candida Antarctica Lipase B into the same cavities of mesocellular foam, to generate a “metalloenzyme-like” hybrid catalyst for the dynamic kinetic resolution of a primary amine. The close proximity of the two catalytic species led to an enhanced cooperativity between them and resulted in an overall more efficient tandem process.
List of Publications

This thesis is based on the following publications, referred to in the text by their Roman numerals I-V. Reprints were made with the kind permission from the publishers and the contribution by the author to each publication is clarified in Appendix A.

I. Tuning of the Electronic Properties of a Cyclopentadienylruthenium Catalyst to Match Racemization of Electron-Rich and Electron-Deficient Alcohols
Oscar Verho, Eric V. Johnston, Erik A. Karlsson, Jan-E. Bäckvall

II. The Mechanism of Racemization of sec-Alcohols Catalyzed by a Cyclopentadienyl Ruthenium Complex- Investigation of CO Exchange
Madeleine C. Warner, Oscar Verho, Jan-E. Bäckvall

III. Highly Dispersed Palladium Nanoparticles on Mesocellular Foam: An Efficient and Recyclable Heterogeneous Catalyst for Alcohol Oxidation
Eric V. Johnston, Oscar Verho, Markus D. Kärkäs, Mozaffar Shakeri, Cheuk-W. Tai, Pål Palmgren, Kristofer Eriksson, Sven Oscarsson, Jan-E. Bäckvall

IV. Well-Defined Palladium Nanoparticles Supported on Amino-Functionalized Siliceous Mesocellular Foam: A Heterogeneous Catalyst for Chemically-Induced H₂O Oxidation
Oscar Verho, Markus D. Kärkäs, Torbjörn Åkermark, Eric V. Johnston, Karl P. J. Gustafson, Cheuk-W. Tai, Jan-E. Bäckvall, Björn Åkermark
Submitted for publication
V. Co-immobilization of an Enzyme and a Metal into the Compartments of Mesoporous Silica for Cooperative Tandum Catalysis: An Artificial Metalloenzyme
Karin Engström†, Eric V. Johnston†, Oscar Verho†, Karl P. J. Gustafson, Mozaffar Shakeri, Cheuk-W. Tai, Jan-E. Bäckvall
† Authors contributed equally to the publication and are presented in alphabetical order.

Publications not included in this thesis:

Application and Mechanistic Studies of a Water Oxidation Catalyst in Alcohol Oxidation by Employing Oxygen-Transfer Reagents
Oscar Verho, Marlène D. V. Dilenstam, Markus D. Kärkäs, Eric V. Johnston, Jan-E. Bäckvall, Björn Åkermark

Highly Enantioselective Cascade Transformations by Merging Heterogeneous Transition Metal Catalysis with Asymmetric Aminocatalysis
Luca Deiana, Samson Afewerki, Carlos Palo-Nieto, Oscar Verho, Eric V. Johnston, Armando Córdova
Scientific Reports 2012, 2, article nr. 851.

Artificial Photosynthesis: From Nanosecond Electron Transfer to Water Oxidation (review)
Markus D. Kärkäs, Eric V. Johnston, Oscar Verho, Björn Åkermark
Accounts of Chemical Research 2013, Early View, DOI: 10.1021/ar400076j

Nanopalladium on Amine-Functionalized Mesocellular Foam: An Efficient Catalyst for Suzuki Reactions and Transfer Hydrogenations
Oscar Verho, Anuja Nagendiran, Eric V. Johnston, Cheuk-W. Tai, Jan-E. Bäckvall
ChemCatChem 2013, 5, 612-618.

Supported Palladium Nanoparticles as an Efficient and Recyclable Catalyst for the Selective Transfer Hydrogenation of Nitroarenes to Anilines
Oscar Verho, Anuja Nagendiran, Cheuk-W. Tai, Eric V. Johnston, Jan-E. Bäckvall
ChemCatChem 2013, Early View, DOI: 10.1002/cctc.201300769
Combined Heterogeneous Metal/Chiral Amine Multiple Relay Catalysis for Versatile Eco-Friendly Synthesis, Hydrogenations and Construction of Quaternary Stereocenters
Luca Deiana, Yan Jiang, Carlos Palo-Nieto, Samson Afawerki, Celia A. Incerti-Pradillos, Oscar Verho, Cheuk-W. Tai, Eric V. Johnston, Armando Córdova
Submitted for publication

Cycloisomerization of Acetylenic Acids to $\gamma$-Alkylidene Lactones Using a Palladium(II) Catalyst Supported on Amino-functionalized Siliceous Mesocellular Foam
Anuja Nagendiran, Oscar Verho, Clémence Haller, Eric V. Johnston, Cheuk-W. Tai, Jan-E. Bäckvall
Submitted for publication

Artificial Water Oxidation: From Heterogeneous to Molecular Water Oxidation Catalysis (review)
Markus D. Kärkäs, Oscar Verho, Eric V. Johnston, Björn Åkermark
Submitted for publication

Electrochemical Preparation of Dispersed Gold Nanoparticles Supported in the Pores of Siliceous Mesocellular Foam: An Efficient Catalyst for Cycloisomerization of Alkynoic Acids to Lactones
Kristofer Eriksson†, Oscar Verho†, Leif Nyholm, Sven Oscarsson, Jan-E. Bäckvall
Manuscript
† Authors contributed equally to the publication and are presented in alphabetical order.

Efficient Palladium Catalyzed Aminocarbonylation of Aryl Iodides Using Palladium Nanoparticles Dispersed on Siliceous Mesocellular Foam
Fredrik G. Tinnis, Oscar Verho, Karl P. J. Gustafsson, Cheuk-W. Tai, Hans Adolfsson, Jan-E. Bäckvall
Manuscript

Highly Enantioselective Synergistic Heterogeneous Catalysis for Asymmetric Cascade Transformations
Luca Deiana, Lorenza Ghizu, Oscar Verho, Eric V. Johnston, Zoltán Bacsik, Niklas Hedin, Armando Córdova
Manuscript
The Combination of a Palladium Nanocatalyst and Lipases for an Efficient Dynamic Kinetic Resolution of Primary Amines
Karl. P. J. Gustafson, Richard Lihammar, Oscar Verho, Jan-E. Bäckvall
Manuscript
# Table of Contents

Abstract ........................................................................................................................................... v

List of Publications ......................................................................................................................... xi

Abbreviations.................................................................................................................................. xvii

1. Introduction.................................................................................................................................... 1
   1.1 Catalysis..................................................................................................................................... 2
       1.1.1 Homogeneous versus Heterogeneous Catalysis ......................................................... 3
       1.1.2 Metal Nanoparticles in Catalysis...................................................................................... 4
       1.1.3 Heterogeneous Supports for the Immobilization of Nanoparticles and Other Catalytic Species ................................................................................................................................. 5
   1.2 Redox Reactions..................................................................................................................... 6
       1.2.1 The Origin of Chirality and Racemization ..................................................................... 7
       1.2.2 Kinetic and Dynamic Kinetic Resolution ......................................................................... 9
       1.2.3 Transition Metal-Catalyzed Aerobic Alcohol Oxidation ............................................ 11
       1.2.4 Water Oxidation in the Natural System .......................................................................... 13
       1.2.5 Artificial Water Oxidation in a Photosynthetic Device .................................................. 16
   1.3 Objectives of this Thesis ....................................................................................................... 19

   2.1 Introduction............................................................................................................................. 21
   2.2 Results and Discussion.......................................................................................................... 24
       2.2.1 Synthesis of Racemization Catalysts .............................................................................. 24
       2.2.2 Preparation of Enantiomerically Pure Substrates for the Racemization Study ................ 25
       2.2.3 Racemization Studies .................................................................................................. 27
   2.3 Conclusions............................................................................................................................ 31

3. The Mechanism of Racemization of sec-Alcohols Catalyzed by a Cyclopentadienyl Ruthenium Complex-Investigation of CO Exchange (Paper II) ........................................ 33
   3.1 Introduction............................................................................................................................. 33
   3.2 Results and Discussion.......................................................................................................... 35
       3.2.1 Investigation of the CO Exchange .................................................................................. 35
3.2.2 Discovery of the tert-Butoxydicarbonylruthenium Complex 34
3.2.3 CO Inhibition Study ................................................................. 38
3.2.4 Outlook on Future Mechanistic Work ..................................... 39
3.3 Conclusions .............................................................................. 41

4. Highly Dispersed Palladium Nano-particles on Mesocellular Foam: An Efficient and Recyclable Heterogeneous Catalyst for Alcohol Oxidation (Paper III) ................................................. 43
4.1 Introduction .............................................................................. 43
4.2 Results and Discussion ............................................................... 44
  4.2.1 Synthesis and Characterization of the Pd^{0}-AmP-MCF Nanocatalyst ................................................................. 44
  4.2.2 Condition Screening .............................................................. 48
  4.2.3 Substrate Scope ................................................................... 49
  4.2.4 Investigation of the Recyclability, Leaching and Scalability .................................................................................. 53
4.3 Conclusions .............................................................................. 56

5. Well-Defined Palladium Nanoparticles Supported on Amino-Functionalized Siliceous Mesocellular Foam: A Hetero-geneous Catalyst for Chemically-Induced H_{2}O Oxidation (Paper IV) .......... 57
5.1 Introduction .............................................................................. 57
5.2 Results and Discussion ............................................................... 58
  5.2.1 Catalytic H_{2}O Oxidation Experiments .................................. 58
  5.2.2 Recycling and Leaching Experiments .................................... 61
5.3 Conclusions .............................................................................. 62

6. Co-immobilization of an Enzyme and a Metal into the Compartments of Mesoporous Silica for Cooperative Tandem Catalysis: An Artificial Metalloenzyme (Paper V) ......................... 63
6.1 Introduction .............................................................................. 63
6.2 Results and Discussion ............................................................... 66
  6.2.1 Synthesis and Initial Evaluation of a Series of Pd/Enzyme Hybrids .............................................................................. 66
  6.2.2 Characterization of Hybrid-GA_{0.1}E_{high} .................................. 70
  6.2.3 DKR of 1-phenylethylamine with Hybrid-GA_{0.1}E_{high} .......... 71
  6.2.4 Recycling Study ................................................................... 73
6.3 Conclusions .............................................................................. 74

Concluding Remarks ........................................................................ 76
Appendix A .................................................................................... 79
Appendix B .................................................................................... 80
Acknowledgements ......................................................................... 81
References ..................................................................................... 84
Abbreviations

Abbreviations and acronyms are used in agreement with the standard of the subject.[1] Only nonstandard and unconventional abbreviations that appear in the thesis are listed here.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmP</td>
<td>Aminopropyl</td>
</tr>
<tr>
<td>CALA/CALB</td>
<td>Candida antarctica lipase A/B</td>
</tr>
<tr>
<td>CBED</td>
<td>Convergent beam electron diffraction</td>
</tr>
<tr>
<td>Conv.</td>
<td>Conversion</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DKR</td>
<td>Dynamic kinetic resolution</td>
</tr>
<tr>
<td>EDC·HCl</td>
<td>N-(3-Dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>ETM</td>
<td>Electron transfer mediator</td>
</tr>
<tr>
<td>HAADF-STEM</td>
<td>High-angle annular dark-field-Scanning transmission electron microscopy</td>
</tr>
<tr>
<td>ICP-OES</td>
<td>Inductively coupled plasma-optical emission spectroscopy</td>
</tr>
<tr>
<td>KR</td>
<td>Kinetic resolution</td>
</tr>
<tr>
<td>MCF</td>
<td>Mesocellular foam</td>
</tr>
<tr>
<td>MOF</td>
<td>Metal-organic framework</td>
</tr>
<tr>
<td>MS 4Å</td>
<td>Molecular sieves (4 ångström)</td>
</tr>
<tr>
<td>NHE</td>
<td>Normal hydrogen electrode</td>
</tr>
<tr>
<td>OEC</td>
<td>Oxygen-evolving complex</td>
</tr>
<tr>
<td>o.n.</td>
<td>Overnight</td>
</tr>
<tr>
<td>PS I/II</td>
<td>Photosystem I/II</td>
</tr>
<tr>
<td>PS-C</td>
<td>Pseudomonas cepacia</td>
</tr>
<tr>
<td>rac.</td>
<td>Racemic</td>
</tr>
<tr>
<td>sec.</td>
<td>Secondary</td>
</tr>
<tr>
<td>SMSI</td>
<td>Strong metal-support interaction</td>
</tr>
<tr>
<td>TCEP</td>
<td>Tris(2-carboxyethyl)phosphine</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission electron microscopy</td>
</tr>
<tr>
<td>TFT</td>
<td>α,α,α-Trifluorotoluene</td>
</tr>
<tr>
<td>TOF</td>
<td>Turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>Turnover number</td>
</tr>
<tr>
<td>WOC</td>
<td>Water oxidation catalyst</td>
</tr>
<tr>
<td>XPS</td>
<td>X-ray photoelectron spectroscopy</td>
</tr>
</tbody>
</table>
1. Introduction

Over the past decades, it has become increasingly apparent that the development of our society and the increased global population greatly impact the planet we all live on. Consequently, there is a major demand for the design of new environmentally-friendly technologies and processes. Chemistry is a scientific discipline that throughout history has played a fundamental role in our society as it has allowed for the development of new materials, products, fuels, and pharmaceuticals. Therefore, in perspective of these future challenges facing mankind, chemistry holds great potential for innovation that can help our society to advance towards a sustainable future. In the field of organic chemistry, the concept of “green chemistry” was created by Anastas and Warner to address this issue, and it highlights twelve important principles to consider when designing sustainable reaction protocols (Figure 1.1). Among these, catalysis perhaps constitutes one of the most important principles as it has revolutionized the field of organic synthesis by enabling for more efficient and selective transformations. This in turn allows the reactions to fulfill several of the other principles of green chemistry.

Figure 1.1. The twelve principles of green chemistry coined by Anastas and Warner to inspire research towards developing more sustainable chemical transformations.
1.1 Catalysis

A catalyst is defined as a chemical species that has the capability of increasing the rate of a reaction without affecting the standard Gibbs free energy, and not undergoing a net-reaction itself (Figure 1.2). Today, catalysis constitutes a fundamental part of the chemical industry and our society, as it is involved in the manufacturing of approximately 90% of all chemical-based products\cite{3} and a majority of the liquid fuels.\cite{4}

Among the many disciplines of catalysis, transition metal catalysis has been particularly fruitful, since it has opened up for protocols that exhibit unprecedented complexity, efficiency and selectivity compared to those of classical reactions. Several of the useful properties displayed by the transition metal elements of groups 3-11 in the periodic table originate from their ability to exist in a variety of oxidation states. Each oxidation state of the transition metal exhibits disparate electronic configurations, which allow them to interact in a specific fashion with different organic molecules. An illustrative example of this versatile nature of transition metals is palladium that in its zero-state, Pd\(_0\), is generally considered to be a nucleophilic species (donor of electrons), while Pd\(^{II}\) usually reacts as an electrophile (acceptor of electrons). Of the many studied transition metals in organic synthesis, the platinum group consisting of ruthenium, rhodium, palladium, osmium, iridium, and platinum stands out for its remarkable utility. These metals have found use in a variety of transformation, such as C-H activation, isomerization, oxidation, reduction and cross-coupling reactions.\cite{5}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{potential_energy_diagram.png}
\caption{Potential energy diagram displaying the difference in activation energy and reaction pathway between a catalyzed and uncatalyzed reaction.}
\end{figure}
In Nature, catalytic processes are mediated by a family of macromolecules called enzymes and they play a crucial role in sustaining life by allowing for metabolic processes to occur under the mild conditions present in living organisms. The natural enzymes constitute the state-of-the-art in catalysis as they can carry out a wide range of transformations with impressive efficiency and selectivity, which generally exceed those of man-made systems. In addition to their high performance, enzymes are also the prime example of green catalysts as they are comprised of non-toxic and bioavailable amino acids and cofactors. As a result of these attractive properties, enzymes have found extensive use in the large-scale production of chemicals and other industrial applications. Particularly the discovery that enzymes can function in organic solvents has revolutionized and greatly accelerated their use as catalysts in organic synthesis.

1.1.1 Homogeneous versus Heterogeneous Catalysis

Catalysis is commonly divided into two categories: homogeneous catalysis, where the catalyst is present in the same phase as the reactant(s) and heterogeneous catalysis, where the catalyst and reactant(s) are in separate phases. Usually, a solid heterogeneous catalyst is used to transform reactants in either the gas or the liquid phase, meaning that the actual chemistry is occurring at the interface between the two phases. Heterogeneous catalysis is currently dominating over homogeneous catalysis by accounting for more than 90% of the volume of industrial processes. The Haber-Bosch ammonia synthesis employing a magnetite (Fe) catalyst, the Co/Fe-catalyzed Fischer-Tropsch process for the conversion of coal to syngas and hydrocarbons, and the titanium-catalyzed Ziegler-Natta polymerization of ethylene are just a few examples of important industrial processes based on heterogeneous catalysis. The success of heterogeneous protocols in industry is mainly associated with simpler separation, higher catalyst stability and the possibility to recycle the heterogeneous catalyst, which are all desirable features from an economical and environmental perspective.

Homogeneous catalysts, on the other hand, have the advantages that they generally display higher activities and selectivities than their heterogeneous counterparts. Moreover, catalyst modifications are more straightforward as molecular catalysts are amenable for rational ligand design, which simplifies mechanistic studies and the development of asymmetric protocols. In contrast, modifications of heterogeneous catalysts usually require extensive interdisciplinary knowledge in physical chemistry, organic chemistry, surface science, and material science.

When designing catalytic processes it is of great importance to establish both the activities and stabilities of the studied catalysts and for this assessment the quantities turnover number (TON) and turnover frequency (TOF) are most commonly used. The TON is mainly a measure of the robustness of
a catalytic system and is defined as the number of reaction cycles that one molecule of the catalyst can perform before it is deactivated. The TOF, on the other hand, reflects the efficiency of a catalytic system and is simply a measure of the TON over a certain time period, which can be given in $s^{-1}$, $min^{-1}$ or $h^{-1}$. It is important to emphasize that these quantities are greatly dependant on the applied reactions conditions, and therefore care has to be taken when using them for the comparison of different catalytic systems.

Also, in the case of heterogeneous systems such as nanoparticle-based catalysts, it can be challenging to clearly determine the true TON and TOF, as it is not always straightforward to establish the exact number of active sites on the catalyst surface. Consequently, the total metal content of a catalyst is in many cases used by convenience for determining the TON and TOF of a heterogeneous catalyst, although this simplification is not entirely in line with the definitions of these quantities.

1.1.2 Metal Nanoparticles in Catalysis

Nanoparticles have recently received considerable attention because of their unique properties and applications in a variety of fields, such as electronics, optics, magnetism, energy technology and chemistry. Particularly in organic chemistry, transition metal nanoparticles have found extensive use as catalysts for a wide range of reactions. In many cases, they exhibit high activity and selectivity in combination with excellent recyclability, which are all hallmarks of green catalysts.

The main factors that govern the reactivity of metal nanoparticles, which are typically clusters comprised of tens to several thousand metal atoms, are their size and shape. Especially when the cluster sizes are reduced below 2 nm, unique activities and selectivities can be obtained. This difference in the catalytic properties of nanoparticles of various size and shapes can primarily be attributed to their surface-to-volume ratio. As depicted in Figure 1.3, smaller nanoparticles contain a higher ratio of surface atoms than larger nanoparticles. This brings about a more efficient arrangement of the metal atoms, where a higher percentage of them are exposed to the surrounding environment and available to participate in reactions. Furthermore, it results in a larger amount of metal atoms that are coordinatively unsaturated. It is most likely these unsaturated sites that give rise to the unique catalytic properties that are not observed for the corresponding bulk metal.

However, these highly reactive and coordinatively unsaturated sites also impose challenges concerning the size-controlled syntheses of nanoparticles and the structural stability of small nanoparticles that are used in organic transformations under harsh reaction conditions. This is ascribed to the so-called “Ostwald ripening effect”, which states that there exists a thermodynamic driving force for the formation of larger particles with low surface-to-
volume ratio, since it maximizes the number of binding interactions between the atoms in the cluster.[21]

The most widely used synthetic strategies for the preparation of nanoparticles involve either chemical or electrochemical reduction of metal ions. The reduction is typically performed in the presence of organic stabilizers or heterogeneous supports to prevent the nanoparticles from agglomerating into larger clusters. Also, since the formation of larger nanoparticles is a thermodynamically driven process, smaller nanoparticle sizes can selectively be prepared by applying kinetic control during the reduction step, i.e. applying a high concentration of a strong reducing agent and/or low reaction temperature.

![Figure 1.3](image)

**Figure 1.3.** Schematic illustration of two nanoparticles with different surface-to-volume ratio. Their size and shape can have profound effects on their physical and catalytic properties.

1.1.3 Heterogeneous Supports for the Immobilization of Nanoparticles and Other Catalytic Species

Contrary to metal chips, colloidal nanoparticles are well soluble in organic solvents, which allow them to be handled and used as homogeneous catalysts. In many cases, they can also be characterized as molecular compounds by conventional spectroscopic techniques.[22] As an alternative, nanoparticles can also be immobilized onto heterogeneous supports, which brings several practical advantages, such as simpler isolation and recycling. These two factors are particularly important when employing nanoparticle-based catalysts for industrial applications, where metal contaminations in the final product can be a topic of major concern.[23]

Today, there exists a large abundance of well-characterized heterogeneous materials that can be used for the immobilization of nanoparticles and other catalytic species. This includes silicas,[24] metal oxides,[25] metal-organic frameworks (MOFs),[26] dendrimers,[27] as well as other polymer[28] and carbon-based materials.[29] Among these materials, special attention has been directed towards those that exhibit a porous morphology as this shields the immobilized catalytic species from mechanical grinding and reduces the
leaching. In addition, porous materials display high internal surface areas, which enable an increased catalyst loading.

Porous materials can be classified into three categories based on their pore sizes: (i) microporous (<2 nm), mesoporous (2-50 nm), or macroporous (>50 nm). For catalytic applications, mesoporous materials are normally preferred as they offer a good balance between internal surface area, protection of the catalytic species, and mass transfer of the substrate molecules in and out of the support material. Although microporous materials possess the highest internal surface area, the small pore size is associated with severe limitations in the mass transfer of organic molecules. Furthermore, the smaller pore size imposes restrictions on the size of the immobilized catalytic species, which in most cases disqualifies metal nanoparticles and enzymes. Macroporous materials, on the other hand, can accommodate large catalytic species and exhibit excellent mass transfer properties, but unfortunately they suffer from reduced internal surface areas. Therefore, lower catalyst loadings and higher leaching are typically observed for heterogeneous catalysts based on macroporous materials.

However, the support material does not only play a passive role in reactions by acting solely as a platform for the catalytic species. There are plenty of evidence for that the support material can also have a profound effect on the catalytic properties of the immobilized species. This phenomenon, termed “Strong metal-support interaction” (SMSI), has been observed for a wide range of metal nanoparticle-based catalysts immobilized on metal oxides, has shown to lead to improved reaction efficiencies and even novel reactivities. This suggests that the classical view of nanoparticles as static and unperturbed entities that rest on a metal oxide surface may not always be correct. Instead, the metal oxide surface can interact strongly and even blend with the nanoparticle to give rise to sites and interfaces with unique catalytic properties.

Analogous effects are believed to exist for other non-metal oxide materials as well, where these supports similar to the ligand of an organometallic complex, can affect the electronics of the coordinated metal and give rise to distant effects on the nanoparticle surface. This would provide an explanation of the previously observed phenomena that two identical nanoparticles, of the same size and shape, can display fundamentally disparate reactivities when they are immobilized on different supports.

1.2 Redox Reactions

Redox reactions constitute one of the most fundamental reactions in chemistry, and include all transformations in which the reacting species undergo changes in their oxidation state. The term “redox” is derived from the two words; (i) reduction, a reaction involving the gain of electrons and a decrease
in oxidation number and (ii) oxidation, a reaction involving the loss of electrons and an increase in oxidation number. These two reactions are closely related and always occur together, as the electron(s) being transferred must be derived from one chemical species and ultimately end up in another. Consequently, a whole redox reaction is often referred to as being comprised of the oxidation and reduction half-reactions.

Redox pair and redox couples are two concepts that are frequently encountered when dealing with redox reactions. A redox pair consists of a reducing agent (capable of reducing another compound) and an oxidizing agent (capable of oxidizing another compound), while a redox couple refers to the reduced and oxidized form of a chemical species, i.e. Ru^{II}/Ru^{III}.

Although, the change in oxidation state between a metal atom and its corresponding metal ion may be the first example that comes to mind when thinking about a redox process, organic molecules can also undergo analogous changes in oxidation state during redox reactions (Figure 1.4).

**Figure 1.4.** To the left: A characteristic galvanic cell illustrating the two half-reactions; (i) oxidation of zinc metal to Zn^{2+} ions and (ii) reduction of Cu^{2+} ions to copper metal. To the right: An example of an organic redox reaction (aerobic alcohol oxidation), where the involved species that undergo a change in oxidation state have been highlighted.

## 1.2.1 The Origin of Chirality and Racemization

Chirality is a phenomenon that arises when a molecule can exist in two distinct structural configurations, which are non-superimposable mirror images of each other (Figure 1.5). For example, a carbon atom binding to four disparate substituents is referred to as a stereogenic center and this arrangement gives rise to two different mirror forms, referred to as enantiomers. Analogously, compounds that contain two stereogenic centers can give two pairs of enantiomers, which are said to be diastereomers of one another. The pres-
ence of additional stereogenic centers further increases the complexity, and
the number of possible stereoisomers increases by $2^n$ (n = total number of
stereogenic centers).

Figure 1.5. A carbon atom that binds to four different substituents can exist in two
enantiomeric forms, which are the mirror images of each other.

In contrast to diastereomers, enantiomers share the same chemical and
physical properties in an achiral environment, with the exception for their
effect on plane-polarized light that is rotated in opposite direction by each
enantiomer. However, in living organisms, where the environment is com-
prised of chiral biomolecules, such as amino acids, carbohydrates and lipids,
two enantiomers can exhibit fundamentally different biological responses.[33]
Consequently, there is a significant interest in the pharmaceutical, agricul-
tural, flavor and fragrance industries to synthesize enantiomerically pure
compounds and study their biological effects separately.[34]

Today, three strategies are employed for the preparation of
enantiomerically pure compounds; (i) chiral pool synthesis, where chiral
natural products are used as building block for more complex mole-
cules,[34,35] (ii) resolution of racemic mixtures (1:1 ratio of both enantiomers)
by a chiral agent,[36] and (iii) asymmetric synthesis using chiral reagents or
catalysts.[6c,37]

The opposite process, racemization, is an entropy-driven reaction where
an enantiomerically pure compound is converted to a racemic mixture by
inversion of its stereocenter. This inversion can be achieved by a variety of
techniques, which can be divided into: (i) thermal racemization, (ii) acid or
base-catalyzed racemization, (iii) enzyme-catalyzed racemization, (iv) race-
mization proceeding via meso-intermediates, (v) racemization by
nucleophilic substitution, (vi) racemization via radical and redox reactions
(vii) photochemical racemization, and (viii) racemization proceeding via
Schiff-base intermediates.[38] At first glance, racemization may seem like a
wasteful process that converts a precious enantiomerically pure compound
into a racemic mixture; however, when it is carried out in combination with
kinetic resolution (KR, vide infra), it is possible to achieve a powerful meth-
odology for asymmetric synthesis.
This thesis deals with racemization reactions of primary amines and sec-alcohols but only with those that proceed via a transfer hydrogenation mechanism, which falls under the redox category. In such a racemization reaction, the substrate will first undergo a dehydrogenation and then because there is no other hydrogen acceptor available, the hydride can only be re-added to the oxidized substrate (Scheme 1.1). Since the stereochemistry is lost during the oxidation of the amine/alcohol, the re-addition of the hydride to the oxidized and achiral intermediate will result in a racemization.

\[
\text{Scheme 1.1. General mechanism for the transfer hydrogenative racemization of primary amines and sec-alcohols.}
\]

1.2.2 Kinetic and Dynamic Kinetic Resolution

KR is a commonly used technique for the separation of enantiomers, and it relies on the different rate of transformation for a pair of enantiomers towards a resolving agent (Scheme 1.2). To date, numerous protocols for KR based on transition metals, organocatalysts or enzymes as resolving agents have been reported.\(^\text{[39]}\)

\[
\text{Scheme 1.2. General scheme for an (R)-selective kinetic resolution (KR).}
\]

Although, KR in many cases enables efficient separation of enantiomers in excellent enantiomeric excesses (ee’s), the maximum theoretical yield of 50% is certainly not in line with the first two principles of green chemistry. In practice, this means that the desired product will need to be purified from the unreacted starting material, which demands for the use of additional sol-
vents and/or energy. Moreover, the resolution requires that the transformation of one of the enantiomers is significantly slower than that of the other enantiomer, which is generally not the case and therefore the reaction has to be stopped well before 50% to ensure a high ee of the product. Alternatively, the reaction can be allowed to exceed 50% if the unreacted starting material is desired in high ee, but this is at the expense of the yield.

Gratifyingly, the drawbacks of KR can be circumvented by combining it with a racemization process, which interconverts the two enantiomers in situ. As a result of this racemization, a dynamic equilibrium is established between the two enantiomers, which provides for a continuous feed of the reactive enantiomers to the resolution process. This extension of the KR methodology is called dynamic kinetic resolution (DKR) and enables the yield to reach 100%, which makes the reactions both more economical and sustainable (Scheme 1.3).

Unfortunately, the design of successful DKR protocols is far from straightforward, as it requires that several parameters are carefully investigated and optimized. The most crucial aspect when designing a successful DKR is to find a suitable racemization catalyst that can operate efficiently under the reaction conditions required for the resolution process.\(^{[40]}\) In this regard, it is important that the two catalysts do not exhibit an inhibitory effect on each other. In addition to the challenges associated with the compatibility between the racemization catalyst and the resolving agent, the KR must also display a high selectivity (E-value\(^{[41]}\) > 20) and the rate of racemization should at least be equal to the rate of the fast-reacting enantiomer (\(k_{\text{rac}} \geq k_{\text{fast}}\)).

In particular, chemoenzymatic DKR has emerged as a vivid research field within asymmetric catalysis.\(^{[40,42]}\) Early applications involved the use of base to racemize the substrate, but recent examples have involved the combination of an enzyme as the resolving agent and a transition metal complex as the racemization catalyst, which has allowed for the preparation of a wide range of compounds in high yields and ee’s.\(^{[40,42,43]}\) In our group, numerous protocols employing different enzymes and various transition metal-based racemization catalysts, have been developed for the resolution of allylic alcohols,\(^{[44]}\) homoallylic alcohols,\(^{[45]}\) sec-alcohols,\(^{[46]}\) chlorohydrins,\(^{[47]}\) diols,\(^{[48]}\) primary amines,\(^{[49]}\) \(N\)-heterocyclic 1,2-amino alcohols,\(^{[50]}\) \(\beta\)-amino esters,\(^{[51]}\) and hydroxy esters.\(^{[52]}\) Furthermore, the DKR methodology has been successfully implemented into the syntheses of some well-known pharmaceuticals, such as bufuralol,\(^{[53]}\) duloxetine,\(^{[54]}\) and salbutamol.\(^{[55]}\)

The compatibility issue between the racemization catalyst and the resolving agent constitutes a major challenge in the field of chemoenzymatic DKR as well. Therefore, despite the large number of homogeneous racemization catalysts for amines and alcohols that have been developed, there is only a handful examples that can operate in the presence of enzymes (Scheme 1.3).\(^{[46,56]}\)
In this perspective, heterogeneous racemization protocols have recently emerged as an attractive alternative to methods involving homogeneous transition metal complexes. To date, several examples of enzyme-compatible heterogeneous racemization catalysts for the resolution of amines and alcohols have been reported, which include Raney Co,[57] Raney Ni,[57] Ru(OH)$_3$/Al$_2$O$_3$,[58] SO$_4^{2-}$/TiO$_2$,[59] VOSO$_4$·5H$_2$O,[60] zeolites,[61] and Pd$^0$ on various supports.[49a,51a,62]

Scheme 1.3. Top: General scheme for an (R)-selective chemoenzymatic dynamic kinetic resolution (DKR). Bottom: Examples of homogeneous enzyme-compatible racemization catalysts.

1.2.3 Transition Metal-Catalyzed Aerobic Alcohol Oxidation

The selective oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones constitutes an important transformation both on laboratory- and industrial-scale organic synthesis.[63] Traditionally, stoichiometric protocols employing high-valent metal reagents (e.g. Cr$^{VI}$ or Mn$^{VII}$)[64] or hyper-valent iodine compounds[65] have been the methods of choice due to their high activity and generality. However, all these reagents are associated with serious drawbacks such as high cost, safety risks in the handling, and stoichiometric production of toxic waste. As a result, significant research during the past decades has been dedicated to the development of new and efficient transition metal-based protocols that utilizes environmentally-friendly oxidants.[63a,66]

In this respect, molecular oxygen (O$_2$) is an attractive oxidant, as it is environmentally friendly, readily abundant, inexpensive, and shows relatively low toxicity. Moreover, it exhibits high efficiency per weight and only gives
H₂O as byproduct when it is reduced. Together, these features make O₂ ideal from a green chemistry perspective. The only drawback of using O₂ for industrial-scale applications is that it requires rigorous safety handling, as it forms explosive mixtures with organic solvent fumes.

Unfortunately, the examples of direct oxidation of organic substrates molecules by O₂ are rare as a consequence of the high energy barrier for the electron transfer between the organic substrate and the oxidant. This high energy barrier originates from the triplet electron configuration of O₂, where two electrons are unpaired and positioned in the degenerate πₓ* and πᵧ* orbitals (Figure 1.6). This prevents O₂ from reacting with most organic substrates, which exist in singlet electron configurations, without the aid of catalysis.

![Figure 1.6. Molecular orbital diagram showing the triplet electron configuration of O₂.](image)

Therefore, the design of catalytic systems, particular in which the transition metal catalyst is directly re-oxidized by O₂, is not a simple task and requires fast electron transfer processes or stabilizing ligands that prevent the reduced metal center from precipitating out of the reaction before re-oxidation occurs (Scheme 1.4a). Despite these challenges, there are protocols available for the selective oxidation of alcohols, where the metal is directly re-oxidized by O₂. The majority of these procedures utilize homogeneous Cu, Pd, and Ru complexes as the substrate-selective redox catalysts.

Another elegant solution to achieve an efficient oxidation process is to facilitate the electron transfer between the organic substrate and O₂ by incorporating so called “electron transfer mediators” (ETMs) that enable the reaction to occur under milder conditions (Scheme 1.4b). This approach shares great resemblance with the strategy employed in Nature’s respiratory chain, where the high-energy barrier for electron transfer is divided into multiple steps, thus generating a low-energy pathway consisting of several smaller energy barriers. Noteworthy in this regard, are the Cu/TEMPO and the Ru/quinone/cobalt macrocycle (CoLₘ) systems that have been successful-
ly employed for the oxidation of a broad range of primary and secondary alcohols in high efficiencies. However, there are also drawbacks associated with the use of additional ETMs, such as (i) increased complexity as a result of the added components that makes reaction optimizations more challenging, (ii) more demanding separation and isolation of product, and (iii) increased possibility for undesired side reactions between ETMs and the organic substrate(s).

![Scheme 1.4](image)

**Scheme 1.4.** a) Direct re-oxidation of a substrate selective-redox catalyst by O₂. b) Biomimetic approach employing ETMs for a low-energy electron transfer.

The most ideal option from a practical and economical perspective would still be to employ a catalytic system where O₂ is directly used to re-oxidize the catalyst, and further to move from homogeneous to heterogeneous catalysis. As previously mentioned, the use of heterogeneous catalysis allows for reduced amounts of metal contaminations in the product, simpler catalyst separation and recycling. Unfortunately, heterogeneous protocols have traditionally exhibited lower activities and selectivities than those based of homogeneous catalysis. Therefore, substantial research has been directed towards the design of new heterogeneous catalytic systems that display higher efficiencies. Among these, nanoparticle catalysts based on Pd have shown particular promise in the aerobic oxidation of alcohols. A wide range of heterogeneous supports has been investigated for this purpose, including, hydroxyapatite, mesoporous silica, MgO, MOFs, TiO₂, and various carbon materials.

### 1.2.4 Water Oxidation in the Natural System

In the context of the severe environmental impacts associated with global warming, it has become apparent that our society will soon need to make a transition towards a carbon-neutral energy economy. Considering that the combustion of fossil fuels makes up the major part of today’s energy produc-
...tion,\cite{80} it is obvious that the transition towards a sustainable energy economy will be drastic and require the development of new innovative technologies. One of the most promising strategies for producing green energy in quantities that will meet the demands of future generations involves the utilization of solar power to produce storable fuels.\cite{81}

Here, Nature has over three billion years of evolution given us an excellent blue-print on how to harness the vast energy supply provided by the sun. This light-driven process, called the photosynthesis, is employed by plant cells, algae and cyanobacteria to convert H$_2$O and CO$_2$ into carbohydrate building blocks and O$_2$.

Upon close examination of the biological machinery responsible for the photosynthesis, it quickly becomes evident how intricate this process is. As depicted in Figure 1.7, the photosynthesis involves the well-orchestrated collaboration of several large protein complexes, such as the photosystem (PS) I and II, the cytochrome-$b_{6}f$, and the ATP synthase.\cite{82} Together, they carry a great number of complex processes in tandem, including light-harvesting, charge-separation, electron transfer, H$_2$O oxidation, reduction of NADP$^+$ and proton gradient-driven ATP synthesis.

![Figure 1.7. Schematic representation of the complex machinery involved in the natural photosynthesis. Reprinted from “P. Vengadesh, Nanocrystals – Synthesis, Characterization, and Applications (Ed. S. Neralla), InTech: Rijeka, 2012, pp 41-60, with kind permission from the publisher.”\cite{83}](image)

Among these reactions, H$_2$O oxidation represents the most impressive reaction from a catalysis perspective, as it requires for the removal of four protons, rearrangement of multiple bonds and O-O bond formation. In the natural system, the H$_2$O oxidation is carried out by a metalloenzyme called the oxygen-evolving complex (OEC), situated on the lumen-side of PS II.
The catalytic site of this metalloenzyme is comprised of an oxo-bridged Mn cubane, which has a calcium atom positioned in its close vicinity. The entire catalytic assembly is kept in place by surrounding amino acid ligands, which apart from giving structural stabilization also participate in catalysis by providing for charge-neutralization and promoting proton-coupled electron transfer.

The mechanism through which the OEC catalyzes H₂O oxidation has been proposed to proceed via the cycling of the Mn cluster through five redox states, denoted S₀–S₄ (Scheme 1.5). In this mechanistic model, named after its creator Bessel Kok, the S₀ state constitutes the resting state of the catalytic cycle and contains the Mn cluster in its most reduced form. In order for the Mn cluster to catalyze H₂O oxidation it must accumulate four oxidizing equivalents and reach the S₄ state. This transition is powered by four consecutive absorptions of photons at a neighboring P₆₈₀ chromophore, which triggers electron transfer from the OEC to the photo-oxidized P₆₈₀*, via a tyrosine residue (Tyr₇) functioning as an ETM. When four oxidative charges have been stored, the cluster carries out the four-electron/four-proton oxidation of H₂O and returns to the S₀ resting state, liberating O₂ and protons in the process.

The electrons and protons generated through this process is ultimately employed to produce chemical energy in the form of ATP and reducing equivalents (e.g. NADPH), which can then be used in the biochemical reactions of the Calvin cycle for the synthesis of carbohydrates.

Scheme 1.5. The Kok cycle describes the mechanism by which the OEC catalyzes H₂O oxidation. In this process, the Mn cluster cycles between five redox states (S₀–S₄) through consecutive photo-oxidation steps.
1.2.5 Artificial Water Oxidation in a Photosynthetic Device

The design of an artificial photosynthetic device that in conformity with the natural photosynthetic machinery can produce carbohydrates as the end products holds little commercial interest. An attractive alternative would be to modify the methodology used by Nature, so that rather than generating various carbohydrates it would be possible to produce storable fuels, such as H\textsubscript{2}, methane or methanol.

One promising way to achieve this is to utilize a three-component solar fuel cell, consisting of a photosensitizer unit, a H\textsubscript{2}O oxidation catalyst (WOC), and a reduction catalyst (Figure 1.8). Although the concept of such solar-powered fuel cells appears simple at first glance, it constitutes a significant challenge from an engineering perspective, as several complicated processes must be coupled together in an efficient manner. First, the photosensitizer must absorb a photon to generate a charge-separated state. This exciton energy should then be used to facilitate an electron transfer from the excited photosensitizer to the reduction catalyst that acts as the electron acceptor. The hole generated at the photosensitizer is subsequently refilled by the WOC, which gets its electrons from the splitting of H\textsubscript{2}O, which produces four electrons and four protons along with O\textsubscript{2} for every two molecules of H\textsubscript{2}O. The electrons and protons liberated by the WOC ultimately end up at the reduction catalyst site, where they are either directly assembled into H\textsubscript{2} or used to reduce CO\textsubscript{2} into methane or methanol.

**Figure 1.8.** Schematic representation of a three-component solar fuel cell for the production of H\textsubscript{2}, comprised of a H\textsubscript{2}O oxidation catalyst (WOC), a photosensitizer, and a reduction catalyst.
Unfortunately, the development of practical and efficient fuel cells based on these principles has been restrained due to limitations in the WOC component. The WOCs developed so far have not exhibited either the efficiency or stability required for incorporation into such a photosynthetic device. Consequently, researchers from several fields have dedicated significant efforts to overcome this bottleneck and to realize solar-driven production of green and sustainable fuels.

Seminal work in the field of artificial $\text{H}_2\text{O}$ oxidation was done by the group of Meyer in 1982, with the preparation of the $\text{cis,cis-}[\{(\text{bpy})_2\text{-}\text{Ru}(\text{H}_2\text{O})(\mu-\text{O})(\text{H}_2\text{O})\text{Ru(\text{bpy})}_2\}]^{4+}$ (also called “the blue dimer”) which constituted the first example of a homogeneous molecular WOC (Figure 1.9). In catalytic $\text{H}_2\text{O}$ oxidation experiments employing Ce IV as the chemical oxidant, the “blue dimer” was found to give a modest TON of 13.2 and TOF of $4.2 \times 10^{-3} \text{s}^{-1}$. The low turnover of 6 was attributed to the unstable $\mu$-oxo bridge, which made the complex susceptible towards oxidative degradation into inactive monomeric species.

![Figure 1.9. The “blue dimer” 6 prepared by Meyer and co-workers.](image)

The key discovery of 6 spurred extensive subsequent research that focused on designing WOCs with improved efficiency and stability. This work has yielded a wide range of mono- and multimetallic homogeneous WOCs based on a variety of transition metals, such as Ru, Ir, Fe, Mn, Co, and Cu. The initial ligand design primarily centered on nitrogen-rich and charge-neutral (i.e. lacking dissociable protons) scaffolds; however, this approach gave rise to metal complexes of relatively high redox potentials that required the use of strong oxidants, such as Ce IV or oxygen-transfer reagents (Oxone, NaOCl or $\text{H}_2\text{O}_2$), to be able to catalyze the oxidation of $\text{H}_2\text{O}$. These oxidants are not feasible for use in a future solar fuel cell, since they cannot be photochemically regenerated. In this regard, the mild one-electron oxidant $[\text{Ru(bpy)}_3]^{3+}$ represents a more attractive alternative, as it can be photogenerated from the corresponding $[\text{Ru(bpy)}_3]^{2+}$-complex 7 (Figure 1.10). However, this oxidant with its low redox potential (1.26 V vs. the normal hydrogen electrode, NHE) imposes challenges in the WOC design,
since in order to assure for an efficient electron transfer from the WOC to the oxidant, the WOC must have a substantially lower redox potential than the oxidant. This can be compared to ceric ammonium nitrate (CAN, common source of Ce\textsuperscript{IV}) that has a higher redox potential of 1.61 vs. NHE, and which is thus compatible with a broader set of WOCs.

The group of Åkermark has made pioneering contributions to the design of WOCs with significantly lower redox potentials, by employing a bio-inspired approach that involves the use of negatively charged ligand architectures. This strategy has been very successful and has afforded several mono- and binuclear complexes (8-12) that have been demonstrated to be highly efficient catalysts for light-driven H\textsubscript{2}O oxidation, when using photo-chemically generated [Ru(bpy\textsubscript{3})\textsuperscript{3+-}]\textsuperscript{37}-type oxidants (Figure 1.10).\textsuperscript{[88]}

**Figure 1.10.** Various mono- and binuclear catalysts (8-12) developed by Åkermark and co-workers for light-driven H\textsubscript{2}O oxidation, shown together with the photosensitizer [Ru(bpy\textsubscript{3})\textsuperscript{2+}]\textsuperscript{7}. L stands for 4-methylpyridine in all cases.
Although, the use of homogeneous WOCs is associated with several advantages, such as (i) high catalytic efficiency, (ii) simple synthesis and characterization, (iii) straightforward tuning of the electronic and steric properties by ligand modifications, and (iv) higher suitability in mechanistic studies, there are also several fundamental issues that might restrict their use in a commercial fuel cell. Of these limitations, catalyst deactivation by ligand dissociation and oxidative degradation are perhaps the most severe obstacles for the applicability and longevity of homogeneous WOCs in a photosynthetic device.

In this regard, heterogeneous catalysts for H\textsubscript{2}O oxidation are more attractive options, as they are more robust, recyclable and can be easily incorporated into the photosynthetic device. To date, several different metal oxides based on Ru\textsuperscript{[89]} Ir\textsuperscript{[90]} Mn\textsuperscript{[91]} and Co\textsuperscript{[91a,92]} have been prepared and shown to be active and stable WOCs. However, in most cases these heterogeneous catalysts suffer from low catalytic activity as they produce less than stoichiometric amounts of O\textsubscript{2} (calculated per bulk metal atom), and are therefore not viable for application in commercial fuel cells at the moment.

Together, the limitations of the current homogeneous and heterogeneous WOCs highlight the continued need for research within the field of artificial H\textsubscript{2}O oxidation, which can facilitate the transition to a green and sustainable energy economy.

1.3 Objectives of this Thesis

This thesis is divided into two parts; (i) homogeneous Ru-catalyzed alcohol racemization, and (ii) heterogeneous catalysis for more efficient and sustainable processes. The thesis starts by describing the synthesis and application of a condensed library of (pentaarylcyclopentadienyl)Ru-complexes in alcohol racemization. It was envisioned that this comparative study would provide for mechanistic insights into the racemization process that could be of value for the future design of more efficient chemoenzymatic DKR protocols.

In the next chapter, the results and conclusions from a mechanistic study on one of the ruthenium complexes are presented. In this work, particular interest was directed towards establishing experimentally that CO dissociation plays a crucial role in the racemization of alcohols, which had previously been predicted by computational studies.

The second part of the thesis, starting with Chapter 4, covers the improved preparation of a heterogeneous catalyst comprised of Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd\textsuperscript{0}-AmP-MCF) and its application in the aerobic oxidation of alcohols. To establish the practical viability of the Pd nanocatalyst in this transformation several important aspects, such as scalability, leaching, and recyclability were investigated.
Chapter 5 describes the use of Pd\(^0\)-AmP-MCF as a catalyst for chemically-induced H\(_2\)O oxidation. To the best of our knowledge, this constitutes one of the most active heterogeneous catalytic systems for chemically-induced H\(_2\)O oxidation reported so far. In addition to its high activity, the Pd nanocatalyst also exhibited excellent recyclability and negligible metal leaching in the experiments involving the one-electron oxidant [Ru(bpy)\(_3\)]\(^{3+}\).

The sixth and final chapter of the thesis deals with the co-immobilization of Pd nanoparticles and the enzyme *Candida Antarctica* Lipase B (CALB) into the same cavities of mesocellular foam (MCF), to create a hybrid catalyst that bears great resemblance with an artificial metalloenzyme. Particularly, we were interested in investigating whether the close proximity of the two catalytic species could confer an enhanced activity in the DKR of a primary amine relative to the corresponding separate component system.
Tuning of the Electronic Properties of a Cyclopentadienylruthenium Catalyst to Match Racemization of Electron-Rich and Electron-Deficient Alcohols (Paper I)

2.1 Introduction

In 2004, our group developed the (pentaarylcyclopentadienyl)Ru-complex 5 and demonstrated that it was a highly efficient catalyst for the racemization of a wide range of sec-alcohols. For instance, complex 5 was capable of fully racemizing enantiomerically pure 1-phenylethanol within 10 min at ambient temperature,[46a,93] which constituted a major improvement compared to other racemization catalysts at that time. In addition, complex 5 was found to be compatible with enzymes, which allowed it to be used in combination with lipases for the DKR of a wide range of sec-alcohols.[44-48,50,53-55]

Complex 5 is proposed to operate through the catalytic inner-sphere redox mechanism depicted in Scheme 2.1.[94] The mechanism starts with the in situ activation of complex 5 by tert-BuOK to form the catalytically active tert-BuO-species 5a, which subsequently undergoes an alcohol-alkoxide exchange with the substrate alcohol, generating 5b in the process. From here, β-hydride elimination gives a ketone-hydride intermediate 5c/5c', in which the ketone remains coordinated until hydride re-addition occurs from either face to afford the racemic alkoxide 5d. Finally, the catalyst undergoes another alcohol-alkoxide exchange and is available to take part in a new catalytic cycle. The involvement of ruthenium hydride, Ph₅C₅Ru(CO)₂H, in the racemization has been ruled out by previous experimental observations.[46a]

The exact identity of the ketone-hydride intermediate has been a target of extensive debate, which originated from the previous technical inability to identify this species experimentally. Based on previous observations of the related Shvo catalyst 1, it was originally proposed that the empty coordination for the hydride was generated through ring slippage of the cyclopentadienyl ring (η⁵ → η³) to form 5c'.[95] However, in light of recent results obtained from mechanistic studies, the route proceeding via CO ligand dissociation to generate 5c now constitute the most probable and widely-accepted mechanism for the alcohol racemization by complex 5 (vide infra, Chapter 3).[94a,b]
A limitation of complex \( 5 \) is the necessity of dry and inert conditions in the racemization and DKR reactions, which arises from the sensitivity of the key \( \text{tert-BuO-species} \ 5a \). Moreover, it has been observed in the case of strongly electron-deficient alcohols, such as chlorohydrins, that the racemization process is slow.\(^{[47]}\) As a consequence, the corresponding DKR reactions require elevated temperatures and/or longer reaction times to afford high yields and \( ee' \)’s.

The slow racemization of electron-deficient alcohols by complex \( 5 \) is believed to arise from an inefficient \( \beta \)-hydride elimination (dehydrogenation) reaction, as these substrates are less prone to undergo oxidation to the corresponding ketones. Therefore, one potential way to address this issue would be to design an electron-deficient analogue of complex \( 5 \) that would be more efficient in the dehydrogenation step. On the other hand, an improvement of the dehydrogenative properties of the racemization catalyst would be associated with a diminished capability to re-add the hydride to the oxidized sub-
strate. However, it was anticipated that the hydride re-addition (insertion) step would be facile for this type of substrates, since the electron-deficient ketone obtained from β-hydride elimination should be efficient in abstracting the hydride from the racemization catalyst. In analogy with this predicted reactivity, the opposite effect is true for electron-rich alcohols, where the hydride re-addition is instead expected to be critical and thus the racemization of these substrates should be promoted by an electron-rich catalyst.

To allow for a detailed evaluation on how the electronic properties of the catalyst affect the racemization rate of various alcohols, the synthesis of three electronically modified analogues of complex 5 were envisioned (Figure 2.1). The knowledge gained from this study would allow for the development of more efficient racemization protocols, which could in turn be valuable for the design of future DKRs.

![Figure 2.1. The proposed library of (pentaarylcyclopentadienyl)Ru-complexes with varying electronic properties.](image)

A similar study was recently conducted by the groups of Kim and Park, where the substituent effects on the catalytic activity of a related racemization catalyst was investigated. The authors concluded that an electron-rich catalyst was “the most efficient and most practical to use in the DKR of sec-alcohols”. However, it is important to point out that no electron-deficient substrates were used in their study, and therefore no racemization reactions involving slow dehydrogenation steps were explored, in which an electron-deficient catalyst would have been favorable to use. Consequently, this made it possible for our group to follow up these results by examining the entire spectrum of catalysts and substrates, ranging from electron-deficient to electron-rich, in an attempt to reveal new beneficial catalyst-substrate matches in the racemization of sec-alcohols.
2.2 Results and Discussion

2.2.1 Synthesis of Racemization Catalysts

The procedure for the preparation of the electronically modified analogues 13-15 were initially designed after the previously reported synthesis of complex 5, proceeding *via* a cyclopentadieone precursor (Route A, Scheme 2.2) [46].

![Scheme 2.2. The proposed Route A used for the synthesis of complexes 5, 13 and 14.](image)

In the case of analogues 13-15, the crucial cyclopentadieone precursors were not commercially available, and had to be synthesized *via* a two-step protocol. In the first reaction, two equiv. of aryl acetic acid 16 are coupled into a bisbenzylketone 17 by the use of N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (DMAP) at room temperature. The bisbenzylketones 17 were in the next step reacted with benzils 18 in a base-catalyzed cyclizative aldol condensation to give the cyclopentadienone precursors 19. Gratifyingly, this reaction proved successful for the synthesis of cyclopentadienone 19a and 19c, affording them in 64% and 83% yield, respectively. However, in the case of the reaction involving the CF₃-substituted compounds 17d and 18d, a complicated mixture of products were obtained, from which 19d could not be isolated. The insufficient nucleophilicity of the corresponding aldol of 17d, originating from the strongly electron-withdrawing CF₃-groups, was invoked as an explanation for this disappointing reaction outcome.

Therefore, the continued synthetic work using Route A focused on the preparation of catalysts 5, 13, and 14 only. From the cyclopentadienone precursors 19 a one-pot reaction involving Grignard-arylation and LiAlH₄-
reduction was carried out and it gave the desired pentaarylcyclopentadienyl ligands 20 in moderate to good yields. Finally, the target (pentaarylcyclopentadienyl)Ru-complexes 5, 13, and 14 were obtained by complexating the corresponding ligands with Ru(CO)\(_{12}\), followed by addition of CHCl\(_3\).

To access analogue 15, a different synthetic strategy was explored, which involved a Pd-catalyzed multiarylation reaction of cyclopentadiene (Route B, Scheme 2.3).[97] The major advantage of this synthetic route was that it allowed for the preparation of the target ligand 20d in one step from simple starting materials. Unfortunately, this reaction displayed poor selectivity and thus gave rise to substantial amounts of tri- and tetra-arylated byproducts. The byproduct formation complicated the purification procedure and resulted in a low yield (19%) of the desired ligand 20d.

Scheme 2.3. The alternative and shorter Route B used for the synthesis of catalyst 8.

Despite the inefficiency of the multiarylation reaction, sufficient amount of 20d could be obtained for further experiments by up-scaling of the reaction. The ligand was then complexated according to the last step of Route A, to give the target CF\(_3\)-substituted analogue 15. It is also important to point out that Route B represents an attractive approach for the preparation of the other ligands 20a-c, as the original study reported on high yields in these multiarylation reactions.[97] However, as enough quantities of complexes 5, 13 and 14 for the racemization study had been obtained by Route A at this point of the project, these reactions were not further investigated.

2.2.2 Preparation of Enantiomerically Pure Substrates for the Racemization Study

To study how the rate of racemization of complex 5 and analogues 13-15 depended on the nature of the substrates, suitable enantiomerically pure sec-alcohols of varying electronic properties had to be synthesized. For this purpose the condensed series of sec-alcohols 23-26 were chosen (Figure 2.2), as they were thought to cover a broad range of electronic properties.
Figure 2.2. Enantiomerically pure sec-alcohols of varying electronic properties prepared for the racemization study.

Substrates \((R)-23\), \((R)-24\) and \((S)-26\) were prepared according to the synthetic routes outlined in Scheme 2.4, while alcohol \((S)-25\) was obtained directly from a commercial vendor. Racemic alcohol \(23\) was prepared from a two-step protocol involving \(\alpha\)-chlorination of the aryl methyl ketone \(27\) by the electrophilic chlorine reagent N-chlorosuccinimide (NCS)\[98\] followed by reduction with NaBH₄. Kinetic resolution of the racemic alcohol \(23\) was performed using *Pseudomonas cepacia* lipase (PS-C) as the resolving agent, affording \((R)-23\) (unreacted enantiomer) in 33% yield and >99% ee. The enantiomerically pure substrate \((R)-24\), on the other hand, was despite its structural similarities to \((R)-23\) synthesized via a different one-step protocol, comprising the nucleophilic epoxide opening reaction of \((S)\)-oxiranylanisole \(29\, >99\%\, ee\) by Li₂CuCl₄.[99] For the synthesis of \((S)-26\), a CALB-catalyzed KR of the commercially available racemic alcohol \(26\) was carried out to give acetate \((S)-30\) in 42% yield and >99% ee, which was then quantitatively hydrolyzed under basic conditions to the corresponding alcohol.

![Scheme 2.4. Synthesis of enantiomerically pure alcohol substrates \((R)-23\), \((R)-24\) and \((S)-26\).](image)
2.2.3 Racemization Studies

As a result of the varying electronic properties of the alcohols used in the racemization study, the reaction conditions (e.g. reaction temperature and catalyst loading) had to be optimized for each substrate individually, in order to allow for a clear comparison of the different complexes.

The racemization study commenced with alcohols \((R)-23\) and \((R)-24\), which have previously been shown to racemize at a low rate when employing complex 5.[47] However, with the newly-synthesized electron-deficient analogues 14 and 15 in hand, it was anticipated that a more efficient racemization could be achieved for these substrates. Indeed, as depicted in Figures 2.3 and 2.4, the highest racemization rates were observed for the most electron-deficient analogue 15, followed by analogue 14. A comparison of the racemization rate of analogue 15 with that of the standard complex 5 revealed a >10 times improvement in efficiency for the racemization of substrate \((R)-23\) at 80 °C. In the case of substrate \((R)-24\), this effect was even more pronounced and resulted in a 30 times faster racemization at 60 °C. The electron-rich analogue 13, on the other hand, exhibited difficulties in racemizing these substrates, as shown by its poor performance in both racemization studies.

![Figure 2.3. Racemization of \((R)-23\). 4.69 µmol (η⁵-C₅Ar₅)RuCl(CO)₂ and 0.19 mmol Na₂CO₃ were mixed in 1.5 mL of toluene, and the mixture was heated to 80 °C. 14.1 µmol tert-BuOK (dissolved in 40 µL of dry THF) was then added. After 10 min, 0.19 mmol enantiomerically pure sec-alcohol \((R)-23\) was added \((t = 0)\) and the mixture was kept at 80 °C. Enantiomeric excess \((ee)\) of the alcohol was determined by periodic aliquots for chiral GC.](image)
Figure 2.4. Racemization of (R)-24. 4.69 µmol (η⁵-C₅Ar₅)RuCl(CO)₂ and 0.19 mmol Na₂CO₃ were mixed in 1.5 mL of toluene, and the mixture was heated to 60 °C. 14.1 µmol tert-BuOK (dissolved in 40 µL of dry THF) was then added. After 10 min, 0.19 mmol enantiomerically pure sec-alcohol (R)-24 was added (t = 0) and the mixture was kept at 60 °C. Enantiomeric excess (ee) of the alcohol was determined by periodic aliquots for chiral GC.

Together, these results demonstrate that the conclusions made by Kim and Park in their previous study regarding electron-donating catalysts being the most efficient for alcohol racemization,[96] no longer apply when the substrate becomes more electron-deficient. Moreover, these results verified our original hypothesis that β-hydride elimination is a critical step in the racemization of electron-deficient alcohols, as demonstrated by the observed reactivity trend of complex 5 and analogues 13-15.

However, in the racemization of electron-rich substrates the ratio of the rates of β-hydride elimination and hydride re-addition will be higher than that for the electron-deficient alcohols. Consequently, it is expected that the overall racemization of electron-rich alcohols would be favored by an electron-rich catalyst, which is more efficient in redelivering the hydride to the intermediate ketone. Gratifyingly, this proved to be the case where the relative rates of complex 5 and analogues 13-15 in the racemization of (S)-25 and (S)-26 at room temperature, displayed the reverse reactivity trend to that of the reactions involving the electron-deficient substrates (Figures 2.5 and 2.6). The results obtained from this study are interesting from a mechanistic perspective, as they suggest that the rate-determining step of the racemization reaction shifts between β-hydride elimination and hydride re-addition based on the electronic properties of the substrate. Therefore it proved to be possible to achieve a more efficient overall racemization by carefully matching the electronic properties of substrate and catalyst.
Figure 2.5. Racemization of (S)-25. 3.80 µmol (η^5-C_5Ar_5)RuCl(CO)_2 and 0.38 mmol Na_2CO_3 were mixed in 1.5 mL of toluene, and the mixture was allowed to stir at room temperature. 11.4 µmol tert-BuOK (dissolved in 40 µL of dry THF) was then added. After sufficient time, 0.38 mmol enantiomerically pure sec-alcohol (S)-25 was added (t = 0) and the mixture was kept at room temperature. Enantiomeric excess (ee) of the alcohol was determined by periodic aliquots for chiral GC. Activation time: complexes 5 and 13: 10 min, analogue 14: 30 min, analogue 15: 60 min.

Figure 2.6. Racemization of (S)-26. 3.80 µmol (η^5-C_5Ar_5)RuCl(CO)_2 and 0.38 mmol Na_2CO_3 were mixed in 1.5 mL of toluene, and the mixture was allowed to stir at room temperature. 11.4 µmol tert-BuOK (dissolved in 40 µL of dry THF) was then added. After sufficient time, 0.38 mmol enantiomerically pure sec-alcohol (S)-26 was added (t = 0) and the mixture was kept at room temperature. Enantiomeric excess (ee) of the alcohol was determined by periodic aliquots for chiral GC. Activation time: complexes 5 and 13: 10 min, analogue 14: 30 min, analogue 15: 60 min.
It is important to clarify that the poor performance of analogue 15, in the racemization of alcohols (S)-25 and (S)-26 (Figure 2.4), was only partially based on a substrate-catalyst mismatch. Upon close inspection of the reaction, it was observed that analogue 15 displayed a significantly slower activation by tert-BuOK than the other complexes at room temperature. Instigated by this finding, a qualitative study was performed where the alcohol substrate (S)-25 was added to each complex at different time points after the addition of tert-BuOK (each “time point” corresponded to a separate reaction) and the initial rate of the racemization reactions were followed by GC. If the complexes were fully activated upon the addition of the alcohol, the initial rates of the racemization should be at their maximum values, while a partially activated complex would give rise to an irregular reaction profile with an initial plateau. From these experiments, it was found that complexes 5 and 13 were fully activated within 10 min, while analogue 14 required a slightly longer activation time (~30 min). As observed earlier, the most electron-deficient analogue 15 was found to undergo the slowest activation and this study showed that it was only partially activated even after 90 min. Additional signs of the insufficient activation of analogue 15, can also be seen from the irregular shape of the racemization curve of substrate (S)-25 (Figure 2.5), where the highest rate was observed after 10 min. Unfortunately, attempts to activate the analogue 15 at elevated temperatures and then perform the racemization at room temperature did not lead to any improved results. Additions of different silver salts to facilitate the removal of the chloride from 15 were also conducted, but all attempts caused the reaction solutions to turn black, which is indicative of catalyst decomposition.

Another observation that was made in the racemization of (S)-26 was that ketone byproduct had been generated by all complexes to varying extent. Interestingly, the amount of ketone formed was found to vary depending on the electronic properties of the complexes in a fashion that was in accordance with a rate-determining hydride re-addition step. As expected, the electron-rich analogue 13 produced the least amount of ketone (5% over 30 min), confirming its efficiency in re-adding the hydride to the intermediate ketone of (S)-26. For the other experiments involving complexes 5, 14, and 15, the amounts of formed ketone followed the anticipated trend and were measured to 6%, 8%, and 7%, respectively. Similar formation of ketone byproducts was not observed for any of the other substrates ((R)-23, (R)-24, and (S)-25).
2.3 Conclusions

A small series of electronically modified analogues of complex 5 was successfully synthesized and evaluated in the racemization of sec-alcohols with varying electronic properties. From this study, it was demonstrated that a faster racemization rate could be achieved by matching the electronic properties of the catalyst with the substrate. Consequently, the electron-deficient analogues 14 and 15 showed to be the most efficient racemization catalysts for the electron-deficient substrates (R)-23 and (R)-24, whereas the electron-rich systems (S)-25 and (S)-26 underwent the fastest racemization with analogue 13. The racemization study also afforded new mechanistic insights by revealing that the relative rates of β-hydride elimination and hydride re-addition vary depending on the electronic properties of the substrate and catalyst. Furthermore, the experiments carried out at room temperature demonstrated that the introduced electronic modifications had a profound effect on the rate of activation of the complexes. Together, the results obtained from this study should be valuable for extending the scope of application of the (pentaarylcyclopentadienyl)Ru-complexes in racemization and DKR of sec-alcohols.
3. The Mechanism of Racemization of sec-Alcohols Catalyzed by a Cyclopentadienyl Ruthenium Complex-Investigation of CO Exchange (Paper II)

3.1 Introduction

In the recent decades, considerable attention has been directed towards mechanistic studies on ruthenium catalysts that are involved in transfer hydrogenation reactions.[94,100] Despite the fact that our group has extensively used complex 5 in the DKR of a wide range of sec-alcohols,[44-48,50,53-55] there has been some ambiguities regarding its mechanism. Particularly, the exact identity of the ketone-hydride intermediate constituted a key topic (cf. intermediates 5c and 5c' in Figure 2.1), which had not been experimentally ascertained by previous efforts.[95]

The mechanism depicted in Scheme 3.1 begins with the generation of the catalytically active tert-BuO-species 5a from the chloride precatalyst 5 and tert-BuOK. This activation event can be observed visually as a characteristic color change of the reaction solution from yellow to orange, and it has also been experimentally verified by $^{13}$C NMR studies.[46b] In detail, this occurs via the formation of the acyl intermediate 31, which subsequently undergoes rapid alkoxide migration from the CO ligand to the ruthenium center, forming the tert-BuO-species 5a in the process. The existence of the intermediate 31 was first predicted by our group using density functional theory (DFT) calculations, and was later confirmed by experimental studies involving NMR and in situ FT-IR.

From here, the tert-BuO-species 5a can undergo an alcohol-alkoxide exchange in the presence of a substrate alcohol, to generate the ruthenium sec-alkoxide intermediate 5b. This step was also suggested by computational studies to proceed via the assistance of the CO ligand; however, such an intermediate remains to be experimentally observed.[94c,d] In the ruthenium sec-alcohol intermediate 5b, racemization occurs via an inner-sphere mechanism, giving a ketone-hydride intermediate in which the ketone remains coordinated to the metal center until it is reduced back to the racemic alkoxide. Since 5b is a coordinatively saturated 18-electron species, a free coordination site must be generated on the ruthenium in order to allow for
racemization by a $\beta$-hydride elimination mechanism. As previously mentioned, the two most plausible pathways from which this empty coordination site can be generated are: (i) $\eta^5 \rightarrow \eta^3$ ring slippage of the cyclopentadienyl ring to give species 32, and (ii) dissociation of one of the CO ligands to afford species 33.

Intermediate 32, resulting from the ring slippage pathway was originally considered as the most probable candidate based on results obtained from mechanistic studies on the related Shvo hydride. CO dissociation was not observed from the latter hydride complex,$^\text{[100b]}$ which led to the assumption that such a process would be unlikely to occur for complex 5 as well. However, subsequent DFT studies revealed that the potential energy barrier for the ring slippage pathway was significantly higher than that of CO dissociation (42 compared to 23 kcal/mmol).$^\text{[94d]}$ In addition, the Ru-O bond of structure 32 was suggested by the calculations to be surprisingly weak, which was in conflict with previous experimental observations. In the racemization of sec-alcohols, the intermediate ketone has been demonstrated to coordinate tightly to the ruthenium center, which prevents complex 5 from acting as an alcohol oxidation catalyst like Shvo’s catalyst 1.

Therefore, in order to shed more light on this particular part of the racemization mechanism, this project was contrived and executed in an attempt to find experimental evidence that supports the computationally predicted CO dissociation pathway.

**Scheme 3.1.** Proposed pathways of the racemization of sec-alcohols catalyzed by complex 5.
3.2 Results and Discussion

3.2.1 Investigation of the CO Exchange

Initially, it was proposed to synthesize a $^{13}$CO-enriched version of complex 5, and use it as a model system for monitoring the release of $^{13}$CO into solution by NMR. The synthesis was carried out according to a previously reported protocol [101] which afforded the desired $^{13}$CO-enriched complex $[^{13}$CO]-5 with a $^{13}$CO-incorporation of 44% (Scheme 3.2).

![Scheme 3.2. Synthesis of the labeled complex $[^{13}$CO]-5.](image)

For the exchange studies, complex $[^{13}$CO]-5 (31 μmol) was dissolved in dry toluene-$d_8$ (2.4 mL) and subjected to tert-BuOK (2.0 equiv.) in an NMR tube. Analyses were conducted using $^{13}$C NMR after the addition of gaseous $^{12}$CO (0.3 or 0.9 equiv). Unfortunately, no peak at 184.7 belonging to free $^{13}$CO could be observed, which was ascribed to the insensitivity of $^{13}$C NMR towards detecting small amounts of dissociated CO in the reaction solution.

Instead, it was decided to directly follow the incorporation of $^{13}$CO over time for complex 5 and its corresponding tert-BuO-species 5a. In practice, this was done by adding gaseous $^{13}$CO (0.3 equiv.) to either of the two ruthenium complexes (40 μmol) in toluene-$d_8$ (0.8 mL) and then following the reaction by $^{13}$C NMR. To allow for a determination of the $^{13}$CO incorporation, the intensities of the Ru-CO signals at 197.1 and 202.8 ppm were compared to those of reference spectra. The CO exchange of complex 5 was found to proceed at a relatively low rate, which warranted for monitoring of the reaction over a time span of 40 h (Figure 3.1a). However, in the case of the tert-BuO-species 5a, the CO exchange was observed to be much more facile (~20 times faster), and therefore aliquots were withdrawn already after 30, 60 and 90 min, respectively (Figure 3.1b).

The more facile CO exchange observed in 5a was explained by the more efficient π-donation by the tert-BuO-ligand in comparison to the chloride of 5. This results in a better stabilization of the transition state towards losing a CO ligand, which facilitates CO dissociation from this intermediate [102].
Figure 3.1. $^{13}$CO incorporation (%) versus time for a) complex 5 and b) complex 5a.

3.2.2 Discovery of the tert-Butoxydicarbonylruthenium Complex 34

Aside from providing insights into the kinetics of the $^{13}$CO incorporation for 5 and 5a, the CO exchange studies also yielded the interesting finding that a new complex formed upon extended reaction times. It was found that the formation of this complex was accelerated by increased CO concentrations (>1 equiv.), which suggests that the special reaction conditions used in the CO exchange study play a key role in its formation. Originally, it was believed to be a decomposition product originating from the highly labile tert-BuO-species 5a. However, upon careful examination of the $^{13}$C NMR spectrum, it was possible to identify the new compound as the carboalkoxydicarbonylruthenium complex 34 (Figure 3.2). This complex gave rise to three characteristic signals in the $^{13}$C NMR spectrum at 109.0 ppm (cyclopentadienyl), 186.5 ppm (acyl) and 200.4 (CO) ppm. Moreover, complex 34 was also characterized by IR, where peaks at 1654 cm$^{-1}$ (acyl), 1983 cm$^{-1}$ (asymmetric CO stretch), and 2037 cm$^{-1}$ (symmetric CO stretch) could be observed. The collected characterization data were in good agreement with the literature values of the related complex Ru(CO)$_2$(COO'Bu)(η$^5$-Me$_5$C$_5$) 35 previously prepared by Suzuki et al.$^{[103]}$ which verified the authenticity of the structural assignment (Figure 3.2).

Figure 3.2. The structure of the tert-butoxydicarbonylruthenium complexes 34 and 35 with some of their characteristic $^{13}$C NMR shifts and IR peaks highlighted.

<table>
<thead>
<tr>
<th>IR peaks</th>
<th>34</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$(CO)$_{\text{terminal}}$</td>
<td>2037</td>
<td>2010</td>
</tr>
<tr>
<td>$\delta$(CO)$_{\text{terminal}}$</td>
<td>1983</td>
<td>1968</td>
</tr>
<tr>
<td>$\delta$(CO)$_{\text{acyl}}$</td>
<td>1654</td>
<td>1637</td>
</tr>
</tbody>
</table>
Interestingly, it also proved to be possible to independently synthesize and isolate complex 34, which was done by subjecting *in situ* formed 5a to a CO atmosphere in toluene for 3 h at room temperature. This protocol furnished complex 34 as a brown and storage stable solid in quantitative yield, after concentration of the reaction solution *in vacuo*.

Unfortunately, the existence of complex 34 proved that the mechanism for the CO exchange was more complex than initially anticipated, thus emphasizing the need of a more advanced mechanistic model (Scheme 3.3). To account for the formation and involvement of 34, a new mechanism was proposed where an empty coordination site on the ruthenium can be generated in two ways; either by dissociation of one $^{12}$CO ligand (Path A) or by alkoxide migration from the ruthenium center to a $^{12}$CO ligand (Path B). In the fully reversible Path A, coordination of $^{13}$CO to intermediates 37/37' leads to the formation of a $^{13}$CO-enriched alkoxide complex ($[^{13}\text{CO}]-5\text{a}$ or $[^{13}\text{CO}]-36$). Particularly notable in Path A is intermediate 37', as this is the 16-electron complex suggested to be responsible for the racemization of *sec*-alcohols. In Path B, on the other hand, $^{13}$CO coordination to the intermediate acyl complexes 38/38' gives rise to the irreversible formation of the carboalkoxydicarbonylruthenium complexes $[^{13}\text{CO}]-34/[^{13}\text{CO}]-34'$.

Scheme 3.3. Proposed mechanism for the CO exchange process (Path A) and the formation of carboalkoxydicarbonylruthenium complexes $[^{13}\text{CO}]-34$ and $[^{13}\text{CO}]-34'$ (Path B).

Multiple supports were found for the irreversible nature of the last step of Path B; (i) $^{13}$C NMR observations indicated that complex 34 constituted the endpoint of the reaction, (ii) the regeneration of 5a from pre-synthesized 34.
by the use of heating and/or reduced pressure proved unsuccessful, (iii) ex-
change studies involving 34 showed no signs of $^{13}$CO-incorporation, and (vi)
recent DFT calculations$^{102a}$ revealed that the formation of 34 from 5a is a
highly exothermic process (34.5 kcal/mol). Complex 34 was also evaluated
as a catalyst for the racemization of sec-alcohols under various conditions,
but as expected it proved to be inactive in all cases, which was ascribed to its
inability to generate a free coordination site for the hydride.

3.2.3 CO Inhibition Study

The results from the CO exchange study provide support for that CO disso-
ciation plays a key role in the racemization mechanism of sec-alcohols cata-
lyzed by complex 5. To obtain further support for this mechanism, it was
decided to investigate how the racemization rate depended on the partial
pressure of CO (Figure 3.3).

The experimental set-up used for this study was reminiscent of a usual
racemization reaction, where complex 5 (0.01 mmol, 1 mol%) was first acti-
vated by addition of tert-BuOK (0.03 mmol, 3 mol%) in dry toluene (2 mL).
After stirring for 10 min, different amounts of CO (250-400 μL, 10.4-16.6 μmol)
were quickly injected by a gas-tight Hamilton syringe, followed by
addition of (S)-1-phenylethanol 25 (1.00 mmol). All reactions were per-
formed in gas-tight microwave vials and were sampled by aliquot withdraw-
als for GC-analysis after 1, 3, and 10 min (after the addition of the substrate
alcohol). Each experiment was reproduced at least twice and the average ee
value for each reaction was plotted against the reaction time. To provide for
a reference of the racemization rate for the uninhibited reaction, a control
reaction was carried out in the absence of CO under otherwise unchanged
conditions.

As anticipated, the racemization rate was shown to be greatly dependent
on the partial pressure of CO, since an inhibitory effect could be detected
upon CO additions exceeding 300 μL (12.5 μmol). For instance, when 300
μL of CO was added, the racemization rate decreased by almost a half. An
increase of the amount of CO to 350 μL (14.6 μmol) resulted in an even
stronger inhibition, where the ee of alcohol (S)-25 was still 85% after 3 min,
which could be compared to 5% ee after the same time for the uninhibited
reaction. An even slower racemization was observed upon addition of 400
μL CO (16.6 μmol), where the alcohol (S)-25 still exhibited an ee of 80%
after 10 min. At higher additions of CO (≥500 μL), no signs of racemization
of (S)-25 could be observed within 10 min, which was attributed to a combi-
nation of strong CO inhibition and facile formation of complexes 34 and 34’
that depleted the amount of the catalytically active 5a. The combination of
these two effects would also explain the non-linear behavior of the CO inhi-
bition, where the window of going from an uninhibited (250 μL) to a com-
pletely inhibited (≥500 μL) reaction was rather narrow.
3.2.4 Outlook on Future Mechanistic Work

Considering that the two studies described in Chapter 2 and 3 have focused on different aspects of the racemization mechanism involving pentaaryl(cyclopentadienyl)Ru-complexes, it is therefore appropriate to conclude the first part of the thesis by discussing how the results from these two studies relate to other mechanistic work done by our group. In light of the results obtained from the CO exchange and CO inhibition experiments, it now seems highly likely that CO dissociation constitute a critical step in the racemization of sec-alcohols catalyzed by complex 5. This observation is in line with previous DFT studies, which had shown that CO dissociation is more energetically favorable than $\eta^5 \rightarrow \eta^3$ ring slippage of the cyclopentadienyl ligand.\[94d\] Hence, the mechanism of complex 5 is expected to involve alcohol-alkoxide exchange, CO dissociation, $\beta$-hydride elimination and hydride re-addition as the key steps.

An important topic to address further in future mechanistic studies is how the overall racemization rate depends on all these steps. Based on the results obtained from the racemization study using the electronically modified analogues of complex 5, it appears that depending on the electronic properties of the substrate alcohol it is either the $\beta$-hydride elimination or hydride re-addition that becomes the rate-determining step. However, previous DFT calculations have revealed that CO dissociation is associated with a high energy barrier, which could imply that it instead constitutes the rate-determining step.\[94d,102\] Together, these contradictory findings regarding the rate-determining step of the racemization highlight that the current mecha-
nistic model might not be complete, which calls for further research on this topic. One interesting question that could be addressed by such future efforts is whether the mechanism begins with CO dissociation from 5b, which generates the 16-electron complex 37' that is actually the catalytically active species cycling through alcohol-alkoxide exchange, β-hydride elimination and hydride re-addition (Scheme 3.4). This mechanistic model[94d] would be consistent with the results from both experimental and computational studies. CO dissociation would then be a step that is positioned outside the catalytic cycle, and which as a result of its high barrier only gives rise to a small amount of catalytically active 16-electron complex 37' that carries out the racemization reaction. This 16-electron species 37' should in turn be expected to be sensitive towards the electronic properties of the attached ligand and the substrate, as demonstrated by the studies described in Chapter 2.

Scheme 3.4. Alternative catalytic mechanism for the racemization of sec-alcohols with complex 5, which could provide for a unification of the experimental and computational results.
3.3 Conclusions

Extensive mechanistic work has been conducted on complex 5 with the aim of elucidating the mechanism for the racemization of sec-alcohols. By the use of $^{13}$C NMR, we managed to show that CO exchange occurs both in the chloride precatalyst 5 and the catalytically-active tert-BuO-species 5a, thus demonstrating that the proposed CO dissociation mechanism is reasonable. The CO exchange in 5a was found to proceed approximately 20 times faster than in 5, which was ascribed to a more efficient $\pi$-donation by the tert-BuO-ligand that stabilizes the transition state for the CO dissociation. This work also provided evidence for the irreversible formation of the tert-butoxydicarbonylruthenium complex 34 at an elevated partial pressure of CO. Moreover, a CO inhibition study was carried out in which the effect of various amounts of added CO on the racemization of (S)-25 was investigated. It could be shown that the racemization rate was clearly inhibited by increasing the partial pressure of CO. Together, the results obtained from this mechanistic work have provided unambiguous support for that CO dissociation constitutes a key step in the racemization of sec-alcohols catalyzed by 5. Future mechanistic work will focus on studying the nature of the CO dissociation step and determine whether it is involved in the catalytic cycle or if it is just an initial activation step that does not need to be passed for each new alcohol.
4. Highly Dispersed Palladium Nanoparticles on Mesocellular Foam: An Efficient and Recyclable Heterogeneous Catalyst for Alcohol Oxidation (Paper III)

4.1 Introduction

As previously discussed in Section 1.2.3, the use of air or molecular oxygen as terminal oxidants for catalytic oxidation of alcohols is associated with many advantages. This approach is particularly attractive from a green chemistry perspective, as it circumvents the use of toxic stoichiometric oxidants and generates H$_2$O as the single byproduct. Unfortunately, the high activation energy barrier of O$_2$ constitutes a fundamental challenge, which has complicated the design of aerobic catalytic oxidation protocols. However, it has lately been realized that heterogeneous systems, especially those based on transition metal nanoparticles, have the ability to directly activate O$_2$ towards reactions with organic substrates.[17a,63a,104]

Recently, our group reported on the synthesis of a heterogeneous catalyst based on Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd$^0$-AmP-MCF) and its application in the racemization of an amine.[49a] This silica-based material has been extensively studied as a support for both metal catalysts and biocatalysts,[24c,51b,105] which is primarily a result of its three-dimensional network of pores that confers a high internal surface area and shields the catalytic species from mechanical grinding, thus reducing the leaching of the catalyst. Furthermore, the MCF material has a high surface concentration of silanol groups that can be grafted with a wide range of functional groups, which enables the immobilization of different catalytic species, ranging from enzymes to nanoparticles and defined transition metal complexes.

Considering the preceding reports on the successful utilization of nanoparticle-based catalysts for aerobic alcohol oxidation, we were also interested in evaluating the Pd$^0$-AmP-MCF for this purpose. Also, observations made during previous work on amine racemization, suggested that the synthetic protocol of the Pd nanocatalyst could be improved. During the recycling experiments of the amine racemization under H$_2$ atmosphere, it was found that the Pd nanocatalyst displayed a significantly lower activity in the
first cycle relative to the subsequent cycles, indicating that the catalyst was not completely reduced from the beginning.\cite{49a} Therefore, this study also aimed at addressing this issue by further optimizing the synthetic protocol of the Pd\textsuperscript{0}-AmP-MCF catalyst.

### 4.2 Results and Discussion

#### 4.2.1 Synthesis and Characterization of the Pd\textsuperscript{0}-AmP-MCF Nanocatalyst

The MCF material used for the immobilization of the Pd nanoparticles was synthesized according to a previous procedure reported by the group of Ying (Scheme 4.1).\cite{106} In this synthetic protocol, an oil-in-water microemulsion is prepared to yield an environment in which the mesoporous composite can be formed from the agglomeration reaction of simpler monomeric silica precursors.

**Scheme 4.1.** Synthetic procedure for the preparation of the siliceous mesocellular foam (MCF) support.

This microemulsion was generated by mixing commercially available triblock copolymer “Pluronic® P123” and mesitylene in a dilute aqueous HCl solution. Tetraethylorthosilicate was then added which undergoes hydrolysis and agglomeration on the surface of the mesitylene/P123 microdroplets, forming a composite around the droplets through hydrogen bonding interactions. In this process, referred to as the aging phase, the encapsulated mesitylene/P123 microdroplets are trapped within the emerging MCF composite, providing the foundation for the pore network of the final support material. At this stage of the reaction, it is possible to selectively enlarge the window size of the pores by the addition of NH\textsubscript{4}F in combination with modulation of the experimental parameters (e.g. temperature and time). After the aging-phase, the MCF composite is obtained as a fine white powder that is subsequently filtered off and washed to remove soluble organic impurities. Finally, the MCF material is calcined at 550 °C to remove the entrapped organic template, leaving behind the hollow pore network.
The porous MCF was characterized by N\textsubscript{2} adsorption and desorption isotherms, where the average pore and window size were measured by the use of the Barrett-Joyner-Halenda method to 29 nm and 15 nm, respectively. Moreover, the specific pore volume and Brunauer-Emmett-Teller surface area were determined to 2.36 cm\textsuperscript{3}/g and 613 m\textsuperscript{2}/g, respectively.

The MCF material was then used as the heterogeneous support for the synthesis of the Pd\textsuperscript{0}-AmP-MCF catalyst, as described in Scheme 4.2. The MCF was functionalized with aminopropyl groups in order to provide for efficient coordination of Pd. This was done by refluxing the MCF with (3-aminopropyl)trimethoxysilane in toluene under inert conditions. The amount of incorporated aminopropyl groups was assessed by inductively coupled plasma-optical emission spectroscopy (ICP-OES), which measured the nitrogen content to 1.52 wt\%.

![Scheme 4.2. The synthesis of the Pd\textsuperscript{0}-AmP-MCF catalyst.](image)

The complexation of the AmP-MCF with Pd to give the Pd\textsuperscript{II}-AmP-MCF precatalyst was performed in H\textsubscript{2}O (pH 8) using Li\textsubscript{2}PdCl\textsubscript{4} as the Pd source. Gratifyingly, it was found that by applying slightly alkaline reaction conditions during the complexation step, it was possible to achieve higher loadings of Pd than in the previous study\cite{49a}. In the original synthetic protocol, the complexation step was carried out at pH 3, under which the majority of the amine ligands are in the protonated state. This drastically reduces the coordinative ability of the amine ligands, resulting in less efficient incorporation of Pd into the catalyst.
Reduction of the coordinated Pd\textsuperscript{II}-AmP-MCF to form the metallic nanoparticles was conducted using 10 equiv. of NaBH\textsubscript{4} in H\textsubscript{2}O, which is the same amount of reducing agent used in the previous protocol. However in the case of the previous study, concerns were initially raised that the highly alkaline conditions caused by the NaBH\textsubscript{4} could result in degradation of the base-sensitive MCF material. Consequently, the reaction solution was adjusted from pH >12 to pH 10 by the use of 0.1 M aqueous HCl in attempts to protect the MCF, but unfortunately this also had a partial quenching effect on the NaBH\textsubscript{4}. In our study, we found out that such a pH adjustment was unnecessary, as the reaction time for the reduction was too short to have a negative effect on the morphology of the MCF. Therefore by avoiding the additions of HCl, the full reducing power of the 10 equiv. NaBH\textsubscript{4} could be retained, thus allowing for a more efficient reduction of the Pd\textsuperscript{II}-AmP-MCF.

The Pd\textsuperscript{0}-AmP-MCF was characterized by several different techniques, including ICP-OES, X-ray photoelectron spectroscopy (XPS), convergent beam electron diffraction (CBED) and transmission electron microscopy (TEM). The Pd content was determined to 8.25 wt% by ICP-OES analysis, which demonstrated the excellent coordination ability of the aminopropyl groups. High angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) and TEM allowed for an assessment of the size and distribution of the Pd nanoparticles, which showed a well-dispersed pattern of nanoparticles in a narrow size range of around 2 nm (Figure 4.1).

![Figure 4.1](image)

**Figure 4.1.** Images taken of the Pd\textsuperscript{0}-AmP-MCF showing well-dispersed Pd nanoparticles and the porous morphology of the MCF material. a) TEM image with 20 nm scale bar. b) HAADF-STEM with 50 nm scale bar.
Furthermore, a combination of CBED and high-resolution TEM analysis confirmed that the observed Pd nanoparticles were crystalline in nature, which verified that the atoms within the nanoparticles were structured in a uniform and ordered arrangement. Analysis by XPS was carried out to determine the Pd oxidation states present in the Pd$^{0}$-AmP-MCF and the Pd$^{II}$-AmP-MCF precatalyst (Figure 4.2).

![XPS spectra of the Pd$^{II}$-AmP-MCF precatalyst (left) and the Pd$^{0}$-AmP-MCF nanocatalyst (right).](image)

**Figure 4.2.** XPS spectra of the Pd$^{II}$-AmP-MCF precatalyst (left) and the Pd$^{0}$-AmP-MCF nanocatalyst (right).

By examining the XPS spectrum of the Pd$^{II}$-AmP-MCF, a characteristic split peak with a maximum at 337.2 eV could be observed, and it was assigned to the 3d core level of a Pd$^{II}$-species. In the XPS spectrum of the Pd$^{0}$-AmP-MCF catalyst, this peak is shifted towards lower binding energies (335.5 eV) and was found to be in close agreement with literature values of bulk Pd metal (334.6 eV).\[107\] The difference in binding energy between the nanoparticulate Pd$^{0}$-species and bulk Pd metal is a result of the ligand interactions present in the Pd$^{II}$-AmP-MCF catalyst. Estimations made from the XPS spectra suggested that the Pd$^{II}$-component in the Pd$^{0}$-AmP-MCF only accounts for a small portion of the total signal intensity. However, it is unclear if this Pd$^{II}$ content originates from unreduced species attached to the support surface or whether the nanoparticles contain some amount of incorporated Pd$^{II}$.\[107\]
4.2.2 Condition Screening

For the initial screening of the reaction conditions, 1-phenylethanol was chosen as the model substrate. Experimental parameters, such as catalyst loading, solvents, reaction temperature and the concentration of O₂ were all varied in attempts to optimize the catalytic protocol (Table 4.1).

The screening was commenced by studying the effect of different solvents at 100 °C with 1.5 mol% Pd, and this revealed that the catalytic system displayed poor performance in polar aprotic solvent, such as MeCN, DMF and sulfolane (Table 4.1, Entries 1-3). Heteroatom coordination of the solvents to the Pd nanocatalyst was invoked as an explanation for the inhibitory effect observed in these reactions. Interestingly, the Pd⁰-AmP-MCF displayed activity in H₂O, but unfortunately a significant decrease in reaction rate could be observed when the atmosphere was changed from pure O₂ to air (Table 4.1, Entries 4-5). Although, H₂O is an attractive solvent from a green chemistry perspective, it was not pursued in this study since we predicted several practical issues associated with its use. For instance, we anticipated that the low solubility of more hydrophobic substrates in H₂O and its low boiling point would impose limitations on this catalytic protocol in terms of activity and generality. Also, the study aimed at selectively converting primary alcohols into aldehydes, and in this respect the use of H₂O as solvent is particularly problematic since it favors over-oxidation to the carboxylic acids.

The best results during the solvent screening were obtained with unpolar solvents, such as α,α,α-trifluorotoluene (TFT), p-xylene and toluene (Table 4.1, Entries 6-13). A particularly high efficiency was noticed when the reaction was carried out in TFT at 100 °C with pure O₂ atmosphere, where acetophenone could be obtained in quantitative conversion within 1 h (Table 4.1, Entry 6). Gratifyingly, it was possible to obtain similar results with air atmosphere, by conducting the reaction in p-xylene at 110 °C (Table 4.1, Entry 13). For the sake of convenience, the latter conditions (p-xylene, 110 °C) were chosen for further studies, as it was expected that the substrate scope study would involve the oxidation of more challenging substrates, which would require elevated reaction temperatures. In this respect, p-xylene with its higher boiling point constitutes a better option than TFT (138 °C vs. 108 °C). It is also more desirable, from a safety perspective, to develop a protocol that does not rely on high O₂ concentrations, since this could limit the applicability of the catalytic system in large-scale processes.

The effect of the catalyst loading on the reaction outcome was also evaluated (Table 4.1, Entries 14 and 15); however, for further experiments it was decided to continue with 1.5 mol% Pd, as this gave the highest activity. In summary, after several screening experiments, the reaction conditions that were chosen for further studies were: alcohol (0.8 mmol), Pd⁰-AmP-MCF (1.5 mol%), under air atmosphere in p-xylene (2 mL) at 110°C.
Table 4.1. Screening of solvent, temperature, O₂ concentration and catalyst loading in the aerobic oxidation of 25, using the Pd⁰-AmP-MCF nanocatalyst.¹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (mol%)</th>
<th>Solvent, Temp</th>
<th>Atm.</th>
<th>Conv. [b] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.50</td>
<td>H₂O, 100 °C</td>
<td>O₂</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1.50</td>
<td>H₂O, 100 °C</td>
<td>Air</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>1.50</td>
<td>DMF, 100 °C</td>
<td>O₂</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.50</td>
<td>MeCN, 85 °C</td>
<td>O₂</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>1.50</td>
<td>Sulfolane, 100 °C</td>
<td>O₂</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1.50</td>
<td>TFT, 100 °C</td>
<td>O₂</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>1.50</td>
<td>TFT, 100 °C</td>
<td>Air</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>1.50</td>
<td>p-xylene, 100 °C</td>
<td>O₂</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>1.50</td>
<td>Toluene, 100 °C</td>
<td>O₂</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>1.50</td>
<td>Toluene, 110 °C</td>
<td>O₂</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>1.50</td>
<td>Toluene, 110 °C</td>
<td>Air</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>1.50</td>
<td>p-xylene, 110 °C</td>
<td>O₂</td>
<td>99</td>
</tr>
<tr>
<td>13</td>
<td>1.50</td>
<td>p-xylene, 110 °C</td>
<td>Air</td>
<td>99</td>
</tr>
<tr>
<td>14</td>
<td>0.75</td>
<td>p-xylene, 110 °C</td>
<td>Air</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>1.00</td>
<td>p-xylene, 110 °C</td>
<td>Air</td>
<td>95</td>
</tr>
</tbody>
</table>

[a] All reactions were carried out on a 0.8 mmol scale in 2 mL of solvent for 1 h.
[b] Conversion of 25 into 39 was determined by GC.

4.2.3 Substrate Scope

The optimized catalytic protocol proved to be compatible with a wide range of primary and secondary alcohols, affording the corresponding aldehydes and ketones in high yield and high selectivity (Table 4.2). In general, benzylic alcohols displayed higher reactivity compared to aliphatic alcohols, which were oxidized more slowly. In the case of the oxidation of benzylic substrates (Table 4.2, Entries 1-5, 7 and 8, 10-13, 17), it was also observed that the substituent on the phenyl group had a profound effect on the reaction rate. The presence of additional steric bulk or electron-withdrawing substitu-
ents was found to significantly retard the reaction. This indicates that coordina-
tion of the substrate by π-interactions to the Pd surface of the nanocatalyst constituted a key step in the reaction. As a result, the unsubstituted and relatively sterically-unhindered substrates 1-phenylethanol 25, 1-indanol 49, and benzyl alcohol 55 gave the fastest reactions, affording the desired products in quantitative yields (against internal standard) within 1 h (Table 4.2, Entries 1, 7, and 10).

Remarkably, addition of electron-donating substituents in the para position to the 1-phenylethanol motif, such as a methyl or methoxy group (Table 5.2, Entries 2 and 3), required three times longer reaction times to go to completion compared to that of the reaction involving 25. This demonstrates that the negative effect arising from the additional steric bulk dominates over the beneficial electronic effect caused by electron-donating substituents. However, the reaction of 4-methoxybenzyl alcohol 57 was found to be an exception to this trend where the two opposing effects were found to cancel out each other, and aldehyde 58 could be obtained in quantitative yield already after 1 h (Table 4.2, Entry 11). On the other hand, the reaction involving the ortho isomer 59 showed to be greatly affected by the steric congestion between the -OMe and the -CH₂OH groups, and thus the reaction demanded a reaction time of 4 h to give comparable yields (Table 4.2, Entry 12).

Substrates that contained either an electron-deficient π-system (Table 4.2, Entry 4) or lacked it altogether (Table 4.2, Entries 6, 9 and 14-16), required increased catalyst loadings and/or elevated reaction temperatures in order to give high yields. The inability of these substrates to effectively coordinate to the catalyst surface was invoked as an explanation for their lower reactivity.

Bulky alcohols, such as 1-(2-naphthyl)ethanol 45, benzoin 51 or 2-naphthalenemethanol 61, could also be converted to the corresponding carbonyl products within 5-6 h in good to high yields (Table 4.2, Entries 5, 8, and 13). The secondary allylic alcohols 71, and 73, displayed a similar reactivity towards the Pd nanocatalyst as 2-octanol 47, demonstrating that a single C=C bond in the allylic position had a small effect on the coordinative ability of these substrates (Table 4.2, Entries 6 and 18-19). However, in the case of the more activated allylic alcohols 69 and 75, facile oxidation reactions were observed and the desired carbonyl compounds 70 and 76 could be afforded in excellent yield within 3 h (Table 4.2, Entries 17 and 20).

Interestingly, the Pd⁰-AmP-MCF also showed to tolerate the heterocyclic alcohols 77 and 79, without suffering from poisoning caused by strong heteroatom coordination to Pd. Hence, the carbonyl compounds 2-thiophencarboxaldehyde 78 and 4-acetylpyridine 80 was obtained in high to excellent yield under the optimized conditions (Table 4.2, Entries 21 and 22). The ability to oxidize heterocyclic alcohols makes the Pd⁰-AmP-MCF an attractive alternative to homogeneous transition metal complexes, which have previously exhibited difficulties in catalyzing these reactions due to the poisoning effect arising from strong heteroatom to metal coordination.¹⁷₄b
Another advantage of this catalytic system is that it selectively gives the aldehyde products over the corresponding carboxylic acids for all the primary alcohols investigated in this study. In all cases, the amount of carboxylic acid was found to be <5%, which is remarkably low considering that stoichiometric amounts of H₂O are formed as a byproduct in the oxidation reactions.

\[
\text{R}_1\text{OH} + \frac{1}{2}\text{O}_2 \xrightarrow{\text{Pd(0)-AmP-MCF, \text{Pd(0)-AmP-MCF}}} \text{R}_1\text{O} + \text{H}_2\text{O}
\]

Table 4.2. Nanopalladium-catalyzed aerobic oxidation of primary and secondary alcohols.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Conv.(^{[b]}) (%)</th>
<th>Yield(^{[c]}) (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{OH} \\
\text{25}
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{39}
\end{array}
\] | 1 | >99 | 96 |
| 2     | \[
\begin{array}{c}
\text{OH} \\
\text{40}
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{41}
\end{array}
\] | 3 | 98 | 97 |
| 3     | \[
\begin{array}{c}
\text{MeO} \\
\text{OH} \\
\text{26}
\end{array}
\] | \[
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{42}
\end{array}
\] | 3 | 98 | 97 |
| 4\(^{[d]}\) | \[
\begin{array}{c}
\text{OH} \\
\text{F} \\
\text{43}
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{44}
\end{array}
\] | 8 | 82 | 82 |
| 5     | \[
\begin{array}{c}
\text{OH} \\
\text{45}
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{46}
\end{array}
\] | 5 | 96 | 94 |
| 6\(^{[d]}\) | \[
\begin{array}{c}
\text{OH} \\
\text{C}_9\text{H}_3 \\
\text{47}
\end{array}
\] | \[
\begin{array}{c}
\text{O} \\
\text{C}_9\text{H}_3 \\
\text{48}
\end{array}
\] | 8 | 82 | 79 |
<table>
<thead>
<tr>
<th></th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>6</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>11</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>13</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>14[^5]</td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
<td>8</td>
<td>98</td>
</tr>
<tr>
<td>15[^5]</td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
<td>8</td>
<td>93</td>
</tr>
<tr>
<td>16[^5]</td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
<td>8</td>
<td>88</td>
</tr>
</tbody>
</table>
4.2.4 Investigation of the Recyclability, Leaching and Scalability

To establish the practical utility of the present catalytic protocol, factors such as recyclability, leaching and scalability were extensively studied. First, the recyclability of the Pd\textsuperscript{0}-AmP-MCF was studied in the oxidation of 1-phenylethanol \textsuperscript{25} by subjecting the catalyst to five consecutive reaction cycles. Between each cycle the Pd\textsuperscript{0}-AmP-MCF was separated from the reaction solution by centrifugation. After extensive washing with p-xylene, fresh solvent and substrate were re-added to the Pd nanocatalyst and a new cycle
was immediately started. In all five cycles, the product acetophenone 39 was obtained in $\geq 98\%$ yield within 1 h. The retained activity of the Pd$^0$-AmP-MCF could also be demonstrated by the use of kinetic experiments, where the conversion was monitored over time for the first and fifth cycle (Figure 4.3). From this figure, it is clear that the catalyst displayed the same activity in the two reactions, thus confirming that no observable deactivation occurred over the first five cycles.

Further support for the high stability of the Pd nanocatalyst were obtained from another recycling study where additional portions of starting material 25 were repeatedly injected to the reaction upon its completion (performed three times). This recycling experiment also showed that product inhibition upon increasing concentrations of 39 did not constitute a serious issue for the Pd nanocatalyst.

![Figure 4.3. Kinetic experiment on the oxidation of 1-phenylethanol 25, first use (—) and the fifth use (—).](image)

The robustness of the Pd$^0$-AmP-MCF was also assessed by TEM, where images were taken of nanocatalyst recovered from the fifth recycling cycle (Figure 4.4a), and compared to those of unused nanocatalyst (Figure 4.4b). Interestingly, the recycled Pd nanocatalyst showed a similar nanostructure to that of unused catalyst, where no significant changes in either the size or the distribution pattern could be observed.
The amount of metal leaching from a heterogeneous catalyst constitutes another important practical aspect, as this can be the determining factor for whether a catalytic system can be used for large-scale industrial applications or not. As previously mentioned, metal impurities in the final product pose a major issue in both the fine chemical and pharmaceutical industry, and it is the primary reason for why heterogeneous protocols are generally preferred over homogenous ones.\cite{8} Gratifyingly, the leaching for the Pd\textsuperscript{0}-AmP-MCF catalyst was found to be low (\(\leq 5\) ppm). To verify that the reactions were truly catalyzed through a heterogeneous mechanism and not by these minor amounts of leached Pd, a hot filtration test was carried out for the oxidation of 1-phenylethanol \textsuperscript{25}. In this experiment, the reaction solution (at 110°C) was filtered after 20 min (68\% conversion of starting material) to remove the heterogeneous catalyst. The solid-free filtrate was then allowed to stir under identical conditions for 24 h to establish whether the oxidation of \textsuperscript{25} continued. As expected, no further reaction was observed, which provided unambiguous evidence that the catalytic system operates solely through a heterogeneous mechanism.

Large-scale experiments were performed on a 500 mmol scale of 1-phenylethanol \textsuperscript{25} (61.1 g), using a Dean-Stark set-up. Initially, the large scale reaction was performed using 6.8 \(\times\) 10\(^{-4}\) mol\% Pd under neat conditions and an air atmosphere at 160 °C. This afforded acetophenone \textsuperscript{39} in 91 \% conversion after 36 h, which corresponded to a TON and TOF of 135000 and 3750 h\(^{-1}\), respectively. In attempts to improve the TON and TOF of the system, the catalyst loading was lowered to 1.7 \(\times\) 10\(^{-4}\) mol\% Pd and the atmosphere was changed to pure O\(_2\) (Figure 4.5). To our delight, this gave a conversion of 82\% of \textsuperscript{25} to \textsuperscript{39} (77\% isolated yield), which correspond to an excellent TOF of 25800 h\(^{-1}\) (up to 44\% conversion) and an impressive TON of over 450000. It is also important to point out that auto-oxidation of the starting material occurs to some extent under these conditions. Therefore,
after establishing the background reaction the TOF and TON for the latter large-scale reaction were corrected to 23900 h\(^{-1}\) and 365000, respectively. Despite these corrections, the TON obtained with the Pd\(^{0}\)-AmP-MCF is to our knowledge, among the highest ever reported for a heterogeneous catalyst employed in the aerobic oxidation of alcohols.\[^{67b,69i,108}\]

![Graph](image)

**Figure 4.5.** Oxidation of 1-phenylethanol (25) to acetophenone (39) on a 500 mmol scale, using 1.7 \(\times\) 10\(^{-4}\) mol\% Pd and neat conditions under air atmosphere at 160 °C.

### 4.3 Conclusions

We have described an improved synthesis of a Pd\(^{0}\)-AmP-MCF nanocatalyst, provided extensive characterization data, and applied it in the aerobic oxidation of a wide range of primary and secondary alcohols. In general, the desired aldehyde and ketone products could be obtained in high yields within short reaction times, when the reactions were performed in \(p\)-xylene under air atmosphere at 110 °C. The Pd nanocatalyst was found to be highly stable, which was demonstrated by its excellent recyclability and small metal leaching in the oxidation of 1-phenylethanol 25. Moreover, the protocol was found be highly scalable, and as a result the oxidation reaction could be carried out on a 500 mmol scale, giving impressive TON and TOF values of more than 365000 and 23900 h\(^{-1}\), respectively. Collectively, these features make the Pd\(^{0}\)-AmP-MCF an attractive heterogeneous catalyst for the preparation of aldehydes and ketones on an industrial scale.
5. Well-Defined Palladium Nanoparticles Supported on Amino-Functionalized Siliceous Mesocellular Foam: A Heterogeneous Catalyst for Chemically-Induced H₂O Oxidation (Paper IV)

5.1 Introduction

To allow for the realization of a practical artificial photosynthetic device that has the capability to produce storable and sustainable fuels, an efficient and robust WOC must first be developed. In the light of this situation, a large number of research groups from several different fields have tried to solve this issue by developing various homogeneous and heterogeneous systems based on metals, such as Ru, Ir, Fe, Mn, Co, and Cu. Unfortunately, the WOCs developed so far have still not displayed the combination of efficiency and stability that is necessary for incorporation into a commercial fuel cell. In the case of the current heterogeneous WOCs, the primary limitation has been their low catalytic activity, as most of them are only capable of evolving O₂ at substoichiometric levels (the amount of O₂ produced is less than the amount of metal used), which is far from sufficient for practical applications.

A potential way to solve this problem and concomitantly access more active WOCs would be to examine nanstructured transition metal catalysts, which constitute a relatively underexplored frontier in H₂O oxidation catalysis at the moment. In organic chemistry, it has been demonstrated on several occasions that unique reactivities and selectivities can be achieved by the use of heterogeneous catalysts comprised of ≤2 nm metal nanoparticles. One of the most frequently applied metals for this purpose is Pd, which has been found to be highly efficient and selective for a wide range of transformations, including C-H activation, oxidation, reduction and C-C bond forming reactions. However, despite the rich variety of WOCs developed within the field of artificial H₂O oxidation, there has for a long time existed a conspicuous lack of Pd-based systems for this transformation. It was not until very recently when Kwon et al. successfully showed that subnanometer Pd cluster anchored onto an ultrananocrystalline electrode could function as an electrochemical catalyst for H₂O oxidation. Independently from this
seminal study, we investigated the possibility of using the Pd\textsuperscript{0}-AMP-MCF as a heterogeneous catalyst for chemically-induced H\textsubscript{2}O oxidation, employing either Ce\textsuperscript{IV} or [Ru(bpy)\textsubscript{3}]\textsuperscript{3+} as terminal oxidant. It was envisioned that the desirable nanostructure of this Pd nanocatalyst could enable a unique H\textsubscript{2}O oxidation reactivity that has not been observed previously for molecular Pd complexes or bulk Pd metal.

5.2 Results and Discussion

5.2.1 Catalytic H\textsubscript{2}O Oxidation Experiments

The initial evaluation of the Pd\textsuperscript{0}-AmP-MCF for catalytic H\textsubscript{2}O oxidation was conducted using Ce\textsuperscript{IV} as the chemical oxidant. The outcome of the reaction was determined on the basis of the concomitant O\textsubscript{2} evolution, which was followed by real-time mass spectrometry. Interestingly, an immediate evolution of O\textsubscript{2} could be observed upon addition of an aqueous CAN solution (~42 equiv. Ce\textsuperscript{IV}) to the Pd nanocatalyst, which over the course of 50 min reached a TON of approximately 0.8.

Having established that the Pd\textsuperscript{0}-AmP-MCF catalyst could indeed mediate H\textsubscript{2}O oxidation, it was thereafter decided to determine whether this catalyst was compatible with the mild one-electron oxidant [Ru(bpy)\textsubscript{3}]\textsuperscript{3+}. As previously stated, this oxidant is more practical in an artificial photosynthetic device since it can be photochemically regenerated from the corresponding [Ru(bpy)\textsubscript{3}]\textsuperscript{2+-complex} and thus allows for the H\textsubscript{2}O oxidation process to be driven by light. These catalytic experiments were performed under neutral conditions (0.1 M phosphate buffer, pH 7.2) employing excess of [Ru(bpy)\textsubscript{3}]\textsuperscript{3+}. To our delight, the Pd\textsuperscript{0}-AmP-MCF was also found to evolve substantial amounts of O\textsubscript{2} under these conditions, achieving a high TOF of of 2.7 × 10\textsuperscript{-2} s\textsuperscript{-1} per bulk Pd content (Figure 5.1a). In comparison to the catalytic activity observed for previously reported heterogeneous materials,\textsuperscript{[112]} it becomes apparent that the performance of the Pd\textsuperscript{0}-AmP-MCF constitutes a significant leap forward in the field of heterogeneous H\textsubscript{2}O oxidation catalysis. Moreover, the TON for the Pd nanocatalyst was measured to 10, which makes it one of the few heterogeneous systems that can exceed a stoichiometric production of O\textsubscript{2} and truly have a catalytic role in the reaction.

To determine that the evolved O\textsubscript{2} originated from the solvent H\textsubscript{2}O and not from any other oxygen source, the [Ru(bpy)\textsubscript{3}]\textsuperscript{3+}-driven experiment was repeated with isotopically labelled H\textsubscript{2}O (H\textsubscript{2}\textsuperscript{18}O, Figure 5.1b). The amounts of proportionally enriched O\textsubscript{2} evolved from this reaction were also quantified by real-time mass spectrometry. From the ratio of the isotopologues \textsuperscript{18,18}O\textsubscript{2}/\textsuperscript{16,16}O\textsubscript{2} and \textsuperscript{18,16}O\textsubscript{2}/\textsuperscript{16,16}O\textsubscript{2}, it was confirmed that the solvent H\textsubscript{2}O is the sole source of the oxygen in the generated O\textsubscript{2}. 

58
Figure 5.1. a) Kinetic curves for O₂ evolution by the Pd nanocatalyst vs time. Conditions: An aqueous phosphate buffer solution (0.1 M, pH 7.2, 0.5 mL) was added to the oxidant [Ru(bpy₃)](PF₆)₃ and the Pd nanocatalyst. (▲) Pd nanocatalyst (20 μg, 15.1 nmol), [Ru(bpy₃)](PF₆)₃ (7.0 mg, 7.0 μmol), (●) Pd nanocatalyst (250 μg, 0.19 μmol), [Ru(bpy₃)](PF₆)₃ (45 mg, 45 μmol). Chemical H₂O oxidation catalyzed by the Pd nanocatalyst in isotopically labeled H₂O (15.5% H₂¹⁸O). Experimental conditions: Reactions were carried out in an aqueous phosphate buffer solution (0.1 M, pH 7.2, 0.5 mL, 15.5% H₂¹⁸O) with the Pd nanocatalyst (0.36 mg, 0.27 μmol Pd) and [Ru(bpy₃)](PF₆)₃ (5.30 mg, 5.30 μmol). (■) ¹⁶,¹⁶O₂, (●) ¹⁶,¹⁸O₂, (▲) ¹⁸,¹⁸O₂.

Also, to verify that the Pd nanoparticles were required for the observed O₂ evolution, control experiments were performed both without Pd⁰-AmP-MCF and with pristine AmP-MCF. Both these control experiments affirmed the catalytic role of the Pd nanoparticles in the H₂O oxidation event, as no O₂ evolution could be detected in their absence.

To demonstrate the unique reactivity of the Pd⁰-AmP-MCF, its activity was compared to those of commercial Pd/C and Pd(OH)₂/C in the [Ru(bpy)₃]³⁺-driven H₂O oxidation. The distribution of the Pd in these two commercial heterogeneous catalysts was assessed by the use of HAADF-STEM, showing that both catalysts contained Pd particles of a very broad size range, which was unevenly distributed across the carbon support surface (Figure 5.2). This is in sharp contrast to the nanostructure of the Pd⁰-AmP-MCF, which exhibits a well-dispersed pattern of Pd nanoparticles in a narrow size range (1.5-2.6 nm). In the catalytic H₂O oxidation experiments, the two commercial catalysts were found to be inferior when compared to the Pd nanocatalyst, as they were only capable of evolving negligible amounts of O₂, when subjected to corresponding amounts of [Ru(bpy)₃]³⁺. This clearly demonstrates that the impressive performance of the Pd⁰-AmP-MCF catalyst can be ascribed to its favorable nanostructure, which permits access to a reactivity that is not possible to achieve with other commercially available heterogeneous catalysts with disordered Pd distributions.
Figure 5.2. Images taken of commercial heterogeneous Pd catalysts by HDAAF-STEM. a) Pd/C with 0.2 μm scale bar. b) Pd/C with 50 nm scale bar. c) Pd(OH)$_2$/C with 0.2 μm scale bar. d) Pd(OH)$_2$/C with 50 nm scale bar.
5.2.2 Recycling and Leaching Experiments

In order to be able to justify the use of heterogeneous catalysts over their homogeneous counterparts, it is of great importance to establish both their stability and the degree of metal leaching under the applied reaction conditions. For this purpose the \([\text{Ru(bpy)}_3]^{3+}\)-driven \(\text{H}_2\text{O}\) oxidation was chosen as the model reaction, as it is of the most practical relevance for future research in solar energy conversion schemes.

The results from the recycling study are shown in Figure 5.3a, and verify that the Pd nanocatalyst could be successfully re-used without any substantial decrease in activity. This is an encouraging observation as it confirms that these types of heterogeneous nanoparticle based catalysts show a potential long-term stability, which is one of the most important requirements to fulfill for a WOC component within a photosynthetic fuel cell. To further demonstrate the robustness of the \(\text{Pd}^0\)-AmP-MCF, it was recovered and analyzed by HAADF-STEM after use in a catalytic \(\text{H}_2\text{O}\) oxidation experiment. As expected, the Pd nanocatalyst showed to retain its nanostructure and no observable changes in either particle size or dispersion could be seen (Figure 5.3b). In combination, the recycling experiment and the STEM-analysis suggested that the cease in \(\text{O}_2\) evolution that was observed after approximately 15 min in the catalytic experiments (cf. Figure 5.1a), is not due to degradation of the heterogeneous catalyst but rather to decomposition or depletion of the \([\text{Ru(bpy)}_3]^{3+}\) oxidant.

Liquid aliquots were also withdrawn from the recycling study to allow for the determination of the Pd leaching under the applied reaction conditions. From ICP-OES analysis, the Pd leaching of the first and second cycle was determined to 0.8 ppm and 0.2 ppm, respectively. This is a remarkably low value considering that \(\text{H}_2\text{O}\) oxidation catalysis is associated with highly oxidative conditions, and provides support that the simple aminopropyl groups are capable of retaining the Pd nanoparticles on the support surface throughout the reaction. This is a somewhat surprising result given that amine-containing ligands have been shown to undergo facile oxidation in homogeneous systems under \(\text{H}_2\text{O}\) oxidation conditions that ultimately lead to degradation of the molecular complex,\(^{113}\) and suggests that the currently used heterogeneous approach is less aggressive towards the grafted organic ligands.
5.3 Conclusions

We have reported on the successful application of the Pd⁰-AmP-MCF for chemically-driven H₂O oxidation, using either Ce⁴⁺ or [Ru(bpy)₃]³⁺ as the terminal oxidant. When employing the mild one-electron oxidant [Ru(bpy)₃]³⁺, the Pd nanocatalyst displayed a remarkably high TOF of 2.7 × 10⁻² s⁻¹, which is one to two orders of magnitude higher than those of previously reported heterogeneous metal-based materials. Also, in contrast to most of the previously reported heterogeneous protocols for this reaction, the Pd⁰-AmP-MCF was capable of evolving quantities of O₂ that exceeded the amount of catalyst used. Complimentary to its high catalytic activity, the Pd nanocatalyst also exhibited many of the typical benefits associated with a heterogeneous catalyst, such as straightforward and cost-effective synthesis, high stability, excellent recyclability and low metal leaching. Together, the results obtained from this study on the Pd⁰-AmP-MCF highlight the potential of nanostructured catalysts holds for advancing the field of heterogeneous H₂O oxidation catalysis.
6. Co-immobilization of an Enzyme and a Metal into the Compartments of Mesoporous Silica for Cooperative Tandem Catalysis: An Artificial Metalloenzyme (Paper V)

6.1 Introduction

Despite the tremendous progress that has been made within the field of catalysis during the last century, man-made catalytic protocols are still inferior when compared to the processes occurring within living cells. In living systems, enzymes function in a cooperative and well-orchestrated fashion to achieve highly efficient and selective “one-pot” tandem catalyzed transformations, in which simple building blocks are converted into complex molecules under mild reaction conditions.\(^{[114]}\) In this respect, the metalloenzymes constitute perhaps the most impressive examples, as they are generally involved in many important and intricate multi-step processes, such as \(\text{H}_2\text{O}\) oxidation,\(^{[84a, 115]}\) photosynthesis,\(^{[82]}\) and nitrogen fixation.\(^{[116]}\) Their remarkable catalytic performance is made possible by the metal-containing cofactors that are incorporated into the enzyme structures, which permit access to a broader scope of reactivity that cannot be accomplished with the chemistry of the amino acids alone.

Ever since the seminal work done by Wilson and Whitesides in 1978 (Figure 6.1),\(^{[117]}\) extensive research has been dedicated towards the construction of artificial metalloenzymes containing non-natural metal cofactors. The aim of this research has been to develop catalysts that combine the rich chemistry of the transition metals with the activity and selectivity of natural enzymes, in attempts to achieve unprecedented and highly efficient chemical transformations. Numerous methods to create artificial metalloenzymes have been reported so far;\(^{[118]}\) however, most of them involve the anchoring of an organometallic species to a protein, either via covalent, dative, or supramolecular interactions. Although many impressive catalytic protocols have been accomplished by the use of this methodology,\(^{[118]}\) they are still limited by the fact that the catalytic activity of the metalloenzyme arises solely from the introduced metal species, meaning that the protein only serves as a ligand controlling the enantioselectivity.
Figure 6.1. The first example of an artificial metalloenzyme was reported by Wilson and Whitesides, and made use of the irreversible binding between the protein avidin and its natural ligand biotin. The biotin ligand was transformed into an Rh-catalyst, which within the chiral protein binding pocket could catalyze the enantioselective hydrogenation of $\alpha$-acetamidoacrylic acid.

In this perspective, we sought an alternative method for creating artificial metalloenzymes that combined the unique reactivities of both the enzyme and the transition metal species. Currently, there only exist a handful of examples of catalytic entities, which display this proposed bifunctionality. Kim and co-workers have reported on a bifunctional metalloenzyme mimic, which was created by the generation of Pt nanoparticles within a bacterial aminopeptidase. This catalyst was successfully employed in a two-step cascade reaction, involving first the enzyme-catalyzed amide bond cleavage of glutamic acid $p$-nitroanilide followed by a Pt-catalyzed reduction of the liberated $p$-nitroanilide to $p$-phenylenediamine (Scheme 6.1).[119]

Scheme 6.1. A two-step cascade reaction catalyzed by a bifunctional metalloenzyme mimic.
Recently, Filice et al. made use of the same method to introduce Pd nanoparticles into the interior of a lipase, to create a biohybrid that could be used as a catalyst for several organic transformations.\cite{Filice2009} Another interesting concept for the deracemization of amines that was reported by Foulkes et al. made use of living catalytic entities.\cite{Foulkes2015} Here, *Escherichia coli* bacteria were engineered to simultaneously express monoamine oxidase enzymes into the intracellular environment and bind Pd nanoparticles onto their outer membrane, and together these two catalytic species cooperatively performed the desired cascade reaction.

A general and more attractive strategy for the construction of metalloenzyme mimics proposed by our group was to co-immobilize the transition metal species and the enzyme within the same cavities of a mesoporous support. This would bring the transition metal catalyst and the enzyme together in a close proximity, allowing them to operate more efficiently in a cooperative fashion. Furthermore, this approach would provide access to the advantages of heterogeneous catalysis, which involve simple separation and recycling of the catalyst.

To demonstrate the utility of this co-immobilization method, the DKR of a primary amine was chosen as the model reaction. This transformation constituted a suitable choice as our group had previously reported on separate heterogeneous protocols for the KR and racemization of these substrates. The Pd\textsuperscript{0}-AmP-MCF catalyst was in the original study disclosed as an efficient and enzyme-compatible catalyst for the racemization of a primary amine, and consequently it could be used in combination with CALB in a DKR reaction.\cite{Amiral2015} Recently, we also reported on the immobilization of CALA onto the same MCF material, by employing a glutaraldehyde-based Schiff base-coupling strategy.\cite{Cortes2015} The resulting MCF-supported CALA displayed significantly higher E-value (500 vs 27) and thermostability in the KR of \(\beta\)-amino esters than unsupported CALA.

In theory, it was proposed that the synthesis of such a bifunctional hybrid catalyst could be achieved by simply combining the two previous protocols for enzyme and Pd nanoparticle immobilization. This would provide for a single and recyclable catalytic entity that would be capable of performing both half-reactions of a DKR, *i.e.* racemization and kinetic resolution (Figure 6.2).
Figure 6.2. General principle for the cooperative tandem catalysis performed by the proposed hybrid catalyst in the DKR of 1-phenylethylamine.

Results and Discussion

6.2.1 Synthesis and Initial Evaluation of a Series of Pd/Enzyme Hybrids

Considering the past success of using CALB as a resolving agent in the DKR of primary amines, it was a natural choice to select this lipase as the enzyme constituent for the hybrid catalyst. For the synthesis of the hybrid catalyst, it was first decided to start from the Pd\(^0\)-AmP-MCF catalyst (7.91 wt% Pd) and chemically modify its free aminopropyl groups so they could accommodate CALB. Elemental analysis verified the viability of this proposed strategy by determining the Pd:N ratio of the Pd nanocatalyst to〜1:1.4, which indicated that there existed a large number of aminopropyl groups on the material surface that did not coordinate to any Pd.

In accordance with the previous protocol for immobilization of CALA onto the MCF support, glutaraldehyde was again chosen as the enzyme linker for the hybrid catalyst. As shown in Scheme 4.2, post-functionalization of the Pd\(^0\)-AmP-MCF commenced by stirring it together
with glutaraldehyde in phosphate buffer (pH 8) at room temperature for 24 h. In this reaction, one end of the glutaraldehyde linker is attached to the aminopropyl groups of the support via an imine bond (Schiff base-coupling), while the other end is free to connect to the enzyme in the next step. By exploiting the lysine residues on the surface of the CALB, the enzyme can then be covalently linked to these glutaraldehyde functionalities via another Schiff base-coupling.

**Scheme 6.2.** Two-step synthesis of the Pd/CALB hybrid from the Pd\(^0\)-AmP-MCF nanocatalyst, employing a glutaraldehyde-based Schiff base-coupling strategy.

In practice, the immobilization of CALB was performed in a similar manner to the previous step, *i.e.* by stirring the glutaraldehyde-functionalized Pd\(^0\)-AmP-MCF catalyst (hereon referred to as Pd\(^0\)-GA-AmP-MCF) together with the enzyme in phosphate buffer (pH = 7.2) at room temperature overnight. To establish the optimal loadings of both components, different hybrid catalysts with varying amounts of glutaraldehyde (0.1, 0.5, and 2.0 equiv. with respect to the aminopropyl groups on the support) and CALB (5.5 wt% (low) and 17 wt% (high) of enzyme with respect to the Pd\(^0\)-AmP-MCF) were prepared and evaluated in the racemization and KR of 1-phenylethylamine.

As apparent from Figure 6.3, the racemization activity of the hybrid catalysts was found to be greatly affected by the amount of glutaraldehyde used in the post-functionalization step. To allow for an accurate quantification of the glutaraldehyde-induced deactivation of each hybrid, the kinetic profiles of the hybrid racemization reactions were compared to that of the unfunctionalized Pd\(^0\)-AmP-MCF catalyst.

For this comparison, the slopes of the graphs were extracted from the linear regime and used to establish a relative racemization rate to the standard reaction involving unfunctionalized Pd\(^0\)-AmP-MCF (which was set to 100%). The hybrid with 0.1 equiv. of glutaraldehyde, was found to maintain 75% of the racemization activity, whereas the hybrids with 0.5 equiv. and 2.0 equiv. glutaraldehyde displayed more pronounced deactivation (only 49% and 16% of the activity were preserved). It is not clear why the glutaraldehyde linker has such a dramatic negative influence on the racemi-
zation rate, but one explanation could be that the aldehyde moieties quench the intermediate Pd hydride species which are responsible for the racemization. Interestingly, the amount of immobilized enzyme, on the other hand, did not seem to have any noticeable influence on the racemization rate, as seen from the similar results of hybrid-GA0.1-E\textsubscript{high} and hybrid-GA0.1-E\textsubscript{low}.

![Figure 6.3](image.png)

**Figure 6.3.** Racemization of (S)-1-phenylethylamine 81 catalyzed by Pd\textsuperscript{0}-AmP-MCF and the various hybrids. The reactions were performed using 0.60 mmol amine and 6.00 μmol Pd catalyst under 1 atm. of H\textsubscript{2} at 80 °C.

Next, we probed the activities and enantioselectivities of the hybrid catalysts in the KR of 1-phenylethylamine 81 at 80 °C (Table 6.1). By omitting the hydrogen atmosphere it is possible to evaluate the hybrids strictly on a KR basis, as the Pd nanoparticles do not exhibit any racemization activity in the absence of H\textsubscript{2}. In contrast to the racemization, the KR reaction was not affected by varying amounts of glutaraldehyde, and was instead found to solely depend on the amount of immobilized CALB. By using the hybrid catalyst that contained the lower CALB loading, a conversion of 18% could be achieved within 1 h with a product ee of 99% (Table 6.1, Entry 1). As expected, more efficient KRs were obtained by employing the hybrids that housed higher enzyme loadings and to our delight the ee’s remained excellent in all cases (Table 6.1, Entries 2-4). The minor variations in KR activity that was observed among the hybrid catalysts were ascribed to the small differences in the CALB loading between them. Gratifyingly, the hybrids gave similar results to that of “Pd-free” CALB-MCF (attached via the same glutaraldehyde linker), demonstrating that the co-immobilization strategy keeps the two species separated and prevents them from deactivating each other.
Table 6.1. Kinetic Resolution (KR) of 1-phenylethylamine \( \text{81} \) by the hybrid catalysts and a CALB-MCF reference.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hybrid</th>
<th>( ee_p ) [%]</th>
<th>CALB [wt%][b]</th>
<th>Conv.[c] [%]</th>
<th>E-value[c][d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H-GA(<em>{0.1})-E(</em>{\text{low}})</td>
<td>99</td>
<td>5.20</td>
<td>18</td>
<td>&gt;200</td>
</tr>
<tr>
<td>2</td>
<td>H-GA(<em>{0.1})-E(</em>{\text{high}})</td>
<td>99</td>
<td>15.6</td>
<td>36</td>
<td>&gt;200</td>
</tr>
<tr>
<td>3</td>
<td>H-GA(<em>{0.5})-E(</em>{\text{high}})</td>
<td>99</td>
<td>14.4</td>
<td>36</td>
<td>&gt;200</td>
</tr>
<tr>
<td>4</td>
<td>H-GA(<em>{2.0})-E(</em>{\text{high}})</td>
<td>99</td>
<td>17.0</td>
<td>40</td>
<td>&gt;200</td>
</tr>
<tr>
<td>5</td>
<td>CALB-MCF</td>
<td>99</td>
<td>17.0</td>
<td>39</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1-phenylethylamine \( \text{81} \) (0.60 mmol), ethylmethoxy acetate \( \text{83} \) (1.20 mmol), \( \text{Na}_2\text{CO}_3 \) (50 mg) and hybrid catalyst (10 mg) were dissolved in toluene (1 mL) and stirred at 80 °C for 1 h. [b] Determined by elemental analysis (ICP-OES). [c] Determined by GC analysis. [d] Calculated from the \( ee \) of starting amine and product amide, using the equations developed by Chen et al.\(^{[122]}\)

At first glance, it might seem unexpected that the CALB loading did not correlate with the amounts of glutaraldehyde in the hybrids. However, it is important to clarify that 0.1 equiv. of glutaraldehyde is more than sufficient for immobilizing the amounts of enzyme that was used in this study. The initial motivation for using excess amounts of glutaraldehyde was to ensure an efficient incorporation of CALB into the hybrids. We envisioned that a firm anchoring of the CALB in the hybrid was of key importance as it would allow for an improved recyclability of the catalyst, and therefore we had to settle with the inhibitory effect of the glutaraldehyde linker on the racemization rate.

Based on the results obtained from the racemization and the KR, the hybrid synthesized from 0.1 equiv. of glutaraldehyde and 17 wt% CALB (hybrid-GA\(_{0.1}\)-E\(_{\text{high}}\)) was chosen for characterization and DKR experiments.
6.2.2 Characterization of Hybrid-GA$_{0.1}$E$_\text{high}$

Elemental analyses by ICP-OES determined the CALB and Pd content of the hybrid to 15.6 wt% and 4.80 wt%, respectively. To our delight, these data showed that the glutaraldehyde-based immobilization strategy allowed for a highly efficient incorporation of enzyme, as 92% of the loaded CALB were successfully attached to the support.

Another crucial piece of information that needed to be established was if the immobilized enzymes were distributed evenly over the support. Unfortunately, it is not possible to directly observe enzymes by TEM, and therefore a method had to be devised that allowed for the visualization of the CALB (Scheme 6.4). For this purpose, it was chosen to tag the CALB with Au nanoparticles as they can be easily attached to free thiol groups on enzymes and would give a strong response on TEM. CALB has three disulfide bridges present on its surface, which could be cleaved by treatment with tris(2-carboxyethyl)phosphine (TCEP). The TCEP-treated CALB was subsequently mixed with commercially available colloidal solutions of Au nanoparticles (2 nm and 5 nm), to furnish Au nanoparticle-tagged CALB. For practical reasons, ICP-OES analysis was only done on the Au nanoparticle-tagged enzyme residue that was collected from the 2 nm reaction, and it showed that 14% of the CALB had been successfully tagged with Au nanoparticles. Although, this method gave a low degree of enzyme tagging, this partially Au nanoparticle-tagged CALB was still considered to be sufficient for use in further TEM experiments, which only aimed at qualitatively determining the enzyme distribution.

This characterization study was performed by first stirring Pd$_0$-GA$_{0.1}$-AmP-MCF with the residue containing Au nanoparticle-tagged CALB (2 nm and 5 nm) in phosphate buffer at room temperature overnight, and then analyzing the resulting Au-tagged hybrid catalyst by HAADF-STEM (Figure 6.4). Both the 5 nm (Figure 6.4a) and 2 nm (Figure 6.4b) Au nanoparticle-tagged hybrid catalysts exhibited a well-dispersed distribution of the Au particles, which confirmed that the enzymes were evenly distributed onto the support. From Figure 6.4c, it is clear that the CALB/Au-nanoparticle conjugate could enter a pore and position itself in close proximity to the Pd nanoparticles. To affirm that the Pd nanoparticle distribution was not affected by the enzyme immobilization step, non-tagged hybrid catalysts were also studied by HAADF-STEM (Figure 6.4d). From this experiment, it could be confirmed that the Pd nanoparticles retained both their size and distribution after the enzyme had been anchored. Together, the results obtained from the TEM analyses on the Pd nanoparticle and CALB distributions, showed that the two catalytic-species were greatly intermixed, which is a prerequisite for efficient cooperativity during catalysis.
6.2.3 DKR of 1-phenylethylamine with Hybrid-GA$_{0.1}$E$_{\text{high}}$

The initial attempts to use hybrid-GA$_{0.1}$E$_{\text{high}}$ in the DKR of 1-phenylethylamine 81 were conducted at 80 °C, as both the KR and the racemization had been found to proceed efficiently at this temperature. However, as shown in Table 6.2, this temperature was found to be unsuitable for the DKR reaction, since the desired amide (R)-82 could only obtained in moderate yield (Table 6.2, Entry 1) after 24 h. The low yield of the (R)-82 suggests...
that the CALB underwent deactivation under these conditions upon prolonged reaction times. This enzyme deactivation process was unfortunately not noticed during the KR screening phase, as those reactions were significantly faster and reached near completion within 1 h. Therefore, it was decided to lower the temperature to 70 °C in an attempt to decrease the enzyme deactivation (Table 6.2, Entry 2). To our delight, this provided the amide \((R)-82\) in 95% yield and 99% ee after 16 h. Moreover, by employing molecular sieves 4Å (MS 4Å) the reaction could be further improved, furnishing \((R)-82\) in quantitative yield and 99% ee (Table 6.2, Entry 3). Interestingly, the separate component DKR reactions with \(\text{Pd}^0\)-AmP-MCF and CALB-MCF displayed significantly lower efficiencies than those of the hybrid catalyst (Table 6.2, Entries 4 and 5). This demonstrated the utility of the co-immobilization strategy and provided evidence that a more efficient DKR could be achieved by bringing the two catalytic species closer together.

**Table 6.2.** Comparison study of hybrid-GA\(_{0.1}\)-E\(_\text{high}\) and the separate component system in the DKR of 1-phenylethylamine 81.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time [h]</th>
<th>Temp. [°C]</th>
<th>Yield [%][b]</th>
<th>ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H-GA(<em>{0.1})-E(</em>\text{high})</td>
<td>24</td>
<td>80</td>
<td>45</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>H-GA(<em>{0.1})-E(</em>\text{high})</td>
<td>16</td>
<td>70</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>H-GA(<em>{0.1})-E(</em>\text{high})[c]</td>
<td>16</td>
<td>70</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Pd-MCF/CALB-MCF})</td>
<td>16</td>
<td>70</td>
<td>66</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>(\text{Pd-MCF/CALB-MCF}[c])</td>
<td>20</td>
<td>70</td>
<td>89</td>
<td>99</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: All the reactions were carried out in toluene (2 mL) under 1 atm. of hydrogen gas with 1-phenylethylamine 81 (0.60 mmol), ethyl methoxy acetate 83 (1.20 mmol), dry \(\text{Na}_2\text{CO}_3\) (50 mg), and pentadecane as internal standard. Depending on the experiment, either hybrid catalyst (30 mg, 15.6 wt% CALB, 4.80 wt% \(\text{Pd}\)) or separate \(\text{Pd}^0\)-AmP-MCF (18 mg, 7.91 wt%) and CALB-MCF (28 mg, 17 wt%) were used. [b] Determined by chiral GC-analysis. [c] Performed with MS 4Å.
6.2.4 Recycling Study

An important advantage of this heterogeneous methodology for creating artificial metalloenzyme mimics is the possibility to recycle the catalyst. The evaluation of the reusability of hybrid-GA₀.₁E₉₁ was done for the DKR of 1-phenylethylamine, which was performed both with and without MS 4Å (Table 6.3). The hybrid-GA₀.₁E₉₁ proved to be recyclable in both cases, but unfortunately a substantial decrease in efficiency was observed over consecutive cycles. In the case of the second cycle, it was still possible to achieve high yields and excellent ee’s of amide (R)-82 by extending the reaction time. However, in the third cycle this did not prove to be possible, at least not within practical reaction times, and thus (R)-82 was only obtained in modest yield.

Table 6.3. Recycling study of the hybrid-GA₀.₁-E₉₁ with and without MS 4Å in the DKR of 1-phenylethylamine 81.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle</th>
<th>Time [h]</th>
<th>Yield [%][b]</th>
<th>ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>16</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>16</td>
<td>68</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>72</td>
<td>42</td>
<td>99</td>
</tr>
<tr>
<td>4[c]</td>
<td>1</td>
<td>16</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>5[c]</td>
<td>2</td>
<td>16</td>
<td>74</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>48</td>
<td>82</td>
<td>99</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: All the reactions were carried out in toluene (2 mL) under 1 atm. of hydrogen gas at 70°C with hybrid catalyst (30 mg, 15.6 wt% CALB, 4.80 wt% Pd), 1-phenylethylamine 81 (0.60 mmol), ethyl methoxy acetate 83 (1.20 mmol), dry Na₂CO₃ (50 mg), and pentadecane as internal standard. [b] Determined by chiral GC-analysis [c] Performed with MS 4Å.

Monitoring of the reactions by chiral GC revealed that the decreased activity of the hybrid could be attributed to the enzyme component, since the Pd-catalyzed racemization was found to proceed efficiently throughout the reactions of all cycles. To determine the source of this decreased acylation activity of the hybrid, several control experiments were carried out. First, we wanted to ascertain that the glutaraldehyde indeed formed stable linkages between the enzyme and support surface, thus preventing leaching of CALB. This was performed by analyzing the hybrid catalyst before and after use in a
DKR reaction by ICP-OES, to see if the CALB content had decreased. These analyses showed that the CALB leached to a slight extent (∼5%); however, it was not sufficient to account for the significant deactivation observed for hybrid-GA₀₁E_{high}. Therefore, enzyme denaturation was proposed as the major cause for the diminishing acylation activity. To rule out the possibility that leached Pd species were involved in this deactivation process, an aliquot was withdrawn from the reaction mixture of a DKR and analyzed by ICP-OES. From this leaching test, it was shown that the amount of leached Pd was very low (<0.1 ppm), suggesting that leaching of the Pd species did not play a major role in the enzyme deactivation event.

This hypothesis was further verified by a KR recycling study of the “Pd-free” CALB-MCF that was conducted at 70 °C for prolonged reaction times, which showed a similar deactivation. In this recycling study, CALB-MCF was subjected to three consecutive KR reactions with a reaction time of 24 h each, in which the reaction outcomes were determined by GC after 1 h. In this way, we mimicked the reaction conditions of the DKR recycling study and could unambiguously show that the enzyme denaturates spontaneously on the polar silica surface upon elevated reaction temperatures in the absence of Pd. Similar deactivation has previously been observed for other enzymes immobilized on polar supports.[123]

6.3 Conclusions

We have successfully prepared a heterogeneous Pd/CALB hybrid catalyst and employed it for the DKR of a primary amine. The hybrid catalyst displayed a significantly higher efficiency than the corresponding separate component system for this transformation, demonstrating that the co-immobilization strategy enables for a better cooperativity between the two catalytic species. Further work on the Pd/CALB hybrid catalyst will focus on investigating new heterogeneous materials and enzyme linking strategies to allow for an improved recyclability and minimization of the Pd inhibition.

In general, this co-immobilization method holds great promise for the development of new catalytic tandem protocols, since it could be extended towards other combinations of catalysts that are not compatible with one another.
Concluding Remarks

This doctoral thesis covers five different topics in catalysis, which together highlight the tremendous power catalysis possesses to help streamlining chemical processes. The first two projects describe mechanistic work done on homogeneous (pentaarylcyclopentadienyl)Ru-complexes in the racemization of sec-alcohols, providing key insights into the mechanism by which these catalysts operate. A detailed understanding about the underlying mechanism of any given chemical process is of high importance as it constitutes the foundation from which continued optimization and catalyst design is performed. From our studies, we could establish that CO dissociation plays a key role in the racemization mechanism and that a more efficient racemization can be achieved by matching the electronic properties of the catalyst with the substrate alcohol. This knowledge will be of great value in the future development of new and more efficient DKR protocols.

The second half of the thesis deals with the design of Pd-containing heterogeneous catalysts for various chemical transformations. The Pd⁰-AmP-MCF catalyst was found to be an efficient catalyst for both aerobic alcohol oxidation and H₂O oxidation, which demonstrated that it is relevant both in organic synthesis and for sustainable energy technologies. This particular catalyst possesses several attractive properties, such as high efficiency, high versatility, excellent recyclability, low metal leaching and high compatibility with other catalytic species, which might allow it to progress beyond the academic sphere and find use in industry.

Chapter 6, covered the preparation of a “metalloenzyme-like” hybrid catalyst, consisting of Pd nanoparticles and CALB as the catalytically active components, for use in the DKR of a primary amine. The co-immobilization strategy developed within this study holds great promise as it could enable the successful combination of catalytic species that are intrinsically incompatible with each other. Ultimately, this could lead to the creation of new and highly efficient tandem cooperative catalytic protocols that could revolutionize tomorrow’s chemical synthesis.

Before concluding, I would also like to take the opportunity to briefly express my personal opinions on the fundamental role of chemistry in our society and give my prediction on how this discipline will evolve during the coming decades. Among the natural sciences, chemistry is perhaps the most important discipline as it has the capability to transform almost all industrial processes and have a direct impact on our everyday lives. Particularly in the
perspective of global warming and the imminent energy crisis, specific attention should be dedicated towards making our processes green and sustainable, so that we can ensure a good future for the coming generations. To be able to achieve this goal in practice, I believe it is crucial that we approach these problems in an interdisciplinary manner, and make use of the knowledge of all disciplines of chemistry. I hope this message has been conveyed with this thesis, which has illustrated several examples on how the know-how of biochemistry, inorganic chemistry and organic chemistry can be married and used to solve several different scientific challenges. Finally, I would also like to emphasize that this thesis did not aim at accentuating neither homogeneous nor heterogeneous catalysis as the single answer for every given scientific problem. Both homogeneous and heterogeneous catalysis have their own advantages and disadvantages, so therefore one should have an open mind and choose the most appropriate methodology after the specific situation at hand.
Appendix A

The author’s contribution to publications I-V:

I. Performed the major part of the synthetic and experimental work. Wrote the article.

II. Contributed to the experimental work and to the writing of the article.

III. Performed a significant part of the catalyst synthesis and the catalytic evaluations. Contributed to the writing of the article.

IV. Contributed to the experimental work, and wrote the major part of the article.

V. Devised the synthetic method of the hybrid catalyst, performed the Pd nanocatalyst synthesis and the racemization studies. Wrote the article.
Appendix B

Reprint permissions were kindly granted for each publication by the following publishers:


IV. -

Acknowledgements

I would like to express my sincerest gratitude to:

*Prof. Jan-Erling Bäckvall* for accepting me as a graduate student and allowing me to work with the thing I love the most, chemistry. Thank you for your great inspiration and encouragement. I am particularly grateful for the fact that you allowed me to pursue my own ideas, which I believe have helped me to develop as a chemist.

*Prof. Björn Åkermark* for all the fruitful discussions and support throughout the years. It has been truly inspiring to take part in your research, and I certainly hope that we someday can enjoy the day, when energy is green and plentiful. Also big thanks for playing a key role in arranging my first bachelor diploma work, which led me into this path I am currently on.

*Prof. Stuart Schreiber* for hosting my three month exchange at Broad Institute and giving me the opportunity to work with a highly stimulating project. Although, it was a very demanding journey, I can never say that I regretted partaking on it, rather I would say I greatly enjoyed it and learned a lot from it. Moreover, it allowed me to get a glimpse of a world that I hadn’t encountered before, and which I hope to return to again soon.

*Eric, Markus, Karl, Anuja, Tove and Fredrik* for proof-reading this thesis and providing valuable comments on how to improve it.

*All my collaborators/colleagues* which I have had the pleasure of working with during these years: Hans Adolfsson, Emma Bratt, Marléne Dilenstam, Karin Engström, Kristofer Eriksson, Feifei Gao, Karl Gustafsson, Clemence Haller, Eric Johnston, Erik Karlsson, Magnus Johansson, Markus Kärkäs, Anuja Nagendiran, Leif Nyholm, Sven Oscarsson, Pål Palmgren, Byron Purse, Mozaffar Shakeri, Henrik Svengren, Henrik Sörensen, Cheuk-Wai Tai, Fredrik Tinnis, Hoa-Lien Tran, Alexey Volkov, Wei Wan, Madeleine Warner, Haoquan Zheng, Xiaodong Zou, Torbjörn Åkermark. Of these, I would particularly like to highlight...

*Eric Johnston* for being the best possible supervisor during my master work. It is almost beyond comprehension, how much I have learned from
you about chemistry and “how to make things happen”. You are a brilliant and efficient chemist, and it has been really inspiring to learn from you and work together with you during the first half part of my Ph. D. Unfortunately, these qualities are overshadowed by the fact that you are also a great friend, which is the thing I first come to think about regarding you☺ I hope we can continue to work together in the future.

Markus Kärkäs for all the enjoyable moments (at the department and on various parties and travels) and valuable scientific discussions. You are a great chemist and I know that you will be successful in whatever you do! I also considering you as one of my closest friends, and I hope that we can have many more fun moments together. Also, many thanks for the truly amazing cover picture, which I believe is a piece of modern art.

Anuja Nagendiran for being a great colleague with a constant positive spirit, which can cheer up anyone, anytime! You have been invaluable throughout the years and been highly contributing on all the projects we have had together. Also, you have been a great friend to discuss non-work related topics with. Your future is bright!

Cheuk-Wai Tai for always having the time to run all those TEM-experiments which I bothered you with. You have always been helpful and never ever complained, despite the fact that I often contact you with rather short notice. I am looking forward to continued collaborations. You are mine and our group’s window to the nanoworld.

All of the past and present people at the Department of Organic Chemistry. It has been a pleasure to spend time with you all, in and outside the laboratory. You have granted me with many fond memories, which I will never forget.

All past and present people in my office, “The Broffice.” I know it is safe to say that I will never again have the privilege to spend my time in an office as awesome as this. In a way you are my second family, as I have shared both sad and happy moments together with you, and you have always been there with your support. *brofist*

My diploma-workers: Marlène Dilenstam and Clémence Haller. It has truly been an honor to be your supervisor and to help you in your journey through chemistry. You have both showed great devotion and curiosity, which has been a great source of inspiration for me. I wish you the greatest luck in the future. Just make sure to tell me everything☺
All of the past and present The TA-staff: Thank you for keeping the department going, so that the rest of at the department could safely focus on the science part.

My friends in Boston (particularly my great supervisor Jason Law) for making my first long-time stay abroad a memorable and fun experience. I hope to see you all again soon, and GO RED SOX!

The Córdova group for the fruitful Exselent-collaboration between our and your group, on the merging of amino- and heterogeneous catalysis.

The “Innebandy gang” for all the fun and exciting Tuesday’s.

Berzelii Center Exselent and all of its involved partners/members for all the stimulating meetings and discussions. These events have made me realize that the future is heterogeneous.

The foundations and agencies that have supported me economically during the exchange and the many conferences. I want to acknowledge the following: Berzelii Center Exselent, Gålöstiftelsen, Kungliga vetenskapsakademien, Lars Hiertas minnesfond, Långmanska kulturfonden, Magn. Bergvalls stiftelse, Stockholm universitets donationsstipendier, Svenska Kemistsamfundet, Ångpanneföreningens forskningsstiftelse. Your support has all been very important for me and it has allowed me to learn so many new things, both about chemistry and the world.

The agencies funding our group’s research for making the science possible! Many thanks to Berzelii Center Exselent, the Swedish Research Council and the European Research Council (ERC AdG 247014). We also acknowledge the Knut & Alice Wallenberg foundations for the equipment grant for the electron microscopy facilities.

My great friends from outside the Department: Andres Ramos, Francis Menkes Pi, and Sida Yin. Thank you all for the great moments in life and sorry for all the times I have been mean to you, when playing videogames and Munchkin. I have been extremely lucky to find such great friends as you.

My family for the never-ending support with everything. There are no words to describe all the things you have done for me, and it is because of you that I am the person I am today. Mamma, Pappa, Maria och Teresa, ett stort tack för allt! Hoppas jag kan fortsätta göra er stolta. Jag ska se till att bjuda er till Nobelmiddagen när det väl blir dags ; )
References


