Biomimetic Reactions
Water Oxidation and Aerobic Oxidation

Lien-Hoa Tran
To my family
Abstract

This thesis deals mainly with two oxidation reactions: water oxidation and aerobic oxidation, both of which have been applied in a biomimetic fashion. In the former reaction molecular oxygen is generated whereas in the latter it was used as terminal oxidant in oxidation reactions.

The first part of this thesis describes the synthesis of different ruthenium and manganese complexes that could potentially act as catalysts for water oxidation. This part includes a discussion of the stability and reactivity of a new manganese(III) amide-type complex, that has been used as a catalyst for both epoxidation of stilbene and alcohol oxidation.

The second part of this thesis discusses the synthesis of two new hybrid catalysts consisting of hydroquinone linked cobalt(II) salophen and cobalt(II) salmdpt, which have been used as oxygen-activating catalysts in aerobic oxidation reactions. The former catalyst was applied to the Pd-catalyzed reactions such as 1,4-diacetoxylation of cyclohexadiene whereas the latter was applied to the Ru-catalyzed oxidation of secondary alcohols to ketones. Moreover, these two hybrid catalysts could be used in the Pd-catalyzed carbocyclization of enallenes. In all cases molecular oxygen was used as the stoichiometric oxidant.
List of publications

This thesis is based on the following papers, which will be referred to by Roman numerals:

I. *A New Square Planar Mn$^{III}$ Complex for Catalytic Epoxidation of Stilbene*
   Lien-Hoa Tran, Lars Eriksson, Licheng Sun, and Björn Åkermark

II. *An Efficient and Selective Oxidation of Alcohols to Carbonyl Compounds and Carboxylic Acids Catalyzed by A Dinuclear Ruthenium Complex Using Iodosobenzene as Terminal Oxidant*
   Lien-Hoa Tran and Björn Åkermark

III. *Synthesis of New Hybrid Hydroquinone/Cobalt Schiff Base Catalysts: Efficient Electron-Transfer Mediators in Aerobic Oxidation*
    Byron W. Purse, Lien-Hoa Tran, Julio Piera, Björn Åkermark, and Jan-Erling Bäckvall

IV. *Efficient Synthesis of Hybrid Hydroquinone-Cobalt Schiff Base Oxidation Catalysts*
    Eric V. Johnston, Erik A. Karlson, Lien-Hoa Tran, Björn Åkermark and Jan-Erling Bäckvall

V. *Efficient, Aerobic Ruthenium-Catalyzed Oxidation of Secondary Alcohols via Multistep Electron Transfer*
    Lien-Hoa Tran, Eric V. Johnston, Erik A. Karlsson, Byron W. Purse, Björn Åkermark, and Jan-Erling Bäckvall
    *Manuscript*

Reprints were made with permission from the publishers.
## Contents

1. Introduction ................................................................. 1
   1.1 Water Oxidation ......................................................... 1
       1.1.1 Natural photosynthesis ........................................ 1
       1.1.2 Proposed mechanisms for formation of dioxygen .......... 4
       1.1.3 Artificial photosynthesis ..................................... 5
       1.1.4 Components in model systems ................................. 7
           1.1.4.1 Photosensitizer ......................................... 7
           1.1.4.2 Electron acceptor ....................................... 8
           1.1.4.3 Electron donor (Water oxidation catalysts) ......... 9
       1.1.5 Other metal complexes for water oxidation ................. 12
       1.1.6 Synthetic model systems ...................................... 13
       1.1.7 Objectives of this part of thesis ............................ 14
   1.2 Catalytic oxidation of organic substrates \textit{via} a biomimetic approach 15
       1.2.1 Palladium-catalyzed aerobic oxidation employing electron transfer mediator .......................................................... 17
       1.2.2 Palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes ........ 19
       1.2.3 Palladium(II)-catalyzed cyclization of enallenes .......... 21
       1.2.4 Ruthenium-catalyzed aerobic alcohol oxidation .......... 22
   1.3 Metal-catalyzed epoxidation reactions ............................... 25
       1.3.1 Stoichiometric oxidants ...................................... 27
       1.3.2 Mechanism of the epoxidation ............................... 27
2. Epoxidation of stilbene (\textit{Paper I}) .................................... 29
   2.1 Results and discussion .............................................. 30
       2.1.1 Synthesis of a new manganese(III) amide complex and its X-ray structure ................................................................. 30
       2.1.2 Epoxidation of stilbene using Mn$^{\text{III}}$ amide complex .......... 32
       2.1.3 Oxidation of alcohol using Mn$^{\text{III}}$ amide complex as catalyst .... 34
       2.1.4 Oxidation of Mn$^{\text{III}}$ to Mn$^{\text{V}}=\text{O}$ ................................. 34
Abbreviations

The abbreviations are used in agreement in standards of the subject. Only non-standard and unconventional ones that appear in the thesis are listed here.

bpy  2,2'-Bipyridine
BQ  Benzoquinone
DCM  Methylene chloride
DET  Diethyl tartrate
ETM  Electron Transfer Mediator
HQ  Hydroquinone
m-CPBA  m-Chloroperbenzoic acid
MIMS  Multi-isotope Imaging Mass Spectroscopy
MV$^{2+}$  Methyl viologen
NAD$^+$  Nicotinamide Adenine Dinucleotide (Oxidized form)
NADH  Nicotinamide Adenine Dinucleotide (reduced form)
NADP$^+$  Nicotinamide Adenine Dinucleotide Phosphate (Oxidized form)
NADPH  Nicotinamide Adenine Dinucleotide Phosphate (reduced form)
NHE  Normal Hydrogen Electrode
NMO  N-Methylmorpholine N-oxide
OEC  Oxygen Evolving Complex
Pheo  Pheophytin
PPTS  Pyridium p-toluenesulfonate
PSI  Photosystem I
PSII  Photosystem II
Salmdpt  Bis[3-(salicylideneimino)propyl]methylamine
TBHP  tert-butylhydroperoxide
THP  Tetrahydropyranyl
terpy  2,2’:6’:2”-Terpyridine
Tyr$_z$  Tyrosine$_z$
1 Introduction

Our modern society has reached its complexity by consuming enormous amounts of energy. For a long time, this was not a major concern but in the past few decades it has become clear, that our predominant energy sources are connected to socially or environmentally problematic effects. Fossil fuels (natural gas, coal, oil, etc) have been major energy sources but, in recent years, we have realized that their supply is limited and that our oil will run out in the near future. Due to the increasing energy consumption in today’s society and the greenhouse effect we have to find a solution. An attractive option is the developments of artificial systems that are capable of absorbing sunlight and convert its energy into fuel. It is also important to decrease the use of energy, both in private consumption and in industrial production. In industry, this means among other things, more selective chemical processes using environmentally friendly raw materials. Industrial oxidation is of particular interest because the goal is now to replace stoichiometric heavy metal-based oxidants by molecular oxygen or hydrogen peroxide which are truly environmentally friendly oxidants.

1.1 Water oxidation

1.1.1 Natural photosynthesis

Photosynthesis is one of the most important processes on earth, by which green plants and some other organisms use solar energy to convert carbon dioxide and water into biomass such as carbohydrates (eq. 1). In this process, water acts as an electron source, being oxidized to molecular oxygen, which is a requisite for our existence.\(^1\)

\[
6 \text{CO}_2 + 6 \text{H}_2\text{O} + \text{sunlight} \rightarrow \text{C}_6\text{H}_12\text{O}_6 + 6 \text{O}_2 \quad (1)
\]

---

A number of enzymes embedded in the thylakoid membrane are involved in the process of photosynthesis. These enzymes include photosystem I (PSI), photosystem II (PSII), the cytochrome b/f complex and the ATP synthase. Each of the two photosystems has its own reaction center: these are designated P700 and P680 respectively (Figure 1).

![Figure 1. A schematic representation of a thylakoid membrane including PSI, PSII, Cytochrome b/f complex and ATP synthase, (Q=quinone, PC=plastocyanin).](image)

The process of photosynthesis is initiated in PSII by the absorption of a photon by chlorophyll P680 (Figure 2). When P680 is excited, it becomes strongly reducing and transfers an electron to the primary electron acceptor, pheophytin (Pheo) (1), which has a porphyrin structure, giving P680⁺ and Pheo⁻ (Figure 3). Pheo⁻ then further transfers this electron very rapidly to two quinones (menoquinone (QA) (2) and ubiquinone (QB) (3)). This leads to a charge separation that is subsequently used in photosynthetic reactions. However, P680⁺ is a strongly oxidizing and unstable species which has a potential of 1.2 V vs NHE. It is therefore rapidly reduced by an electron from a nearby tyrosine, (Tyrz), which is located about 10-12 Å away, to regenerate its ground state.
This Tyr$_z$ clearly plays a fundamental role in PSII because it functions as an electron transfer mediator between P680 and a manganese cluster (the so-called Oxygen-Evolving Complex (OEC)) where the actual oxidation of water is catalyzed by a tetranuclear manganese cluster. The electron transport from Tyr$_z$ to P680$^+$ has to be fast in order to prevent back reaction with the quinones. To make this feasible, the Tyr$_z$ interacts with another amino acid, histidine 190 (His$_{190}$) which can act as proton acceptor and by hydrogen bonding can promote fast electron transfer to P680$^+$. The neutral radical Tyr$_z^\cdot$ in turn abstracts an electron from the Mn cluster. The four electrons abstracted in the water oxidation are ejected one by one via Tyr$_z$ to repeatedly regenerate P680. Then after four consecutive photoinduced electron transfer events, the manganese cluster, which serves as a reservoir for oxidizing equivalents, recovers all four electrons by oxidizing two molecules of water to molecular oxygen. The electrons expelled by PSII are transported to PSI where the excitation of P700 initiates electron transfer down a redox chain of different cofactors to NADP$^+$, giving NADPH.

**Figure 2.** A schematic picture of the PSII in natural photosynthesis shows how an electron moves from one protein complex to another.

![Diagram of PSII electron transfer](image)

**Figure 3.** Structures of electron acceptors in PSII: i) Pheophytine (Pheo) (1), ii) Menoquinone ($Q_a$) (2), and iii) Ubiquinone ($Q_b$) (3).
1.1.2 Proposed mechanisms for dioxygen formation

Great efforts have been made to understand the mechanism of natural photosynthesis and still it is an open question how the oxidation of water takes place. An important breakthrough was the first crystal structure determination of PSII by Zouni et al. in 2001. Because the resolution of only 3.8 Å, the exact structure of the central manganese cluster could not be determined. Subsequent structure determinations with resolution of 3.5 Å and 3.0 Å together with extensive spectroscopic studies tentatively suggest a cubic structure containing three manganese and one calcium ion, which are linked to a forth manganese ion (for a recent summary, see ref[3]). There are a number of proposals for the mechanism of the dioxygen formation and five different options are depicted in Scheme 1. They involve bridge rearrangements (entry 1), nucleophilic attack on Mn=O (entry 2), radical coupling (entries 3 and 4) and coupling of bridging oxygen and coordinated water (entry 5). It is believed that the mechanisms in (entry 2) and (entry 5) are the most plausible descriptions of how water oxidation takes place in natural photosynthesis. As epoxidation can also proceed via a Mn=O intermediate, it seemed worth investigating whether such a species can be formed before testing the water oxidation.

Scheme 1. Proposed mechanisms for dioxygen formation.

1.1.3 Artificial photosynthesis

In the field of artificial systems, many research groups have long tried to mimic PSII in natural photosynthesis. In the past few decades, many attempts have been made to develop different systems for splitting of water into molecular hydrogen and oxygen, but the progress so far has been moderate. The general artificial system consists of three important functions extracted from the photosynthetic machinery: a photosensitizer (P), an electron acceptor (A) and an electron donor (D) (Figure 4).
In analogy to PSII in natural processes, the photosensitizer $P$ should trap a photon from the sunlight and eject an electron from its excited state to the acceptor $A$. The strongly oxidizing species $P'$ should regain the electron from water via a mediator linked to an electron donor $D$, preferably a Mn cluster. However, the major difference between natural and artificial photosynthesis is that instead of using the reducing equivalents at the acceptor side $A$ to reduce carbon dioxide, we wish to reduce protons to molecular hydrogen, which could be used as a pure and renewable fuel.

In our laboratory, we have developed a few prototype systems with the intention of obtaining a functional mimic of the oxygen evolving complex of PSII, that is coupled to photoinduced charge separation (Figure 5). In one such dual-component system, electron transfer was observed but the water oxidation was unsuccessful probably due to oxidative decomposition of the ligand. Therefore, a more robust mimic of the OEC needs to be developed. Recent studies have shown that synthetic manganese complexes are capable of catalyzing the oxidation of water to molecular oxygen, but these processes have not yet been coupled to photoinduced charge separation.

---

Figure 4. Electron transfer processes in an artificial photosynthesis system that consists of a photosensitizer ($P$), an acceptor ($A$) and a donor ($D$).

Figure 5. Electron transfer in Mn-Ru dyads.

---

1.1.4 Components in Model Systems

A better understanding of the three different components (photosensitizer, electron acceptor and electron donor) of artificial photosynthesis is required, so brief overviews of these components are given in the following sections.

1.1.4.1 Photosensitizer

Photoinduced charge separation is the central part of the artificial process. As mentioned earlier, this is the starting point from which the solar energy is absorbed and an electron is raised into an excited state level followed by transferring to an acceptor, converting the excitation energy into redox energy. However, there are still some considerations that need to be taken into account. Since we want to mimic the photosensitizer of PSII, a photosensitizer that absorbs sunlight and has a suitable redox potential, both in the ground state and excited state, is required. It is also important that it has reversible redox behavior and is inert to chemical side reactions. A useful photosensitizer should (i) form with high quantum yield, e.g. to be reached with high efficiency following light absorption, (ii) have a relative long excited state lifetime in order to eject the electron to the acceptor side before decaying to the ground state, and (iii) be stable and have reversible redox properties.

Several model systems such as porphyrins, phthalocyanines and polypyridine complexes fulfill these requirements to different extent. Ruthenium(II) polypyridyl complexes such as Ru\(^{ll}(bpy)_{3}\), a d\(^6\) transition-metal complex with octahedral geometry, (Figure 6), are commonly used as photosensitizers in artificial processes because they fulfill the criteria listed above.\(^7\)\(^9\) It is noteworthy that these ruthenium complexes can undergo rapid electron transfer reactions due to the small re-organization energy of the complex i.e. the structures of the complexes, [Ru(bpy)\(_{3}\)]\(^{2+}\) (4) and [Ru(bpy)\(_{3}\)]\(^{3+}\) do not change significantly upon oxidation or reduction.

---


\(^8\) M. R. Wasielewski, *Chem. Rev.* 1992, 92, 435

Figure 6. Structure of 4) Ru\textsuperscript{II} (bpy\textsubscript{3}) and 5) Ru\textsuperscript{II} (tpy\textsubscript{2}).

Other types of complexes such as Ru\textsuperscript{II}(tpy\textsubscript{2}) (5), which resemble Ru\textsuperscript{II}(bpy\textsubscript{3}), have also been used as photosensitizers.\textsuperscript{10} These two types of ruthenium complexes have very similar ground state properties but the former complex has a huge disadvantage – the lifetime of its excited state (250 ps at r.t.\textsuperscript{11})\textsuperscript{11} is much shorter than the lifetime of the latter (\approx 900 ns). One could explain that the unfavorable bite angles of the terpyridine ligands enforce a less octahedral coordination and lead to a weaker ligand field in Ru\textsuperscript{II} (tpy\textsubscript{2}) than in Ru\textsuperscript{II} (bpy\textsubscript{3}).

1.1.4.2 Electron acceptor

The most commonly used external electron acceptors in artificial photosynthesis are bipyridinium ions like methyl viologen (6) (MV\textsuperscript{2+}, Figure 8) and quinones. The reason why such methyl viologen is commonly used is that they have the correct redox potentials and also change color to violet whenever they accept an electron from the photosensitizer. Acceptors such as [Co(NH\textsubscript{3})\textsubscript{5}Cl\textsuperscript{2-}]\textsuperscript{12} are also useful. The advantage of this acceptor is that the electron transfer to Co\textsuperscript{III} is essentially irreversible.\textsuperscript{12}

Figure 7. Structure of methyl viologen (MV\textsuperscript{2+}).

\textsuperscript{12} J. R. Winkler, T. L. Netzel, C. Creutz, N. Sutin, \textit{J. Am. Chem. Soc.} 1987, 109, 2381
1.1.4.3 Electron donor (Water oxidation catalysts)

A vast number of different catalysts such as Mn and Ru complexes have been reported to be useful for catalyzing the water oxidation. However, most of these catalysts require a very strong oxidant such as CeIV. Therefore a better methodology which uses milder oxidants needs to be developed. The natural process uses a complex of four manganese ions for water oxidation, so it is worth considering the same metal in artificial process. The low cost of manganese compared to noble metals is an additional advantage. The OEC is currently the main issue in the field of artificial photosynthesis since this is the most difficult part in mimicking PSII. Furthermore, the detailed structure of the natural OEC and the mechanism of the water oxidation are still not known in complete detail.

During a period of twenty years, several dinuclear manganese- and ruthenium complexes have been prepared and examined (Figure 8). Unfortunately, most of these catalysts were not sufficiently robust to split water into dioxygen efficiently and in several cases the results were irreproducible.14,15

![Figure 8](image_url)

**Figure 8.** 7) Meyer’s catalyst, 8) Llobet’s catalyst, 9) Thummel’s catalyst, 10) Sasaki’s catalyst, 11) Crabtree’s catalyst, and 12) McKenzie’s catalyst.

---

In 1982, Meyer et al.\(^\text{16}\) reported a remarkable homogeneous \(\mu\)-oxo bridged dinuclear ruthenium catalyst 7 (Figure 8) for water oxidation using very strong oxidants such as Ce\(^{IV}\). However, the \(\mu\)-oxo bridge of this complex is suspected to decrease its stability, so some modifications are needed. Recently, Llobet\(^\text{17}\) and Thummel\(^\text{18}\) independently reported modifications of Meyer’s \(\text{cis,cis-[(bpy)}_2\text{Ru(H}_2\text{O)}_2\text{]}\text{O}^{2+}\). Llobet and co-workers designed a more stable and rigid complex using tridentate terpy ligand to replace bpy and used 3,5-bis(pyridinyl)pyrazole as the bridging ligand instead of \(\mu\)-oxo bridge 8 whereas Thummel and co-workers have used \(\text{bis}-\text{tridentate ligands and pyridazine and chloride as bridging ligands 9}\). These modified catalysts are intended to improve the water oxidation. In 1994, Sasaki et al.\(^\text{15}\) reported another homogeneous dinuclear manganese porphyrin complex 10 as an efficient water oxidation catalyst. Crabtree and co-workers described in 2001 a new \(\text{di(\mu-oxo)}\) dinuclear manganese complex 11 that could evolve O\(_2\) from water employing NaClO or KHSO\(_5\) as the terminal oxidant. In 2005 McKenzie et al.\(^\text{19}\) reported a new dinuclear manganese complex 12 that is capable of performing water oxidation using tert-butylhydroperoxide (TBHP) or Ce\(^{IV}\) as the terminal oxidant. They used several analytical methods such as a Clark electrode and MIMS to demonstrate the oxygen evolution.

In our laboratory, we have recently synthesized three different dinuclear ruthenium complexes that catalyze the water oxidation employing Ce\(^{IV}\) as terminal oxidant (Figure 9).\(^\text{20}\) Complex 13 resembles the Thummel’s catalyst. The other two complexes 14 and 15 have negatively charged ligands (a carboxylate and phenolate) and a different \(\text{trans}\) structure. The negatively charged ligand give these complexes have lower oxidation potentials of the coordinated ruthenium, presumably by increasing stability of the high-valent metal complexes.

Most recently, both Meyer\textsuperscript{21} and Thummel\textsuperscript{18,22} reported the two first new monomeric ruthenium complexes that are efficient as water oxidation catalysts; many scientists thought this impossible (Figure 10).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{\textbf{Figure 10.} i) Meyer’s monomERIC Ru complex (16), ii) Thummel’s monomeric complex (17).}
\end{figure}

Interestingly, a very important breakthrough in this chemistry was announced by the research groups of Hill\textsuperscript{23} and Bernhard\textsuperscript{23}. They independently reported for the first time a new, inorganic and homogeneous tetranuclear ruthenium cluster (Rb\textsubscript{8}K\textsubscript{2}[[Ru\textsubscript{4}O\textsubscript{4}(OH)\textsubscript{2}(H\textsubscript{2}O)\textsubscript{4}](\gamma-SiW\textsubscript{10}O\textsubscript{36})\textsubscript{2}]25H\textsubscript{2}O) that could efficiently oxidize water to molecular oxygen using [Ru(bpy)\textsubscript{3}]\textsuperscript{3+} as terminal oxidant (Figure 11).\textsuperscript{23}

![Figure 11. Structure of the Ru-cluster.](image)

1.1.5 Other metal complexes for water oxidation

In addition to manganese or ruthenium complexes that have been used as powerful water oxidation catalysts other transition metals including iridium and cobalt complexes have also been reported to catalyze water to molecular oxygen using different terminal oxidants. Very recently Bernhard and co-workers have synthesized a new iridium complex \textit{cis-}[Ir\textsuperscript{III}(L)\textsubscript{2}(H\textsubscript{2}O)\textsubscript{2}]\textsuperscript{+} (where L = 2-(2-pyridyl) phenylate anion) which has been used as water oxidation catalyst in the presence of Ce\textsuperscript{IV} as terminal oxidant (Figure 12).\textsuperscript{24} Nocera \textit{et al.} have also recently reported that the water oxidation could be performed in aqueous solutions containing Co\textsuperscript{2+} and phosphate, using Ru(bpy)\textsubscript{3}\textsuperscript{3+} as terminal oxidant.\textsuperscript{25}


1.1.6 Synthetic Model Systems

The construction of artificial model systems that combine a photosensitizer with an electron acceptor and an electron donor is not an easy task and remains a major challenge. So far the only functional mimic of PSII is an OEC mimic coupled to a photosensitizer.\textsuperscript{6,12,26} A number of factors must be considered in constructing an artificial system including: (i) the distance between donor and photosensitizer, (ii) re-organization energy \textit{i.e.} the structure of the metal complexes \([\text{Ru(bpy)}_3]^{2+}\) and \([\text{Ru(bpy)}_3]^{3+}\) should not change too much upon oxidation or reduction, (iii) electronic coupling, \textit{i.e.} how the metals interact in a di- or polynuclear metal complex, (iv) the stability of the high-valent metal complexes, and (v) the robustness of the ligand.

Sun and Åkermark have developed a mimic of the donor side system of PSII that features a \textit{tris}(bipyridyl)ruthenium(II) complex covalently linked to a manganese(II) complex (18, Figure 13). This coupled system gave the first intramolecular multi-electron transfer, from the manganese(II) complex to the ruthenium(III) complex. By flash photolysis, they were able to observe stepwise three-electrons transfer in the presence of an electron acceptor.\textsuperscript{6}

Figure 13. Electron transfer from the excited state of Ru$^{II}$* to penta-amminechlorocobalt chloride (Co$^{III}$).

1.1.7 Objectives of this part of the thesis

Because the acceptor side of PSII seems to pose fewer difficult problems than the donor side, we have put more focus on design and development of a new metal catalyst for water oxidation. Therefore, the overall goal of this part is to develop metal complexes which are able to function as catalysts for oxidation of water to molecular oxygen. Thus the intention was to prepare catalysts using ligands that are resistant to oxidative degradation and capable of stabilizing metal ions in high oxidation states.
1.2. Catalytic oxidation of organic substrates via a biomimetic approach

The metal-catalyzed oxidations of organic compounds play a paramount role in the organic synthetic organic transformations, and have many applications in industrial processes. There is a growing demand for efficient and mild catalytic methods for oxidizing organic compounds with molecular oxygen or hydrogen peroxide, as aerobic oxidations have the potential to be efficient, inexpensive and environmentally friendly. There are a few examples in which a transition metal is directly re-oxidized by either molecular oxygen or hydrogen peroxide. However, in most cases, re-oxidation has proved unsuccessful because the electron transfer between the transition metal (e.g Pd or Ru) and the oxidant (O₂ or H₂O₂) is much slower than the reduction of the metal. In 2000, Sheldon and co-workers reported a new approach to aerobic alcohol oxidation employing a water-soluble palladium(II) complex as the substrate-selective redox catalyst.

In water oxidation, electrons and oxygen are generated from water. This is, in many respects, the reverse of oxidation of organic substrates by molecular oxygen, in which electrons are abstracted by oxygen to generate water and an oxidized organic substrate.

In a metal-catalyzed oxidation, two electrons are transferred from the substrate to the metal, which becomes reduced. In order to sustain catalysis the reduced metal has to be re-oxidized, preferably by molecular oxygen or hydrogen peroxide.

The direct re-oxidation of transition metal catalysts such as Pd⁰ or Ru⁰ to Pd¹ or Ru¹ by molecular oxygen or hydrogen peroxide often has a high activation barrier (Scheme 2), and this may lead to catalyst deactivation by pathways that compete with the slow re-oxidation.

---


29 G. J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, Science, 2000, 287, 1636
Two strategies have been developed to overcome this problem in palladium catalysis. The first is to carry out Pd(I)-catalyzed oxidation reactions in the presence of ligands that stabilize Pd(II) and prevent formation of metallic palladium. In this way, the slow aerobic oxidation is feasible or even facilitated. The second strategy is to use one or more redox couples that form an electron transport chain. This strategy is referred to as “biomimetic” because of its fundamental parallel to Nature’s aerobic respiration (Figure 14). By mimicking this natural process, several oxidation reactions such as 1,4-diacetoxylation, alcohol oxidation, amine oxidation, and carbocyclization could be developed.

![Scheme 2. Oxidation with a substrate-selective redox catalyst.](image)

In the respiratory chain (Figure 14), organic substrates are dehydrogenated by NAD$^+$ to generate an oxidized organic species as well as NADH and H$. The generated NADH reduces ubiquinone (UQ) to afford ubiquinol (UQH$_2$), which transports the electrons to the electron acceptor, cytochrome...
These electrons are further transported to the reduced form of cytochrome c oxidase, which finally delivers them to molecular oxygen, which is reduced to water upon reacting with nearby protons. This multistep approach divides the high-energy barrier into many smaller energy barriers that can be overcome sequentially and consequently it allows the process to occur under milder conditions. This example illustrates how the redox couple NAD+/NADH + H⁺ together with the dehydrogenase, acts as a substrate-selective catalyst.

1.2.1 Palladium-catalyzed aerobic oxidation employing electron transfer mediators

Catalysts based on palladium are extremely versatile and catalyze such diverse reactions as aromatic coupling, allylic substitution, and oxidation of alcohols. They are therefore widely used in organic synthesis. The invention of the Wacker process in 1956 marked a breakthrough in both palladium chemistry and homogenous catalysis (Scheme 3). This large scale industrial process, whereby ethene is converted to acetaldehyde, is catalyzed by a combination of palladium(II) and CuCl₂. This combination is a typical example of a coupled system, where the Pd⁰ is the catalyst for oxidation of the alkene. CuCl₂ is the electron transfer mediator for re-oxidizing Pd⁰ and is itself re-oxidized by molecular oxygen in a very rapid reaction.

The disadvantage of the Wacker process is the use of chloride ions, which can be problematic due to the formation of chlorinated by-products. They can also have a negative effect on the reaction rate. Furthermore, the chlor-
ride is also corrosive to some industrial reaction vessels. In the last few decades, our laboratories have developed a number of chloride-free coupled systems in which an oxygen-activating catalyst (cobalt(II) salphen, cobalt(II) porphyrin and iron(II) phthalocyanine) and a hydroquinone (HQ)/benzoquinone (BQ) electron transport mediator (ETM) operate together to perform the re-oxidation of the metal by molecular oxygen (Scheme 4).

![Scheme 4](image-url)

**Scheme 4.** Electron transfer facilitated by an Electron Transfer Mediator (ETM), whereas ML$^{m}$ = iron(II) phthalocyanine, cobalt(II) salphen.

These coupled systems are based on stepwise low-energy electron transfer which resemble biological processes. However, it has been shown that if any of these components (Pd, ETM or oxygen-activating catalyst) is absent, the reaction stops entirely. The chloride-free coupled system could be applied in a range of different aerobic oxidation such as Pd-catalyzed 1,4-addition to conjugated dienes, allylic acetoxylations, oxidation of terminal olefins to the corresponding methyl ketones, and Pd-catalyzed enallene carbocyclization (Scheme 5).

---

1.2.2 Palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes

In the early 1980s, Bäckvall et al. reported the stereoselective 1,4-diacetoxylation of 1,3-dienes. The 1,4-oxidation reaction has been further developed in Bäckvall’s laboratories and has become a very useful synthetic method in organic chemistry laboratories as well as in industry. Substrates such as cyclic or acyclic dienes can be readily oxidized to highly functionalized products using palladium(II) acetate as the catalyst. Various nucleophiles, including alcohols, halides and functionalized amines can be introduced both inter- and intramolecular to the 1- and 4-position of the dienes with high regioselectivity. The stereoselectivity in 1,4-diacetoxylation of 1,3-dienes can be directed to form the cis adduct by adding a catalytic amount of LiCl (Scheme 6), whose chloride ions block the coordination of acetate to palladium and prevent the cis-migration. In contrast, when a large excess of LiOAc was used, the reaction yielded mainly the trans product, likely because the palladium-bound acetate group performs an intramolecular nucleophilic attack on the molecule.

37 J. E. Bäckvall, Palladium-Catalyzed 1,4-Additions to Conjugated Dienes, Review in Metal-catalyzed Cross-Coupling Reactions, Ed. A. de Meijere and F. Diederich, Wiley, VCH, Weinheim, 2004, pp 479
Scheme 6. Stereoselectivity in the 1,4-diacetoxylation of 1,3-cyclohexadiene.

It is worth mentioning that the coordination of benzoquinone to palladium also plays a crucial role in determining the stereoselectivity of 1,4-diacetoxylation of 1,3-dienes.\textsuperscript{40} This coordination results in an activated intermediate as shown in the scheme above that can facilitate a second nucleophilic attack. However, if no chloride ions are present, this attack takes place through a cis-migration of the palladium-bonded acetate via a ($\pi$-allyl)palladium complex, giving rise to the trans adduct.

As discussed earlier, the aerobic 1,4-oxidation reaction can be applied in a one-pot triple catalytic cycle as shown in Scheme 7. In the coupled oxidative diacetoxylation, a catalytic amount of $p$-benzoquinone was used to re-oxidize Pd$^0$ to Pd$^{II}$ and the hydroquinone generated from this reaction was readily be re-oxidized by molecular oxygen together with an oxygen-activating catalyst, ML$^m$.

1.2.3 Palladium(II)-catalyzed cyclization of enallenes

Transition metal-catalyzed cycloisomerization reactions of enallenes have been extensively studied but there is still a need for more efficient and stereoselective methods are still needed and would be of interest to the pharmaceutical industry. In 1988, Trost et al. reported the first metal-catalyzed carbocyclization of enallenes. They showed that allenes are excellent functional groups for cyclization via isomerizations catalyzed by bimetallic Ni-Cr complexes. A few years later, Lee et al. published a ruthenium-catalyzed cyclization and Itoh et al. reported on rhodium-catalyzed cyclization of enallenes. Bäckvall and co-workers reported on the Pd-catalyzed oxidative carbocyclization of enallenes to generate bicyclic systems (Scheme 8). This reaction also works with diene-enallenes and a wide range of external nucleophiles such as carboxylic acids, alcohols, and thiols, to give a 1,4-addition reaction across the diene and formation of a cyclic system.

---

They have also published a Pd-catalyzed aerobic carbocyclization of enallenes employing the triple-component system shown below in Scheme 9.

**Scheme 9.** Carbocyclization of enallenes using the triple coupled system.

1.2.4 Ruthenium-catalyzed aerobic alcohol oxidation

The selective oxidations of alcohols to the corresponding carbonyl compounds plays a central role in organic synthesis. The classical oxidation methods, which employ stoichiometric amounts of inorganic oxidants such as CrO₃, Mn₄⁺ or Ru salts etc, are still used in both the academic laboratories and in the pharmaceutical industries. Most of these oxidants are highly toxic and environmentally polluting, resulting in an increasing demand for mild, efficient catalytic methods that use environmentally friendly oxidants such as molecular oxygen and hydrogen peroxide. In 1978, Mares et al. reported for the first aerobic oxidation of secondary alcohol to the corresponding carbonyl compound employing RuCl₃ₙH₂O.

In the early 1990s Bäckvall and co-workers reported the first chloride-free alcohol oxidation using a triple catalytic system, in which ruthenium

---

catalyst was the substrate-selective catalyst, 1,4-benzoquinone acted as an ETM and a Co(salen) complex was the oxygen-activating catalyst (Scheme 10). This combined system oxidized a wide variety of alcohols to the corresponding carbonyl compounds in good to excellent yields.

![Scheme 10. Ru-catalyzed aerobic alcohol oxidation using the triple coupled system.](image)

Analogous to Nature’s aerobic respiration, the dehydrogenation of alcohol is carried out by the Shvo catalyst (21) (Scheme 11), a low-valent dinuclear ruthenium complex that corresponds to NAD+/NADH + H+ and a benzoquinone that replaces UQ / UQH2. In order for the hydroquinone to be re-oxidized to benzoquinone in the artificial process, molecular oxygen has to operate together with an oxygen-activating metal macrocycle and produces water as the exclusive by-product. During the past decade Bäckvall and coworkers reported the Shvo catalyst 21 to be an efficient catalyst not only for dynamic kinetic resolution (DKR) of secondary alcohols, but also for dehydrogenation of alcohols. It is believed that 21 dissociates into a coordinatively unsaturated dienone dicarbonyl 22 (an 16-electron species) and 23 (an 18-electron species) at elevated temperatures (Scheme 11). The mononuclear ruthenium complex 22 is very active for the dehydrogenations of alcohols and amines, whereas 23 is very active for hydrogenations of ketones and imines, therefore both catalytic entities are involved in the catalytic cycle (Scheme 10).

---

As in the palladium chemistry outlined above, coupled systems could also be applied to the Ru-catalyzed aerobic oxidations including the Ru-catalyzed aerobic oxidation of alcohols to ketones\(^54\) and of amines to the imines (Scheme 12).\(^54\)

\[\text{Scheme 11.} \text{ The proposed dissociation of the Shvo catalyst.}\]

\[\text{Scheme 12.} \text{ Ru-catalyzed oxidation reactions for coupled catalytic systems.}\]

1.3 Metal-catalyzed epoxidation reactions

Several models invoke a high-valent manganese(V) oxo species as a key intermediate in both water oxidation and epoxidation. High-valent metal complexes are normally very difficult to isolate. However, the first high-valent Mn=O species was reported by Groves and Stern who isolated three different porphyrin Mn$^{IV}$=O in 1987.\textsuperscript{55} A few years later, Collins \textit{et al.} reported another high-valent manganese(V) oxo species.\textsuperscript{56} As these are rather unstable intermediates, we decided to try to detect these species indirectly by studying their potential as epoxidation catalysts.

Optically active epoxides are versatile intermediates in the synthesis of pharmaceuticals.\textsuperscript{57} Various oxidation methods that convert olefins to optically active epoxides using a combination of a chiral metal complex and co-oxidant have been reported.\textsuperscript{58} In 1980, Katuzki and Sharpless made the first breakthrough in asymmetric epoxidation (AE) using synthetic metal catalysts.\textsuperscript{59} They developed an enantioselective titanium-catalyzed epoxidation of allylic alcohols that employed diethyl tartrate (DET) as a chiral ligand and \textit{tert}-butyl hydroperoxide (TBHP) as the terminal oxidant and obtained good yields and an enantiomeric excess (ee) over 90%. For example, geraniol (24) was epoxidized to 25 in 95% enantiomeric excess with Ti(OPr)$_4$, (+)(DET) and TBHP (Scheme 15).

\begin{center}
\textbf{Scheme 15.} Sharpless epoxidation of allylic alcohols.
\end{center}

Moreover, in the middle of the 1980s, Kochi and co-workers reported that Cr(salen) complexes catalyzed the epoxidation of unfunctionalized alkenes using iodosobenzene as terminal oxidant. In 1990, a second breakthrough in asymmetric epoxidation was announced by the research groups of Jacobsen and Katzuki. They independently reported systems for the catalytic asymmetric epoxidation of a wide variety of unfunctionalized olefins using manganese(salen) complexes (28) and sodium hypochlorite (NaClO) or iodosobenzene as terminal oxidant. Jacobsen et al. found that cis alkenes were epoxidized in good to excellent enantiomeric excess whereas trans alkenes were poor substrates.


In the past decade, Noyori and co-workers have developed a new and efficient method for epoxidation of terminal olefins and also oxidation of alcohols to corresponding carbonyl compounds in the presence of a tungsten catalyst and aqueous H2O2 (Scheme 15).

Scheme 15. Noyori epoxidation

---

1.3.1 Stoichiometric oxidants

The most commonly used oxidants in Mn(salen)-catalyzed asymmetric epoxidation are iodosobenzene (PhIO) and NaOCl, though the utility of iodosobenzene is hampered by its insolubility in organic solvents. However, a variety of other oxidants have also been used. Jacobsen and co-workers carried out Mn(salen)-catalyzed epoxidations at -78 °C using m-CPBA as the oxidant and N-methyl morpholine-N-oxide (NMO) as an additive, leading to significant improvements in enantioselectivity.\(^\text{63}\)

From an environmental point of view, molecular oxygen and hydrogen peroxide are the best choices for terminal oxidants. Various successful H\(_2\)O\(_2\)-based systems have been reported and usually involve nitrogen heterocycles as additives.\(^\text{64}\) Furthermore, Mukaiyama et al. showed that by combining molecular oxygen and pivalaldehyde in the presence of Jacobsen’s catalyst the asymmetric epoxidation of alkenes could be achieved.\(^\text{65}\) By using an additive such as N-alkylimidazole in this system, the enantioselectivity was improved. Zsigmond and co-workers also reported Mn(salen)-catalyzed epoxidation of styrene using molecular oxygen as terminal oxidant, but the isolated yield of styrene oxide was low.\(^\text{66}\)

1.3.2 Mechanism of the epoxidation

In the past few decades, great efforts have been made to understand the mechanism of alkenes epoxidation by Mn(salen) complexes and of water oxidation. It remains unclear how these two reactions occur. However it is believed that in both the epoxidation and water oxidation reactions proceed via a reactive species such as Mn\(^{\text{V}}\)=O. Starting from this species, three different pathways to the epoxide have been proposed (Scheme 16) (A) concerted oxygen atom transfer\(^\text{67}\), (B) via a radical intermediate\(^\text{60,68}\) or (C) via a manganaoxetane intermediate (Scheme 14).\(^\text{69}\)


\(^{67}\) (j) S. Lane, K. Burgess, *Chem. Rev.* 2003, 103, 2457.

\(^{68}\) (a) P. O. Norrby, C. Linde, B. Åkermark, *Tetrahedron,* 1994, 67, 2248


Jacobsen and co-workers reported that alkyl-substituted alkenes were epoxidized in a concerted manner (Scheme 16, pathway A) whereas conjugated alkenes seemed to react via a radical pathway (pathway B). In the mid of the 1990s Åkermark et al. proposed a mechanism for Mn(salen)-catalyzed epoxidation which involves a manganaoxetane intermediate followed by ring opening generating two diastereomeric products (pathway C).

In addition to enantioselectivity, the Mn(salen)-catalyzed epoxidation of conjugated cis alkenes shows varying degrees of stereoselectivity. Both cis and trans epoxides were generated from these alkenes in ratios that depended on the reaction conditions. The choice of oxidant can also influence the stereospecificity. For instance, iodosobenzene gave more trans adduct than hypochlorite. Adding N-oxides also affects the cis/trans ratio to a lesser extent but the solvent effects are greater factors in determining the stereoselectivity of the reaction. Use of polar solvents favors formation of cis adduct, whereas the trans adduct is favored by non-polar solvents.

Scheme 16. Proposed mechanisms for Mn(salen)-catalyzed epoxidation: A: Concerted pathway (R = R₁ = alkyl), B: Radical pathway (R = alkyl, R₁ = aryl, alkenyl, alkynyl) and C: reaction via a manganaoxetane (R = alkyl, R₁ = alkyl, aryl, alkenyl, alkynyl).

---

2. Epoxidation of stilbene (*Paper I*)

High-valent transition metals such as Co\textsuperscript{IV}, Fe\textsuperscript{IV}, Ru\textsuperscript{V}, V\textsuperscript{V}, Mn\textsuperscript{V}, Te\textsuperscript{V}, and Re\textsuperscript{V} play a major role in many catalytic oxidation processes in organic synthesis. It is therefore of general interest to understand whether high-valent transition metals can be stabilized with organic ligands so that new oxidation catalysts can be developed and models for biochemical processes can be found. Due to their high oxidizing potential, those high-valent transition metals tend to oxidize their ligands. A ligand that stabilizes a transition metal in a high oxidation state should therefore be resistant to oxidative degradation.

The highly reactive high-valent manganese(V) oxo species is believed to play a fundamental role in both epoxidation and water oxidation. We have in our laboratories made several unsuccessful attempts to oxidize water using the Jacobsen manganese(II) salen complex and similar catalysts but the problem seems to be destruction of the ligand by the high-valent manganese species. Much effort has been made to isolate such a species but this has proved to be difficult. However, in the past few decades Collins and co-workers isolated a few stable manganese(V) oxo complexes 32 and characterized them by X-ray crystallography (Scheme 17).

![Scheme 17. Structure of manganese(V) oxo complex.](image)

Unfortunately, those high-valent oxo complexes do not catalyze epoxidation reactions, perhaps due to the negative charge of the complexes. As neither Jacobsen’s Mn(salen) complex nor Collins Mn\textsuperscript{V} complex were active for water oxidation, we have tried to prepare related neutral and positively charged amide complexes in the hope that they might catalyze water oxidation to generate molecular oxygen. Furthermore, it seemed possible that if these Mn complexes did not function as a water oxidation catalyst, they could be applied to other oxidation reactions.
2.1 Results and discussion

2.1.1 Synthesis of a new manganese(III) amide complex and its X-ray structure

In order to obtain a neutral mononuclear manganese complex we prepared ligand 38 (Scheme 18). The synthesis was straightforward. In the first step, amide bond formation to give 35 was formed by treating picolinic acid (33) with 2-nitroaniline (34) in pyridine in the presence of triphenyl phosphite, P(OPh)$_3$, which activated the carboxylic acid. The next step was a reduction of the nitro group to an amine 36 by hydrogenation on charcoal, and this was followed by another amide bond formation to obtain ligand 38.

Scheme 18. Synthesis of ligand 13

Figure 15. Crystal structure of ligand 38.
Treating 38 with manganese(II) chloride tetrahydrate and sodium methoxide in methanol in the presence of air gave the manganese(III) amide complex 39 (Scheme 19).

Scheme 19. Synthesis of manganese(III) complex 14

Figure 16. Crystal structure of Mn-amide complex 39.
2.1.2 Epoxidation of stilbene using Mn\textsuperscript{III} amide complex

Manganese complex 39 was used to catalyze the epoxidations of cis- and trans-stilbene. The reaction was fairly high sterospecificity when carried out in acetonitrile using iodosobenzene as the terminal oxidant. In contrast to Jacobsen’s Mn(salen) catalyst, 39 could epoxidize of trans-stilbene to trans-epoxide with fairly high stereoselectivity.

The preliminary results of epoxidation of stilbene employing 39 and iodosobenzene as stoichiometric oxidant in either pure acetonitrile or a mixture of acetonitrile and methylene chloride (5:1), generated stilbene oxide in high conversion. By contrast, tert-butylhydroperoxide (TBHP) or hydrogen peroxide as the oxidants gave either low conversion or no epoxide formation. The initial results demonstrated that a small amount of (E)-stilbene oxide was formed, in addition to the desired (Z)-stilbene oxide (Table 1). However, higher catalyst loading increased the cis-specificity which could be explained that the epoxidation can compete with conversion of the manganese intermediate to a diradical.

Table 1. Epoxidation of cis-stilbene\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>39 (mol%)</th>
<th>E-Stilbene\textsuperscript{b} (%)</th>
<th>Product (%)</th>
<th>Conv.\textsuperscript{c} (%)</th>
<th>Ratio (Z/E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>4</td>
<td>96</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>9</td>
<td>91</td>
<td>100</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>9</td>
<td>91</td>
<td>100</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>10</td>
<td>90</td>
<td>100</td>
<td>5:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were carried out on a 1 mmol scale using 39 (5 mol%), PhIO (5 equiv.) in 2 mL acetonitrile.

\textsuperscript{b}Isomerization of cis-stilbene.

\textsuperscript{c}Determined by HPLC.

To run the epoxidation in a homogeneous fashion, it was crucial to investigate the solubility of the Mn catalyst. An attempt at dissolving the catalyst in acetonitrile showed that the catalyst was well dissolved in this solvent and
had very low solubility in either methylene chloride or benzene. Therefore, we decided to run the epoxidation of cis-stilbene in acetonitrile. In contrast, Jacobsen Mn(salen)-catalyzed epoxidation of olefins were performed in either benzene or methylene chloride. During the course of epoxidation of cis-stilbene we were also able to observe that the minor amount of substrate has isomerized to trans-stilbene. This is reasonable because most of manganese catalysts act as Lewis acids.

The epoxidation of trans-stilbene \((42)\) employing the monomeric manganese(III) complex \((39)\) as the catalyst and iodosobenzene as the terminal oxidant was less facile than the epoxidation of cis-stilbene (Table 2). Also in this case, the major product resulted from cis-addition of the oxygen to the olefin, but a small amount of the isomeric epoxide was also obtained. There are several possible reasons why a manganese-catalyzed epoxidation of alkenes may not be stereospecific. One reasonable explanation is that the reactive species \(\text{Mn}^{4+}=\text{O}\) which maybe formed initially, is converted to a \(\text{Mn}^{3+}=\text{O}\) by the intramolecular oxidation of the coordinated phenolic part of the ligand. Due to this, the epoxidation could occur via a diradical intermediate and therefore the formation of a mixture of \((Z)\) and \((E)\)-epoxide from both cis-stilbene and trans-stilbene could be observed.

![Diagram of epoxidation reaction](image)

**Table 2.** Epoxidation of trans-stilbene.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(39) (mol%)</th>
<th>Conv.(^b) (%)</th>
<th>Ratio ((E/Z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>85</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>80</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>40</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>42</td>
<td>6:1</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out on a 1 mmol scale using \(39\) (5 mol\%), PhIO (5 equiv.) in 2 mL acetonitrile.

\(^b\)Determined by HPLC.
For epoxidation of *trans*-stilbene, it is important that a mixture of solvent acetonitrile/methylene chloride (4:1) is used. This is because the substrate has a very low solubility in pure acetonitrile. Interestingly, the conversion dropped off when the loading of the catalyst was increased and simultaneously a much higher stereospecificity was obtained.

### 2.1.3 Oxidation of alcohol using Mn\textsuperscript{III} complex as catalyst

In addition to the epoxidation, several attempts were made to oxidize both primary and secondary benzyl alcohols to the corresponding carbonyl compounds by employing 39 as a catalyst and iodosobenzene as a stoichiometric oxidant. The initial results demonstrated that this manganese complex did catalyze the selective oxidation of benzyl alcohol to benzaldehyde and 1-phenylethanol to acetophenone using iodosobenzene as the terminal oxidant. The aliphatic alcohols 1-octanol and 2-octanol were also oxidized to the corresponding carbonyl compounds though in fairly low conversion. However, attempts to oxidize a cyclohexane to cyclohexanol failed.

### 2.1.4 Oxidation of Mn\textsuperscript{III} to Mn\textsuperscript{V}=O

The main goal of this project was to isolate a high-valent manganese oxo species that could react with an oxygen nucleophile to form an O-O bond. High-valent manganese oxo species are known to be very electrophile and therefore very susceptible to any nucleophile. If an oxygen nucleophile were used it might perform a nucleophilic attack on the Mn\textsuperscript{V}=O, in principle forming an O-O bond. An interesting question, though, is whether an Mn\textsuperscript{V}=O species could be isolated as these species are reactive and unstable. Therefore, we have made several efforts to isolate the high-valent Mn\textsuperscript{V}=O species by altering both oxidant (*e.g.* m-CPBA, PhIO, TBHP) and solvent (MeCN, CH\textsubscript{2}Cl\textsubscript{2}), but failed (Table 3).
Table 3. Attempt in oxidizing Mn$^{	ext{III}}$ to Mn$^{	ext{V}}$=O$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhIO</td>
<td>MeCN</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PhIO</td>
<td>CH$_2$Cl$_2$</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TBHP</td>
<td>MeCN</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>TBHP</td>
<td>CH$_2$Cl$_2$</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>$m$-CPBA</td>
<td>MeCN</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>$m$-CPBA</td>
<td>MeCN</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out on a 1 mmol scale and used excess of oxidant in 2 mL solvent.

One reason could be oxidation of the phenol to give a manganese(IV) oxo species and a phenoxy radical, leading to the diradical mechanism and low stereospecificity of epoxidation. However, further oxidation of this radical presumably leads to degradation of the ligand. In order to overcome this problem, we have developed a new system that could be resistant to oxidative destruction of the ligand where we substituted the two tert-butyl groups by hydrogens or chlorines (Figure 17). Our hope was that this amide type of ligands (44 and 45) could stabilize high oxidation state of the metal so that we could use it as a catalyst for water oxidation and also other oxidation reactions.

![Figure 17. Analogues to ligand 38.](image-url)
2.2 Conclusions

Attempts were made to prepare several types of Mn-amide complexes were made but only complex 39 could be isolated. The Mn catalyst 39 was used to catalyze the epoxidations of cis- and trans-stilbene. The stereoselectivity of the epoxidation reaction was relatively high for both cis- and trans-epoxide. Catalyst 39 has also been used to oxidize several alcohols to the corresponding carbonyl compounds. For instance, benzyl alcohol was selectively oxidized to benzoic acid in full conversion. Oxidations of primary and secondary aliphatic alcohols were also achieved but gave fairly low conversions.

Great efforts were also made to prepare Mn\(^V\)=O by oxidizing 39 with different oxidants such as m-CPBA, PhIO and TBHP but such a complex could not be isolated.

Water oxidation was also attempted, but oxygen formation could not be detected.
3. An efficient Ru$^{\text{III, III}}$ catalyst for selective oxidation of alcohols to corresponding carbonyl compounds (*Paper II*)

Inspired by McKenzie’s dinuclear manganese complex (12, Figure 8) which has carboxylate as a ligand we aimed to prepare a new dinuclear ruthenium complex with two carboxylate ligands and a bridging phenolic ligand. By using three negatively charged ligands we were hoping to be able to prepare a useful oxidation catalyst based on high-valent ruthenium. We did in fact prepare a Ru$^{\text{III, III}}$ dinuclear ruthenium complex. The catalyst 52 was tested in a few water oxidation experiments employing either Ce$^{\text{IV}}$ or TBHP as a terminal oxidant but unfortunately no O$_2$ evolution from water was observed. Although this dimeric ruthenium complex is not a water oxidation catalyst we thought it would be interesting to see whether it could catalyze other types of oxidation reactions such as epoxidation and the oxidation of alcohols to corresponding carbonyl compounds.

3.1 Results and discussion

3.1.1 Synthesis of a new dinuclear ruthenium complex (52)

The synthesis started with the preparation of the intermediates 47 and 49, which were then reacted to give 50. Hydrolysis followed by reaction with RuCl$_3$·xH$_2$O in methanol resulted in complex 52 (Scheme 20).
Scheme 20. Synthesis of ruthenium complex 52.

The preparation of dimeric ruthenium complex 52 proved straightforward and all the starting materials are commercially available. When synthesizing the Ru complex an inorganic salt, NaCl was formed as a by-product. This waste-product could be easily removed by dissolving the crude product in 1-butanol and then performing an aqueous extraction. After removing the organic solvent by evaporation, a black ruthenium complex 52 was obtained.

Attempts were made to oxidize water to molecular oxygen using 52 as catalyst and CeIV or TBHP as stoichiometric oxidant. Unfortunately, no O2 evolution from water could be detected.

However, 52 can be used as a catalyst for efficient and selective oxidation of alcohols to corresponding carbonyl compounds. To find the optimum reaction conditions, benzyl alcohol was used as model substrate and different temperature, solvent and oxidants were examined (Table 4). The initial results demonstrated that the choice of the solvent plays a major role in the reaction. By altering the solvent the reaction can be controlled and can therefore be stopped at the aldehyde stage. When a non-polar aprotic solvent such as toluene (entry 1) or chloroform (entry 5) was used the benzaldehyde could be isolated within 30 min but if the reaction time was prolonged to 3 hours the over-oxidized product, benzoic acid could be observed. Moreover, if the benzoic acid is the desired product then a more polar solvent such as acetonitrile (entry 4) or water (entry 6) should be the best choice (Table 4).
employing four different oxidants; PhIO, TBHP, H$_2$O$_2$. Next, the choice of oxidant was investigated. The reaction was carried out by employing four different oxidants; PhIO, TBHP, H$_2$O$_2$, and urea-H$_2$O$_2$. When PhIO was used as a stoichiometric oxidant, benzyl alcohol could be selectively oxidized to benzaldehyde within 30 min whereas with TBHP only benzoic acid was observed. Unsurprisingly, H$_2$O$_2$ was not a good choice of oxidant and no product was detected when it was used. However, the epoxidation of cis-stilbene to cis-stilbene oxide employing 52 as catalyst and PhIO as terminal oxidation give epoxide but only with low conversion.

In addition to the dinuclear ruthenium complex, four other dimeric complexes, including Co$_{III}$ $^{III}$ (56), Fe$_{III}$ $^{III}$ (57), Mn$_{III}$ $^{III}$ (58), Cu$_{II}$ $^{II}$ (59), were synthesized and characterized by ESI-MS (Scheme 21).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. ($^\circ$C)</th>
<th>Rxn time (min)</th>
<th>Product</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhIO</td>
<td>Ph-Me</td>
<td>90</td>
<td>20</td>
<td>54</td>
<td>≥99</td>
</tr>
<tr>
<td>2</td>
<td>TBHP</td>
<td>Ph-Me</td>
<td>90</td>
<td>180</td>
<td>55</td>
<td>≥99</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O$_2$</td>
<td>Ph-Me</td>
<td>90</td>
<td>180</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>TBHP</td>
<td>MeCN</td>
<td>70</td>
<td>180</td>
<td>55</td>
<td>≥99</td>
</tr>
<tr>
<td>5</td>
<td>PhIO</td>
<td>CHCl$_3$</td>
<td>50</td>
<td>30</td>
<td>54</td>
<td>≥99</td>
</tr>
<tr>
<td>6</td>
<td>PhIO</td>
<td>H$_2$O</td>
<td>90</td>
<td>180</td>
<td>55</td>
<td>≥99</td>
</tr>
<tr>
<td>7</td>
<td>Urea- H$_2$O$_2$</td>
<td>Sulfolane</td>
<td>90</td>
<td>180</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*All reactions were performed on a 1 mmol scale using 52 (1 mol%), PhIO (1 equiv.) in 1 mL solvent.

* Determined by GC.
Comparison with the dinuclear ruthenium complex (52) where two acetate bridging ligands coordinated to ruthenium atoms, all these four transition metal complexes were isolated with one acetate and one methoxy bridging ligand coordinate to the metals ions. The explanation for this behaviour is that the ruthenium atom is bigger than the other transition metals (Co, Cu, Fe and Mn), and therefore requires a larger bridging ligand such as acetate in place of a methoxy group. All these dinuclear complexes have been tested in alcohol oxidation and as well as in epoxidation reactions. The preliminary results revealed that with these four different catalysts the oxidation of alcohols works almost as efficient as catalyst 52 (Table 5). However, the epoxidation of cis-stilbene using these catalysts failed.

Scheme 21. Complexation with different metals.
Table 5. Oxidation of benzyl alcohol using catalyst 56-59.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Ratio (%) (9 : 10)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>PhIO</td>
<td>CHCl₃</td>
<td>50</td>
<td>89 : 11</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>PhIO</td>
<td>CHCl₃</td>
<td>50</td>
<td>85 : 15</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>PhIO</td>
<td>CHCl₃</td>
<td>50</td>
<td>86 : 14</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>PhIO</td>
<td>CHCl₃</td>
<td>50</td>
<td>75 : 25</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>TBHP</td>
<td>MeCN</td>
<td>70</td>
<td>9 : 91</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>TBHP</td>
<td>MeCN</td>
<td>70</td>
<td>27 : 73</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>TBHP</td>
<td>MeCN</td>
<td>70</td>
<td>13 : 87</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>TBHP</td>
<td>MeCN</td>
<td>70</td>
<td>26 : 74</td>
<td>90</td>
</tr>
</tbody>
</table>

aAll reactions were carried out on a 1 mmol scale using 56 – 59 (1 mol%), PhIO (1 equiv.) in 1 mL of solvent for 23 h.
bDetermined by GC.

3.2 Conclusions

We have synthesized different transition metal complexes which could be useful for oxidizing water molecule to dioxygen. Attempts to use the dimeric ruthenium complex 52 to catalyze the water oxidation to molecular oxygen were made to detect oxygen evolution from water, using Ce⁴⁺ or TBHP as stoichiometric oxidants, failed. However, the preliminary results revealed that all five dinuclear metal complexes could be used in catalytic alcohol oxidation but only ruthenium catalyst could efficiently and selectively oxidize alcohols to corresponding carbonyl compounds. Thus, the best reaction condition for selective oxidation of benzyl alcohol to benzaldehyde was to perform the reaction at 90 °C in either toluene or chloroform using iodosobenzene as terminal oxidant. From the environmentally friendly point of view, toluene should be chosen over chloroform as the solvent. However, when a more polar solvent like acetonitrile is used benzoic acid will be the desired product. Using 52 as catalyst for epoxidation of cis-stilbene to cis-stilbene oxide resulted in a low conversion. The other complexes 56-59 were not active as epoxidation catalysts under similar conditions.
4. A new hybrid catalyst, Co^{II}(salophen)-HQ for aerobic Pd^{II}-catalyzed 1,4-diacetoxylation reaction (*Paper III*)

In early 1980s Bäckvall and co-workers reported the first 1,4-oxidation reaction.\(^3\) The reaction is very useful because it allows a broad range of nucleophiles that to be selectively added to the diene. A few years later, they developed a triply catalytic coupled system which could be used for Pd-catalyzed 1,4-diacetoxylation of 1,3-cycloadiene. In this reaction, Co(salophen) was used as oxygen-activating agent and benzoquinone as electron transfer mediator. A large amount of benzoquinone was used, leading to large amount of organic waste products. However, the amount of oxidant can be considerably reduced by running the reaction under aerobic conditions where only catalytic amounts of BQ are sufficient, with molecular oxygen as oxidant. We have recently developed two new hybrid catalysts where we combined CoL\(_2\) (where L\(_2\)= salophen/salmdpt) and benzoquinone into one supermolecule. The efficiency of these hybrid catalysts was improved by the use of a bifunctional CoL\(_2\)-hydroquinone which acts as both the oxygen-activating catalyst and the electron transfer mediator. In our system, the hydroquinone is now a part of the cobalt(II) complex and therefore extra benzoquinone does not need to be added. Furthermore, this modification should lead to a low-energy electron transfer analogous to the ones that occur in biological systems (*cf.* the respiratory chain). This dual-coupled catalytic system has been applied to a variety of biomimetic aerobic oxidation reactions including Pd-catalyzed 1,4-diacetoxylation, Pd-catalyzed carbocyclization of enallenes and the Ru-catalyzed oxidation of secondary alcohols to corresponding carbonyl compounds.
4.1 Results and discussion

4.1.1 Synthesis of the Co(salophen)-HQ and Co(salmdpt)-HQ

The synthesis of CoL$_2$(L$_2$=salophen (66), salmdpt (68))-HQ was performed in four steps starting with a Pd-catalyzed Suzuki cross coupling of commercially available starting materials, 1-bromo-2,5-dimethoxybenzene (60) and 3-formyl-4-methoxyphenyl-boronic acid (61) affording a dimethoxy-protected precursor 62 (Scheme 23). In the next step, the methyl ethers were cleaved by reaction with excess of BBr$_3$, giving salicylaldehyde-hydroquinone (63), followed by condensation with phenylenediamine (64) in ethanol resulting in the Schiff base ligand (65). In the final step of the synthesis, 65 was treated with a slight excess of Co(OAc)$_2$·4H$_2$O in methanol giving Co(salen)-HQ (66) which was washed with excess of water in order to remove the excess of cobalt acetate.
Much focus has been put on the preparation of the new cobalt catalysts and then testing their performance in aerobic oxidation; therefore the optimization of the ligand synthesis was not considered at this stage. The synthesis described in the Scheme 23 gave a fairly low yield of the ligand, due principally to inefficient Suzuki cross coupling and the demethylation steps. The reason for the poor yield of the first step may be that the 3-formyl-4-methoxy phenyl boronic acid (61) has been protodeboronated before the transmetallation has taken place. It is noteworthy in the following step that the deprotection requires an excess of BBr₃ (6 equiv.) in order to cleave all three methyl ethers. When only 3 equivalents of BBr₃ were used, only the hydroquinone ethers were cleaved. In the last step of the synthesis, the complexation was tried directly after condensation reaction but it turned out that the cobalt complex was not pure. Therefore, 65 had to be purified before the metallation was performed.

The 1,4-diacetoxylation of 1,3-cyclohexadiene using 66 as both the oxygen-activating catalyst and the electron transfer mediator and using molecular oxygen as the terminal oxidant, resulted in an accelerated reaction rate by a factor of four. In contrast to the separate triple-coupled system, the use of Co(salophen) maintained solution homogeneity throughout the course of the reaction, implying a highly efficient Pd⁰ re-oxidation. A preliminary kinetic study revealed that the reaction rate was first-order in both Pd(OAc)₂ and hybrid.
In addition to 1,4-diacetoxylation, the Co(salophen)-HQ was also employed in Pd-catalyzed aerobic enallene carbocyclization. The preliminary result demonstrated that this hybrid also in this reaction is able to facilitate the re-oxidation of palladium and seemed to be more effective than the separate components of iron-phthalocyanine and hydroquinone.

The Ru-catalyzed aerobic alcohol oxidation was carried out using Co(salmdpt)-HQ (68) as both an oxygen-activating agent and an electron transfer mediator. A few attempts to catalyze the aerobic oxidation of 1-phenylethanol with 68 (3 mol%) and Shvo (1 mol%) resulted in full conversion of alcohol to acetophenone in 12 h. As mentioned earlier, in the original procedure required a large amount of BQ (20 mol%) and higher temperature (100 °C).

4.1.2 Proposed mechanism for aerobic Pd$^0$ reoxidation

The mechanism of 1,4-diacetoxylation probably involves a cobalt(III) peroxo radical intermediate 69 when 68 reacts with molecular oxygen, followed by accepting electrons from a pendent hydroquinone leading to cobalt(IV) oxo complex 70. Since the species 70 is more reactive than 69, the subsequent oxidation of the second hydroquinone is expected to be faster and 71 forms. The oxidized form 71 must accept four electrons in order to regenerate the reduced form 69, which occurs by re-oxidizing two Pd$^0$ atoms (Scheme 24).

![Scheme 24. Re-oxidation of Pd$^0$](image-url)
4.2 Conclusions
We have shown that both Co(salophen)-HQ (66) and Co(salmdpt)-HQ (68) could be prepared via a four-step synthesis. We also showed that by covalently linking the hydroquinone to the cobalt complex, electron transfer was significantly improved. The hybrid catalyst (66) was a highly efficient oxygen activator and electron transfer mediator in Pd-catalyzed aerobic 1,4-diacetoxylation and aerobic enallene carbocyclization, whereas 68 was a highly efficient oxygen activator and electron transfer mediator in Ru-catalyzed aerobic alcohol oxidation.
5. A new efficient synthetic route to the hybrid catalyst used in biomimetic aerobic oxidation (*Paper IV*).

In the previously reported synthesis of the hybrid catalysts Co(salophen)-HQ (66) and Co(salmdpt)-HQ (68), the two first steps, a Suzuki cross coupling and a demethylation with BBr₃, gave low yields and required expensive starting materials. Herein, we demonstrate a new, efficient synthetic pathway, which both improves the yield of Pd-catalyzed Suzuki cross coupling product and avoids the use of BBr₃. This is an advantage because this reagent is fairly expensive and hazardous. The new synthetic strategy employs a very cheap hydroquinone as starting material and instead of having methyl ether as protecting group, we used the easily installed and easily removed tetrahydropyran group.

5.1 Results and discussion

5.1.1 New synthetic strategy for the hybrid catalyst

Hydroquinone (72) was chosen as the starting material for the new synthesis. Protection with 3,4-dihydro-2H-pyran in methylene chloride, catalyzed by pyridinium p-toluenesulfonate (PPTS), gave 73 in excellent isolated yield of 97%. In the next step, the protected hydroquinone was ortho-lithiated, followed by treatment with triisopropyl borate which after hydrolysis resulted in boronic acid (74). The crude product 74 was subsequently used in a Pd-catalyzed Suzuki cross coupling with commercially available 5-bromo-salicylaldehyde (75) to give 76. The cleavage of the THP-groups was performed under acidic conditions in methylene chloride in the presence of catalytic amount of PPTS generating 63 in high yield. The following step is the condensation of 63 with 3,3’-diamino-N-methylidipropylamine (67) in ethanol formed the salen-type ligand 78. The final step of synthesis was the metallation of 78 with cobalt(II) acetate in methanol to give 68 (Scheme 24).

The new synthetic route requires six synthetic steps in order to make the target molecule 68. All starting materials used in the Scheme 24 are commercially available and of low cost. The synthesis is straightforward and the protection of hydroquinone (72) with 3,4-dihydro-2H-pyran facilitated the ortho-lithiation because of the chelation of lithium to oxygen atom. Several attempts were made to prepare a boronic acid from the organolithium reagent and different borates such as trimethyl borate and triisopropyl borate were used. However, when trimethyl borate was used, many by-products were formed, making it difficult to purify the product. Therefore, we changed from trimethyl borate to triisopropyl borate and carried out the reaction at -78 °C. The crude product was analyzed by ¹H-NMR spectroscopy which generally showed incomplete hydrolysis. According to ¹H-NMR a small amount of mono-hydrolyzed product was observed. However, even this mono hydrolyzed borate could be used in the Suzuki cross coupling. It is noteworthy that the crude product should not be purified by column chromatography because this cleaves one of the THP protecting groups and allows the molecule to polymerize. Attempts were also made to use potassium trifluoroborate to perform Suzuki cross coupling but this resulted in an isolated yield of 30%. When preparing the potassium trifluoroborate 78, one of the protecting groups was cleaved by the KHF₂ reagent which was used in the reaction (Scheme 25). In comparison to the original procedure, the Suzuki cross coupling was improved significantly with an isolated yield of 94% when a phase-transfer catalysis was used. For the deprotection of THP-groups, it is important that a small amount of base (pyridine) was added in order to prevent any side reactions to take place.
5.2 Conclusions

We have report on a new and efficient synthetic strategy for a salen-type cobalt complex which has a linked hydroquinone. We managed to lower the cost of preparation of the hybrid by changing the protecting group (THP group) and the starting material (HQ) as well as the optimizing the key step, the Pd-catalyzed Suzuki cross coupling.
6. Highly efficient hybrid catalyst Co(salmdpt)-HQ employed in biomimetic aerobic oxidation of a broad range of secondary alcohols to corresponding carbonyl compounds (Paper V)

Exploratory studies revealed that the hybrid catalyst Co(salmdpt)-HQ is an efficient oxygen-activating agent and electron transfer mediator in the Ru-catalyzed aerobic oxidation of 1-phenylethanol. We therefore decided to investigate the wide scope of the oxidation of different alcohols by applying the dual catalytic cycle to oxidize a wide variety of secondary alcohols to the corresponding carbonyl compounds.

6.1 Mechanism of the alcohol oxidation

To get a better understanding of the alcohol oxidation with the Shvo catalyst it is important to know the mechanism of the reaction. The proposed mechanism for the dehydrogenation of alcohols proceeds by the monomeric ruthenium complex which is known to be one of the products after dissociation of Shvo, is depicted in Scheme 11.\(^1\) The alcohol is prone to coordinate to the complex 22 to give 79 (Scheme 26). 79 (an 18 e\(^-\) complex, with \(\eta^4\)) leads to complex 80 (an 16 e\(^-\) complex, with \(\eta^2\)) after ring slipping. Simultaneous \(\beta\)-elimination and proton transfer in 80 would lead to 81, which would dissociate ketone and give 23. Moreover, this mechanism is consistent with the combined isotope effect observed for the step and also for the reverse reaction.\(^2\)

\(^2\) An outer sphere addition has been proposed by Casey (see ref 50).
6.2 Results and Discussion

Using a combination of the hybrid catalyst and the Shvo catalyst, a broad range of secondary alcohols could be oxidized. To find the optimum reaction conditions, 1-phenylethanol was used as a model substrate and different parameters such as catalyst loading, solvent effect, temperature, and oxygen atmosphere were varied (Table 6). In the first attempt, 1-phenylethanol was heated at 75 °C under oxygen for 12 h with a fairly high catalyst loading: an acceptable conversion (69%) to acetophenone was obtained (entry 1). However, in this experiment, full conversion to acetophenone was not observed. An explanation could be that the catalytic system is fairly rapidly deactivated under an atmosphere of pure oxygen. When using air as terminal oxidant together with Shvo (0.1 mol%) and the hybrid catalyst (1 mol%), a complete conversion was obtained after 14 h at 75 °C (entry 3). Decreasing the reaction temperature resulted in a decreased reaction rate. Nineteen hours reaction time was necessary to achieve full conversion at 65 °C (entry 4) and at 60 °C full conversion was not observed even after 38 h (entry 5).
Table 6. Oxidation of neat 1-phenylethanol.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>21 (mol%)</th>
<th>68 (mol%)</th>
<th>Atmosphere</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv.(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>3.0</td>
<td>O(_2)</td>
<td>75</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.5</td>
<td>Air</td>
<td>65</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>1.0</td>
<td>Air</td>
<td>75</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>1.0</td>
<td>Air</td>
<td>65</td>
<td>19</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>1.0</td>
<td>Air</td>
<td>60</td>
<td>38</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>1.0</td>
<td>Air</td>
<td>65</td>
<td>19</td>
<td>86</td>
</tr>
</tbody>
</table>

\(^a\)The reaction was carried out on a 2 mmol scale.

\(^b\)Determined by GC.

As neat alcohol may not always be the ideal medium for oxidation to ketones, experiments were also performed in a solvent. Three different solvents were tested; toluene, \(o\)-xylene and sulfolane. Sulfolane appeared to be the best solvent, probably because the hybrid catalyst has limited solubility in the other two solvents. The results suggested that concentration of the Shvo could be as low as 0.5 mol\% and 2.5 mol\% of the hybrid was necessary (Table 7). It thus seems that the re-oxidation of the Shvo is the rate determining step. As the air was introduced as a stream, some of product and starting material may have evaporated. To minimize the loss of product this way, we used a mixture of sulfolane and toluene and attached a condenser to the reaction flask. However, a very small amount of product appeared to be deposited in the condenser.

Table 7. Oxidation of 1-phenylethanol by air.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>21 (mol%)</th>
<th>68 (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv.(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>1.5</td>
<td>PhMe (1.0 mL)</td>
<td>75</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>3.0</td>
<td>PhMe (1.0 mL)</td>
<td>75</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>5.0</td>
<td>(o)-Xylene (0.5 mL)</td>
<td>65</td>
<td>20</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>2.5</td>
<td>(o)-Xylene (0.5 mL)</td>
<td>65</td>
<td>20</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^a\)Determined by GC.
After optimizing the oxidation of 1-phenylethanol, two more substrates (2-octanol and cyclohexanol) were tested first under neat conditions as shown above and the results showed that the conversion of both substrates to the carbonyl compounds dropped remarkably (Table 8). However, in sulfolane solution the conversions of 2-octanol and cyclohexanol to 2-octanone and cyclohexanone, respectively increased significantly.

Table 8. Aerobic oxidation of 2-octanol and cyclohexanol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>21 (mol%)</th>
<th>68 (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Octanol</td>
<td>0.1</td>
<td>1.0</td>
<td>Neat</td>
<td>70</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexanol</td>
<td>0.1</td>
<td>1.0</td>
<td>Neat</td>
<td>70</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>2-Octanol</td>
<td>0.1</td>
<td>1.0</td>
<td>Sulfolane</td>
<td>70</td>
<td>32</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexanol</td>
<td>0.1</td>
<td>1.0</td>
<td>Sulfolane</td>
<td>70</td>
<td>32</td>
<td>69</td>
</tr>
</tbody>
</table>

*The reactions were carried out on a 2 mmol scale.
* Determined by GC.
Screening of substrates. A vast number of substrates were investigated in aerobic oxidation employing the dual-coupled system and the results are summarized in Table 9.

![Chemical structure](image)

Table 9. Aerobic oxidation of different secondary alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>21</td>
<td>58</td>
</tr>
</tbody>
</table>

54
The reactions were carried out on a 2 mmol scale.

From these results, it appears that electron donating groups such as a methoxy group caused a slight increase in the conversion. By contrast, a decrease was observed with electron withdrawing group such as chloride and trifluoromethyl group. Replacement of the methyl group of 1-phenylethanol by an ethoxycarbonyl group resulted in a dramatic decrease in conversion (3%, entry 7). Finally, conversions of around 60% only were obtained for aliphatic alcohols (entries 9-12).

6.3 Conclusions

We have now shown that a combination of the hybrid catalyst and the Shvo catalyst could efficiently oxidizes a number of secondary alcohols. We have also determined the minimum catalyst loadings of both catalysts (0.1 mol% of Shvo and 1.5 mol% of hybrid) for these reactions. The aerobic alcohol oxidation could either be performed neat or with a mixture of solvent sulfolane/toluene (3:2) but it is preferentially run in solvent.
7. Concluding Remarks

The theme of this thesis is the design and synthesis of different water oxidation catalysts and also hybrid catalysts that can be applied to aerobic oxidation. The new development of hybrid catalysts where an oxygen-activating part is combined with hydroquinone to a single supermolecule, offers an efficient re-oxidation of both palladium and ruthenium catalysts in aerobic oxidation reactions. Finally, it can be concluded that further efforts must be devoted to the design of a more robust ligand for water oxidation.
Acknowledgements

First of all, I would like to express my deepest gratitude to my supervisor Prof. Björn Åkermark for accepting me as a graduate student and also for your encouragement, your knowledge, your lively ideas and interest, your patience and the support that you have given me during these years. Thank you for letting me working on this difficult and challenging but at the same time very interesting project.

I also would like to thank...

- Prof. Jan-Erling Bäckvall for letting me joining one of your research projects and also thank for your kind interest in my thesis.
- The head of the department, Per Unger for your concern, support and good advice when needed.
- Dr. Tamara Church, Dr. Jakob Norinder, Dr. Eleanor Merritt, and Dr Jan Deska for proofreading this thesis.
- Dr Byron W. Purse, Eric V. Johnston, Erik A. Karlsson, Bao-Lin Lee and Markus Kärkäs for fruitful collaboration.
- All my German Erasmus students: Christina Hain, Max Belitza, Felix Gärtner and Jakob Hey.
- All past and present members of the BÅ, JEB, and LS group.
- All other staff at the Department of Organic Chemistry, especially Britt Eriksson and Olle Bristrand.
- Financial support from the Swedish Foundation for Strategic Research, the Swedish Energy Agency, the Knut and Alice Wallenberg Foundation, and the Nils Löfgren Foundation.
• My close friends outside the university.

• My dearest father for your love and support. Thank you very much indeed for your wise thoughts and perspectives that have guided me through these years. I really miss you very much and you will always be a part of my heart. RIP father.

• My family, especially my mom and my younger sister, for their love and supports have always meant very much to me.

...Oh, are you not on the list?? Well, write your name on the dotted line and underline the appropriate word, and hey presto, you’ve made it...

• Finally, I would especially like to thank.............for all of the support

You’re the best.