

Cooperative electrocatalytic alcohol oxidation: quest for an optimal mediator system

Jeroen Lybaert

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Promotoren: Prof. dr. Karolien De Wael
Prof. dr. ir. Kourosch Abbaspour Tehrani

Promotors

Prof. Dr. K. De Wael, AXES Research Group, Department of Chemistry, Faculty of Sciences, University of Antwerp

Prof. Dr. Ir. K. Abbaspour Tehrani, ORSY Research Group, Department of Chemistry, Faculty of Sciences, University of Antwerp

Board of examiners

Prof. Dr. F. Blockhuys, Department of Chemistry, Faculty of Sciences, University of Antwerp

Prof. Dr. Ir. T. Breugelmans, Faculty of Applied Engineering, University of Antwerp

Prof. Dr. W. Dehaen, LOSA research group, Department of Chemistry, Faculty of Sciences, University of Leuven

Dr. J. Heijl, Process Development Technology Center, Covestro NV

Prof. Dr. B. U. W. Maes, ORSY Research Group, Department of Chemistry, Faculty of Sciences, University of Antwerp

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Chapter 1

Introduction: organic electrosynthesis

1.1. Electrochemistry: a tool for sustainable chemistry

Today, our society is characterized by a striving for greater sustainability. However, it should not be surprising that since we continue to consume, produce and generally live in a non-sustainable way, the opportunities for future generations will decrease. The same sense of urgency present in other domains, should also be present in the chemical industry and be an important driving force for further research. In the search for more sustainability, many directions can be followed and explored.

More specifically, there are many aspects of organic synthesis that can be improved to achieve the sustainable production of different chemicals or pharmaceuticals. The products created by organic synthesis nowadays are indispensable to our society and improve or save the lives of many people. Therefore, it is important that a sustainable production method is available for many valuable products.

Today, some production and reaction processes are called 'green' after improving only a single aspect of the synthesis. In many cases, the term 'green chemistry' is used as window-dressing or as a marketing term to make the public believe that the product is environmentally friendly. However, the best practice for obtaining or evaluating sustainable synthesis is by carefully reviewing every aspect of a specific synthesis, such as starting materials, solvents, catalysts, reaction conditions, waste generated and the properties of the final product. Everything should be optimized following the twelve principles of green chemistry developed by Anastas and Warner in 1998 [1]. These principles (Figure 1.1) provide guidelines for the fulfilment of the requirements for a sustainable reaction.

1. Prevent Waste
2. Atom Economy
3. Less Hazardous Chemical Synthesis
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-Time Analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

Figure 1.1. Twelve principles of sustainable chemistry [1].

It is important to note that these basic principles were formulated to more precisely delineate the direction in which the synthesis of chemicals should evolve. In reality, it is difficult to change existing production processes or procedures such that they heed all these principles. However, when designing new synthesis protocols, it is crucial to see these twelve principles as guidelines aiming to achieve a more sustainable future. They are design rules and should inspire scientists to see where improvement is possible. Because of their broad approach, these principles are often used in different fields and industries in striving for a more sustainable future [2].

Another expected change in society is its further electrification in the coming decades. One of the important driving forces of this is the necessity to reduce carbon emissions and to avoid pollution in growing cities. To limit climate change and the global warming of the atmosphere, the burning of fossil fuels should be reduced and eventually cease completely. In 2015, in Paris, the world finally reached an agreement and was able to establish a pathway aiming to reduce the human carbon footprint. When fossil fuels can no longer be used on the massive scale that occurs today, electricity will become one of the most convenient ways to distribute power and may become a reagent that is necessary in the production process of many different products. One of the more visible examples will be the increasing number of electric

vehicles on the streets, resulting in an improvement in sustainability in the use of transportation. In industry, it can also be expected that different production processes will increasingly use electricity as an energy source.

The use of electricity as the most important source of energy should be combined with a shift to its production using sustainable resources. Two popular methods of producing electricity in a sustainable way today are wind turbines and solar panels. An important factor in this sustainably produced electricity is that there are periods of peak production and periods of limited production, as both sources depend on weather conditions. An example of a typical summer day can be seen in Figure 1.2.

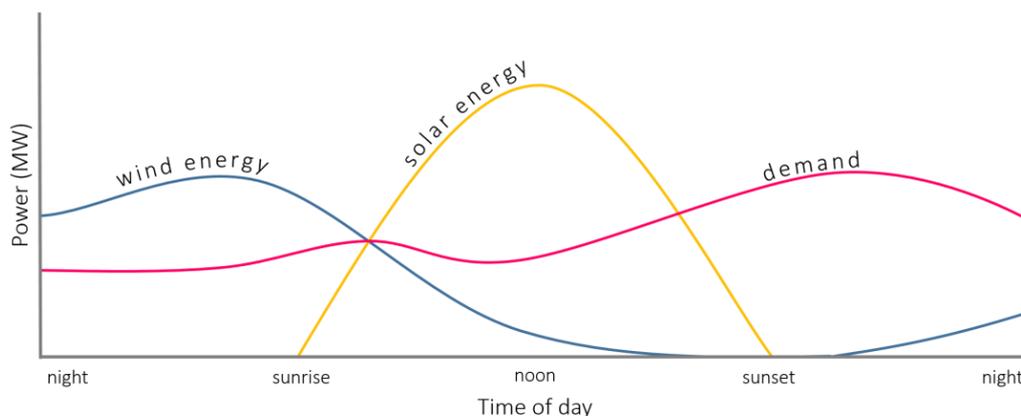


Figure 1.2. Peak production of sustainable electricity.

As electricity production will increasingly depend on sustainable sources, there will be highs and lows in electricity production and also related highs and lows in electricity prices. One way to deal with this flexible electricity production is to combine it with flexible electricity storage. This means that the storage of electricity in flexible batteries will become increasingly important.

An alternative would be to develop flexible production processes that make use of electricity. Periods of peak electricity production are accompanied by periods of low electricity prices, during which there is an opportunity for the production of valuable materials or products using this electricity as a reagent. The use of electricity as a reagent would thus require flexibility in switching 'ON' production depending on electricity price and on customer needs for the products. In the future, there might be an interesting business model that uses electricity

produced in peak times for organic electrosynthesis to make valuable and expensive specialty chemicals or pharmaceuticals.

Electrosynthesis, in general, agrees well with the principles of sustainable chemistry, as it actually uses the electron as a reagent. At a certain potential, the surface of an electrode is capable of adding or removing an electron and, in this manner, inducing the desired chemical modification. By directly using electrons, it is possible to avoid waste, as no stoichiometric oxidant or reductant has to be added.

Another feature that is naturally present when using electrochemistry is selectivity. Every chemical functionality has a specific potential at which oxidation or reduction is possible. This potential is dependent on different circumstances, such as electrode material, solvent, temperature and certain additives. If the right circumstances and the appropriate potential is found, a selective modification of the target functionality can be achieved. In this way, it is possible to avoid waste and achieve a good atom economy.

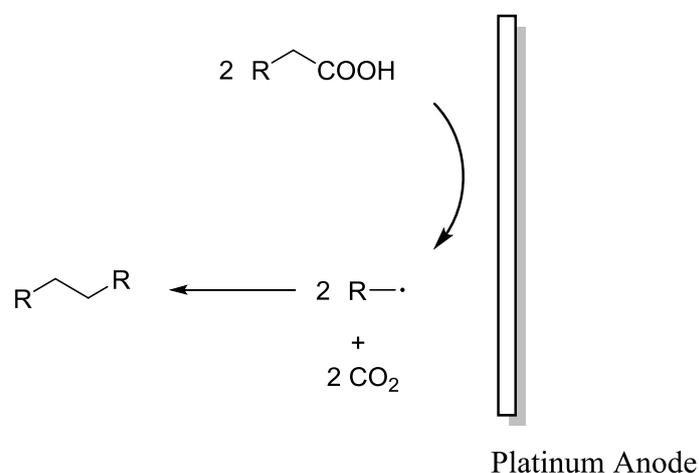
Furthermore, sustainably generated electricity can be used to apply the potential or current needed to perform the electrosynthesis. For example, it has been shown that a simple setup using solar panels in combination with a pair of electrodes and an ammeter can conduct various small-scale electrosynthesis reactions [3,4]. In this manner, sustainable electricity generation is directly connected with electrosynthesis. Of course, a direct connection between the electrochemical cell and the solar panels does not have to be present. The same synthesis reactions are also possible using electricity from the electricity grid, which is expected to become increasingly sustainable in the future.

Electrosynthesis avoids the use of dangerous substances, for example, by the direct activation of the target molecule or by using in-situ generated active species which can react with the target molecule and be used to achieve the desired reaction. In this way, the prior synthesis and transport of dangerous reagents can be avoided.

Electrosynthesis can be easily combined with catalysis. The catalyst can be regenerated at the electrode surface at the appropriate potential, or even a combination of a catalyst and a mediator may be used if no direct regeneration of the catalyst is possible. When an

appropriate combination of catalysts and mediators is found, many organic synthesis reactions can be performed using electrochemical methods.

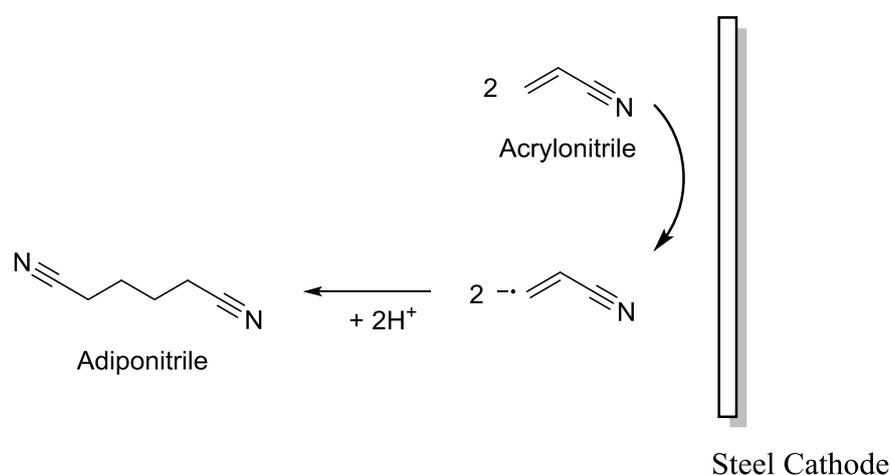
Electrosynthesis has a long history. The search for efficient electrosynthesis reactions has not only been driven by its sustainable character but also by its unique properties. One of the first electrochemical reactions studied was the oxidation of organic carboxylic acids. In the mid-nineteenth century, Kolbe discovered that the electrochemical oxidation of carboxylic acids induces their dimerization to alkanes, with the formation of CO_2 as a byproduct, a process later called the Kolbe reaction [5].



Scheme 1.1. The Kolbe reaction.

In this reaction, the electrochemical oxidation of the carboxylic acid generates a radical and CO_2 , followed by the combination of two radicals to form the corresponding alkane (Scheme 1.1). When an electrochemical synthesis reaction is presented in a scheme, it is important to note that there are always two electrodes necessary to obtain the desired reaction. For example, in Scheme 1.1, only the anode where the oxidation is taking place is pictured. However, this electrode is always accompanied by a cathode, where a corresponding reduction occurs. In aqueous solutions, the reduction reaction at the cathode often involves the reduction of water to hydrogen gas, but there are also other possibilities. To simplify the schemes presented in this introduction chapter, only the reaction and electrode of interest are pictured.

Today, one of the best-known large-scale electrosynthesis reactions used in organic chemistry is the reductive dimerization of acrylonitrile to adiponitrile, which is then further used for the synthesis of nylon [6]. In this process, the reduction of acrylonitrile to propionitrile is an undesired side reaction. The process only became economically viable after it was proven that the addition of quaternary ammonium salt suppressed this side reaction. The ammonium ions are able to shield the radical anion that is formed after reduction and in this manner the dimerization reaction is favoured (Scheme 1.2) [7]. Worldwide more than 300,000 tons of adiponitrile is produced every year [8].



Scheme 1.2. Reaction scheme for the electroreduction of acrylonitrile to adiponitrile.

In addition to organic synthesis, another well-known process of electrosynthesis is chloralkali electrolysis to produce chlorine [9]. At the anode of the electrolysis cell, sodium chloride is oxidized to produce chlorine, while at the cathode the reduction of water to hydrogen gas occurs. Different electrolysis cells have been used in large-scale synthesis. Today, the use of mercury cells is being phased out because of environmental concerns and they are being replaced by modern membrane cells.

1.2. A sustainable oxidation of the alcohol functionality

1.2.1. Classic alcohol oxidation strategies

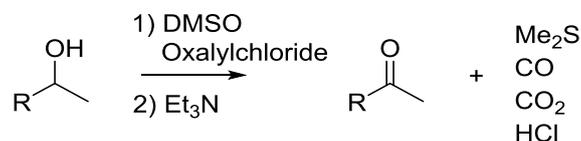
An important and abundant reaction in organic synthesis is the oxidation of the alcohol functionality into aldehydes and ketones. Aldehydes and ketones are very important intermediates in the synthesis of a number of pharmaceuticals and fine chemicals. There are many different reactions that start with ketones or aldehydes because of their reactivity. As a consequence, these compounds are not always stable or not even commercially available. This in contrast with the corresponding alcohols, which explains why often one starts to prepare the desired aldehyde or ketone through the oxidation of alcohols [10].

The synthesis of aldehydes has to be a selective oxidation as the over-oxidation to a carboxylic acid should be avoided. Further, most target molecules commonly contain diverse functional groups such as amines, sulfur-containing groups, alkenes, and heterocycles. Generally, an effective alcohol oxidation must exhibit a good chemoselectivity. Numerous stoichiometric reagents and catalytic oxidation methods have been developed to meet these requirements.

The traditional text book methods for alcohol oxidation reactions are based on the use of toxic chemicals and/or the production of a stoichiometric amount of waste during the process [10]. One of those classic methods utilizes stoichiometric amounts of chromium (VI) as an oxidant, being highly toxic and polluting. For example the Jones–reagent, which is sodium dichromate in diluted sulfuric acid, can be used for the oxidation of secondary alcohols to ketones in acetone. When this oxidant is used for the oxidation of primary alcohols, an oxidation to carboxylic acids will be observed. For the oxidation of primary alcohols to aldehydes, water should be avoided as the solvent. Other chromate salts like pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC) can be used for this specific oxidation. These salts are soluble in solvents such as dichloromethane without the need to add water [10].

A second method to oxidize alcohols is the Swern oxidation (scheme 1.3). In this procedure dimethyl sulfoxide (DMSO) is activated by using oxalylchloride, giving a chlorodimethylsulfoniumion which reacts with an alcohol. In a next step deprotonation takes

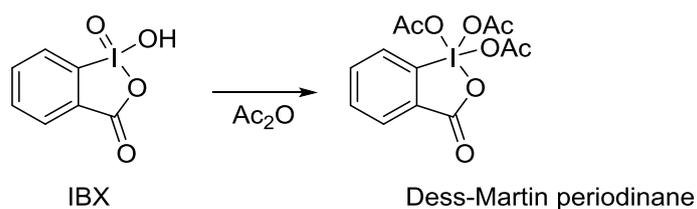
places because of the added base, which is standard triethylamine, and the alcohol gets oxidized accompanied with the formation of dimethylsulfide.



Scheme 1.3. Swern oxidation.

In short, using this procedure carbonyl compounds are obtained in combination with the formation of dimethylsulfide, carbon monoxide, carbon dioxide and hydrogen chloride.

Another popular category is the use of high-valent iodine compounds such as the Dess-Martin periodinane, formed from 2-iodoxybenzoic acid (IBX) with acetic anhydride (Ac_2O) and acetic acid (Scheme 1.4).



Scheme 1.4. Synthesis of Dess-Martin periodinane.

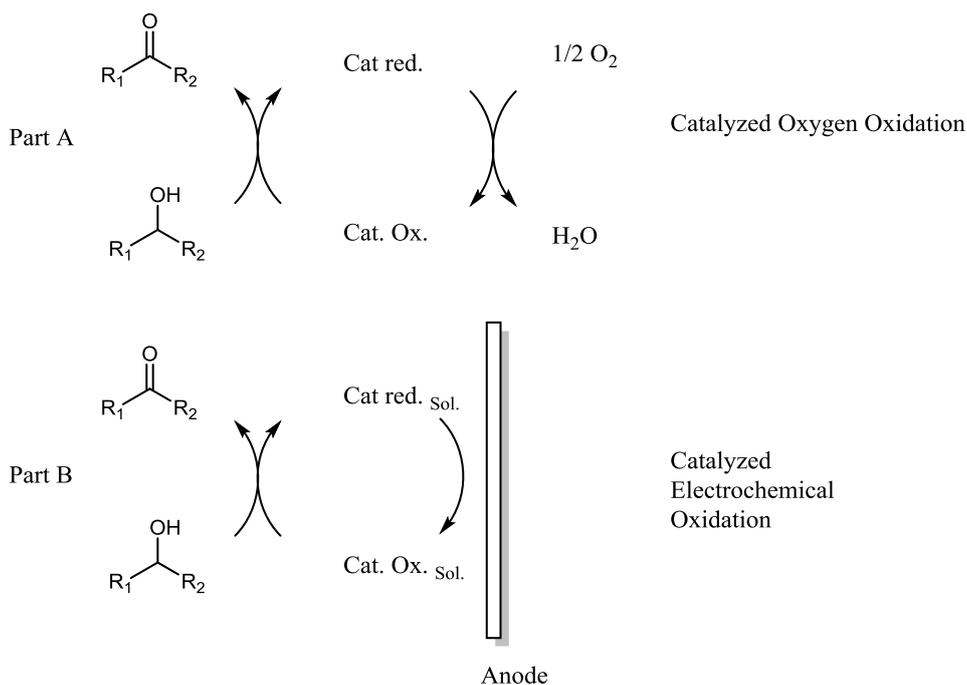
Via this reaction, a high valent iodine compound is obtained with the iodine atom inside a stable five membered ring and surrounded by organic residues. These characteristics makes the oxidant soluble in many organic solvents. It also has a very long lifetime under inert atmosphere at room temperature. Efficient oxidation of alcohols with this reagent can be obtained in dichloromethane at room temperature. Also, IBX is capable of oxidizing alcohols to carbonyl compounds but this reagent is only soluble in DMSO.

Another class of reagents uses stoichiometric amounts of ruthenium [11] or manganese salts [12] for the oxidation of alcohols, generating substantial amounts of waste. The most common used ruthenium compounds are ruthenium tetroxide and the perruthenate or ruthenate anion [11], being the most active for oxidation reactions. A popular manganese compound that is used for alcohol oxidation is manganese dioxide [12].

In general, the different listed methods above all have low atom efficiencies and generate a lot of (toxic) waste. If we look at the different methods, keeping the twelve principles of green chemistry published by Anastas and Warner in mind, multiple opportunities for improvement can be detected.

1.2.2. Sustainable alternatives for alcohol oxidation

From an environmental point of view, there is a necessity for improvement of the oxidation methods or the development of new efficient ones, without the generation of waste. The most important factor to achieve this, is by the choice of an appropriate stoichiometric oxidant without generating a side stream of unwanted products. A popular solution for this problem is to make use of oxygen (or the related hydrogen peroxide) as the stoichiometric oxidant. In order to make oxygen active for the oxidation of alcohols, it has to be used in combination with appropriate catalysts as no direct oxidation of alcohols by oxygen is possible. The oxidation with oxygen results in the desired carbonyl reaction product, aldehydes or ketones, and the sole by-product water (Scheme 1.5, Part A). Compared to the toxic chemicals generated with the classic methods, the generation of water as a by-product is a major improvement. An enormous amount of different approaches were investigated in order to optimize this oxidation reaction. Multiple catalysts have been investigated and developed to obtain an efficient oxidation of broad scale of alcohols with a good chemoselectivity. Most methods make use of transition metals as catalysts, for example copper catalysts used in combination with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) [13]. Other catalysts are based on ruthenium [14], palladium [15], gold [16], iron [17], vanadium [18] or iridium [19]. Many catalysts have been developed but the search for catalysts or catalyst systems with a good chemoselectivity and functional-group compatibility for an efficient oxidation for a broad group of alcohols remains a challenge.



Scheme 1.5. General strategies to obtain a sustainable oxidation of alcohols.

An alternative approach is the use of electricity as the stoichiometric oxidant. For the direct electrochemical oxidation of different alcohols, a large overpotential is needed which makes the approach suffer in selectivity. Most alcohols have an oxidation potential higher than 2.0 V versus the saturated calomel reference electrode [20]. During an electrolysis at these potentials with classic non-modified electrodes, the oxidation of the solvent or the electrolyte present is interfering with the oxidation of the alcohols, preventing a nice clean reaction. Direct electrolysis of alcohols gives only the desired aldehydes or ketones in low selectivity and efficiency.

1.2.3. Towards an electrochemical oxidation of alcohols

1.2.3.1. *Electrode functionalization*

There are two main directions to overcome the large overpotential barrier when one aims at a selective oxidation of the alcohol functionality. First, one can alter the electrode surface making it selective or lowering the oxidation potential of the alcohol functionality. Different strategies have been used to explore this option, with special attention to the oxidation of methanol or ethanol, to explore the use of these alcohol solvents in a fuel cell.

The use of fuel cells to generate electricity is an attractive alternative to power the cars of the future. The most investigated fuel cell is the one powered by hydrogen and oxygen as the fuels. The anode reaction is the oxidation of hydrogen and the reduction of oxygen is the cathode reaction.

Interesting alternative reagents for the anodic reaction in fuel cells are short aliphatic alcohols, for example methanol and ethanol [21]. They have a relatively high energy density (although smaller than hydrogen) and can be electrochemically oxidized. Normally full oxidation to CO₂ is desired. The advantages are that these short aliphatic alcohols are liquid fuels, so existing infrastructure could easily be adapted for the use of these liquids. An additional advantage is the possibility to obtain them from biomass sources. In the fuel cell, the methanol or ethanol should be efficiently oxidized to CO₂ at the lowest potential possible. To achieve this oxidation, a lot of research has been performed in order to obtain the most efficient electrode material. For methanol, the most active metal electrode material is platinum. Different designed electrodes are based on this metal [22]. To get an efficient oxidation, one of the important issues is the formation of intermediates such as CO causing blockage or passivation of the electrode surface. A good electrode should overcome this problem and full oxidation will be more efficient. Different materials and designs have been proposed like for example Pt-based nanostructures, Pt-based alloys or the combination with other metal oxides [22]. For ethanol oxidation a full oxidation to CO₂ is desired as well, which is of course a more challenging oxidation than for methanol. Most electrode material is based on platinum or palladium and also bimetallic and nanostructures have been proposed to increase the efficiency [23].

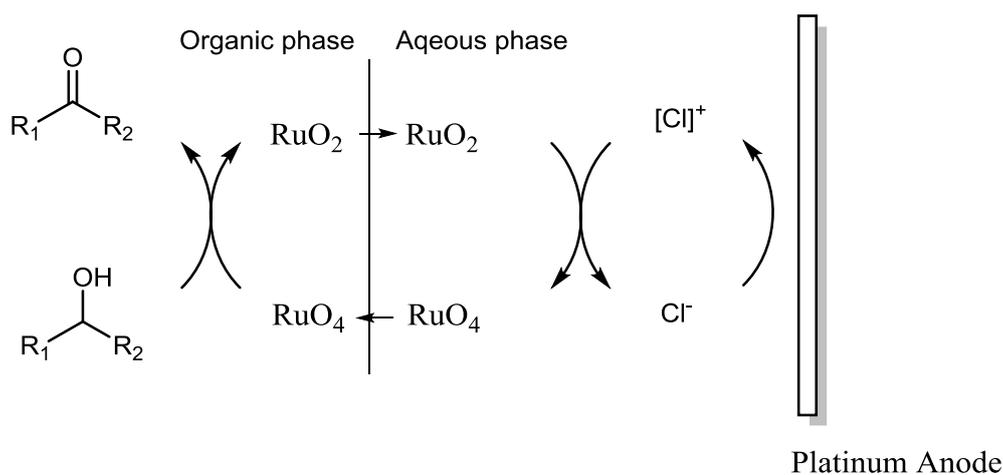
1.2.3.2. The use of an appropriate mediator system

Next to electrode functionalization, an appropriate mediator or combination of different catalysts can be used for the oxidation of alcohols (Scheme 1.5, Part B). The mediators can be divided into different categories such as metal salts, organometallic mediators, halogenides and organocatalysts [24].

In this thesis, new strategies are developed in order to improve the electrochemical mediated oxidation reaction of alcohols. Different catalysts or sets of catalysts are investigated and evaluated. The choice of the catalyst was taken from an organic synthesis point of view, so catalysts with selectivity and a good reactivity were selected. The main goal was to improve the existing synthesis protocols/efficiencies and evaluate the use of the catalysts in an electrochemical setup. More specifically, the use of tetrapropylammonium perruthenate (TPAP), the Shvo complex and neocuproine ligated palladium catalysts for the oxidation of alcohols by electrochemistry were evaluated. A concise description of the state of the art of each catalyst is given in the paragraphs below.

1.3. The use of ruthenium mediators in electrochemical oxidation strategies

Ruthenium catalysts are well known for oxidation reactions, also for alcohols [11]. Ruthenium can exist in a wide range of oxidation states, if stabilized with the appropriate ligands. Ruthenium in a high oxidation state (Ru^{4+} to Ru^{8+}) can be well stabilized by oxo ligands (O^{2-}) and can act as oxidants for example for alcohols. A few strategies have been developed making use of the electrochemical recycling of ruthenium-oxy species for the catalytic oxidation of alcohols, all focusing on RuO_2 . Because of the low solubility of RuO_2 in organic solvents, water has to be added as a solvent or co-solvent. For example, RuO_4 can function as the oxidant in a two phase system of tetrachloromethane and water [25]. In this case, active chloride species (Cl_2 or Cl^+) are generated at the electrode surface in the sodium chloride solution (water phase) and oxidize RuO_2 to RuO_4 , which is responsible for the subsequent oxidation of the alcohol in the organic phase.

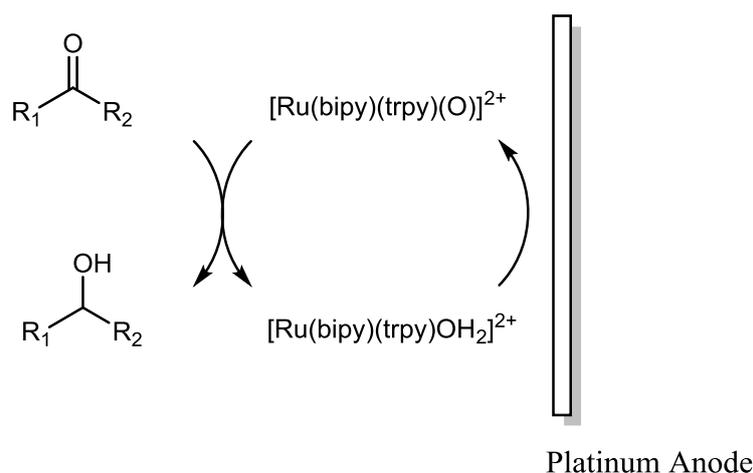


Scheme 1.6. Biphasic oxidation of alcohols by RuO₂ and chloride species.

This approach (scheme 1.6) uses chloride as secondary oxidant and therefore, this method is discarded as a pure electrochemical oxidation of the ruthenium catalyst. Moreover, the reaction is performed in a toxic solvent, considered as an ozone depleting agent [26]. To improve this method, the same author reports on a method in which RuO₂ is directly oxidized at the electrode surface to a Ru⁷⁺ species in an alkaline acetonitrile/water mixture, followed by the Ru⁷⁺ promoted oxidation of alcohols [27]. This second method is presented without any electrochemical investigation of the formed ruthenium species and it is not clear what the exact nature of the catalytic species is.

The described strategy makes use of dissolved active ruthenium species and electrochemical recycling in solution. However, RuO₂ can also be used as (a deposit on) electrode material. In alkaline media, RuO₂ can be electrochemically oxidized to RuO₄²⁻ and RuO₄⁻ which can react with alcohols [28]. Studies have been performed on the oxidation of glucose [29,30] and benzylalcohol [31].

Another method using a ruthenium catalyst, describes the use of oxoruthenium ions stabilized by pyridine ligands. For example, a ruthenium catalyst with a bipyridine (bipy) and a terpyridine (trpy) ligand [Ru^{IV}(bipy)(trpy)(O)]²⁺ can be electrochemically generated from [Ru^{II}(bipy)(trpy)OH₂]²⁺ in a buffer solution (Scheme 1.7). In the beginning of the eighties, such oxidation of the Ru^{II} complex to the oxo stabilized Ru^{IV} complex was described to take place at a relative low potential. A potential of ca 0.8 V versus saturated calomel electrode (SCE) is reported [32].



Scheme 1.7. Electrochemical mediated oxidation of alcohols by $[\text{Ru}^{\text{II}}(\text{bipy})(\text{trpy})\text{OH}_2]^{2+}$.

By using this catalyst in combination with its electrochemical recycling, benzylic alcohols were converted efficiently. Secondary alcohols are oxidized to ketones while for primary alcohols the overoxidation to carboxylic acids is reported. A broad range of alcohols can be oxidized using this catalyst system [33].

Efforts have been made to attach these ruthenium complexes at a carbon electrode. For example, a phenanthroline ligand (phen) can be covalent attached to a graphite felt electrode. Next, the attached ligand reacts with $\text{Ru}(\text{Cl}_3)(\text{trpy})$ and is further modified to achieve an electrode with an attached ruthenium catalyst ($[\text{Ru}(\text{trpy})(\text{phen})(\text{OH}_2)]^{2+}$). This modified electrode is proven to be able to oxidize different alcohols under constant potential [34].

Similar catalysts with different ligands are reported for the electrochemical mediated oxidation of alcohols. For example 3,6-bis(pyrid-2-yl)pyridazine (dppi) was selected as ligand instead of bipyridine [35]. When $[\text{Ru}(\text{trpy})(\text{dppi})(\text{O})]^{2+}$ is obtained by electrochemical oxidation, this species seems to be active for the oxidation of benzylalcohol, although the catalyst was not subjected to electrolysis in research.

Another reported catalyst contains a terpyridine and a 3,5-di-tertbutyl-1,2-semiquinonate (sq) ligand, $[\text{Ru}^{\text{II}}(\text{trpy})(\text{sq})(\text{NH}_3)]^+$. When electrochemically oxidized, it is capable of oxidizing short aliphatic alcohols such as methanol and ethanol in neutral aqueous solution [36].

Not only the oxidation of alcohols is mediated by ruthenium catalysts, also alkenes can be electro-oxidized mediated by ruthenium catalysts. For example the oxidative cleavage of alkenes into acids can be achieved by using the mediator system $\text{RuO}_4/\text{IO}_4^-$, which can be electrochemically recycled [37]. In this mediator system, the periodate is electrochemically regenerated at the electrode surface and can in the following step oxidize the ruthenium catalyst back to ruthenium tetraoxide.

The oxidation of alkenes into an epoxide can be achieved using an electrochemical recycled ruthenium catalyst [38]. The electrochemical oxidation of $[\text{Ru}^{\text{III}}(\text{H}_2\text{O})_4\text{Cl}_2]^+$ generates an active ruthenium species $[\text{Ru}^{\text{V}}(\text{O})(\text{H}_2\text{O})_3\text{Cl}_2]^+$ in acidic media, which is able to oxidize alkenes to the corresponding epoxides with moderate yield.

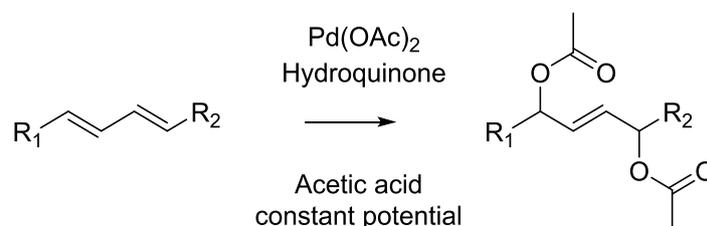
The oxidation of 2-methylnaphthalene to 2-methylnaphthoquinone is reported to be mediated by electrochemical oxidized RuCl_3 in a water acetonitrile mixture [39]. The exact mechanism of this reaction is not clear and relative high potentials were needed in order to obtain the desired product in rather low yields. A similar catalyst, $[\text{Ru}(\text{CH}_3\text{CN})_3\text{Cl}_3]$, was used in a later publication for the electrochemical mediated oxidation of tetralin [40]. Relative high potentials were necessary and no complete oxidation of the tetralin to tetralone during the electrolysis was reported.

For the hydrolytic oxidation of organosilanes to silanols was shown that $[\text{RuCl}_2(\text{p-cymene})]_2$ is the most active catalyst together with electrochemical reoxidation [41]. However, no electrolysis experiments were presented.

1.4. The use of palladium mediators in electrochemical oxidation methods

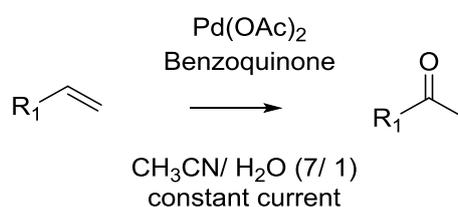
Besides the use of ruthenium salts as a mediator, palladium salts can act as a mediator in electrochemical oxidation reactions. The use of palladium acetate ($\text{Pd}(\text{OAc})_2$) in combination with electrochemistry has been explored for synthetic purposes. It is known that palladium in the zero oxidation state cannot be oxidized directly at the electrode surface. Different approaches have been developed where a palladium salt is combined with the electrochemical oxidation of another mediator. The first examples of the use of palladium acetate in an electrochemical synthesis procedure was in 1987 by both Bäckvall et al. [42] and

Tsuji et al. [43]. Bäckvall used the combination of palladium acetate and benzoquinone in acetic acid for the diacetoxylation of conjugated dienes (Scheme 1.8) [42]. Later, a similar method using palladium acetate and copper acetate was published for the acetoxylation of olefins to saturated esters [44].



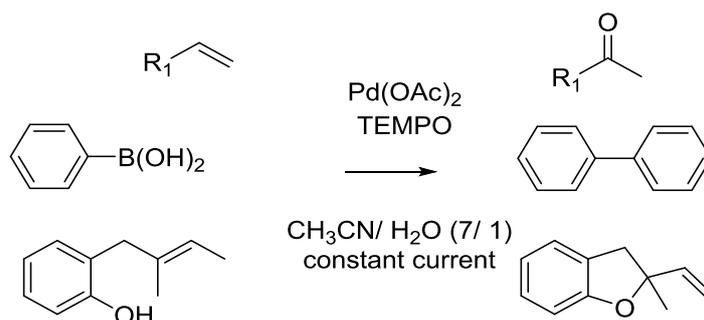
Scheme 1.8. Diacetoxylation of conjugated dienes.

Tsuji on the other hand used the combination of palladium acetate and benzoquinone in an acetonitrile water mixture for a wacker-type oxidation of 1-alkenes to methylketones (Scheme 1.9) [43].



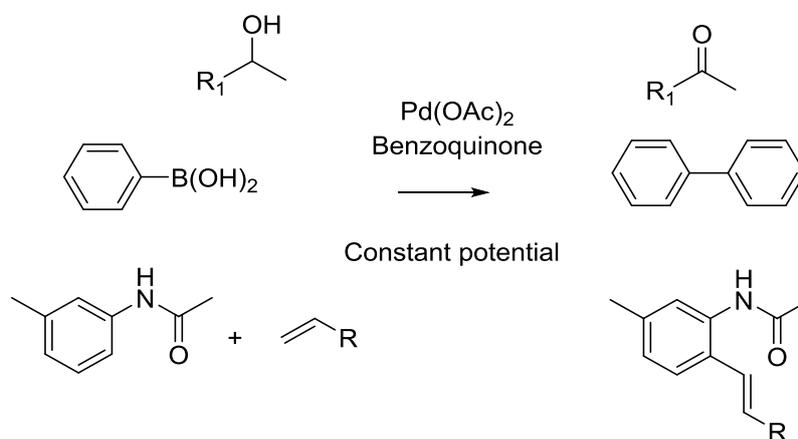
Scheme 1.9. Wacker-type oxidation of alkenes.

In 1992 Miller et al. showed that the addition of perchloric acid has a rate accelerating effect in wacker type oxidations [45]. This method was expanded by using the combination of palladium acetate and other mediators such as tris(4-bromophenyl)amine [46] and TEMPO [47]. When TEMPO was used, it was claimed that the in-situ formed palladium catalyst was a cationic species in the form of $[\text{Pd}(\text{CH}_3\text{CN})_4][\text{X}]_2$ in which the X depends on the anion of the electrolyte used. This combination of TEMPO and palladium acetate could also be used for other reactions such as the wacker-type cyclizations [48] and the synthesis of biaryls from arylboronic acids or arylboronic esters (Scheme 1.10) [49,50].



Scheme 1.10. Oxidation reactions catalyzed by Pd(OAc)₂ and TEMPO.

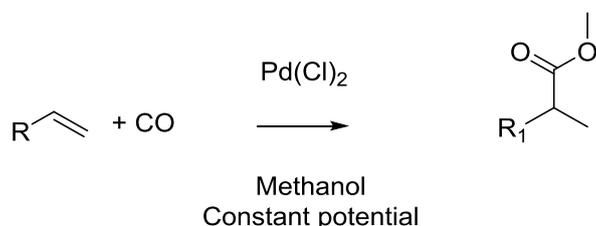
The combination of palladium acetate and benzoquinone as a mediator has been further expanded for other reactions. Amatore et al., developed a method for a Heck-type reaction between an arene and an alkene in acetic acid [51], for an electro-oxidative homocoupling between arylboronic acids or arylboronates [52] and for the oxidation of alcohols (Scheme 1.11) [53]. In the latter reaction, aldehydes and ketones could be obtained in moderate yields using this method. Major drawbacks are the necessity to add equivalent amounts of base and possible catalyst decomposition because of redox active intermediates at the potentials necessary to oxidize the hydroquinone.



Scheme 1.11. Oxidation reactions catalyzed by Pd(OAc)₂ and benzoquinone.

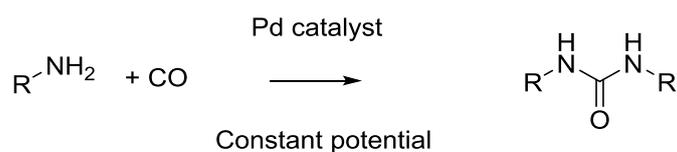
An important difference between the reactions developed by Amatore and the ones by Mitsudo, is that the former is using a constant potential method at the oxidation potential of hydroquinone. The latter is using a constant current method where the exact potential applied during the synthesis is unknown.

A different type of electrochemical oxidation reaction using a palladium catalyst, is the hydroesterification of alkenes with carbon monoxide and methanol. Palladium chloride can be used as a catalyst and the Pd⁰ formed during the reaction can be directly back oxidized at the electrode surface (Scheme 1.12) [54].



Scheme 1.12. Hydroesterification of alkenes.

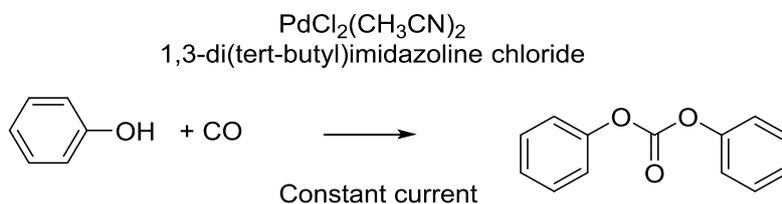
Also alkynes can be used as substrates using the same method to yield unsaturated diesters [55]. Later this method was adapted to retain the triple bond, making it possible to transform terminal alkynes into methylacetylenecarboxylate. In this procedure Pd(OAc)₂(PPh₃)₂ is used as the palladium catalyst and two equivalents of a base like NaOAc or Et₃N has to be added [56]. The electrochemical reoxidation of palladium catalysts under a carbon monoxide atmosphere is then further explored for the synthesis of N,N'-disubstituted ureas from primary amines (Scheme 1.13). Different palladium catalyst are active in this reaction, with the best results obtained by using Pd(PPh₃)₄ or Pd(OAc)₂ [57].



Scheme 1.13. Synthesis of N,N'-disubstituted ureas from primary amines.

Another reaction under carbon monoxide atmosphere is the synthesis of diphenylcarbonate from phenol (Scheme 1.14). The homogeneous palladium catalyst used, (PdCl₂(CH₃CN)₂), is stabilized by an in situ formed N-heterocyclic carbene. The reoxidation at the gold anode is claimed to be stabilized with the addition of the in situ formed N-heterocyclic carbene derived from 1,3-di(tert-butyl)imidazoline chloride [58]. Different anode material was additionally

tested with graphene-3-supported gold particles of a few nanometer being the best for the synthesis of diphenylcarbonate [59].

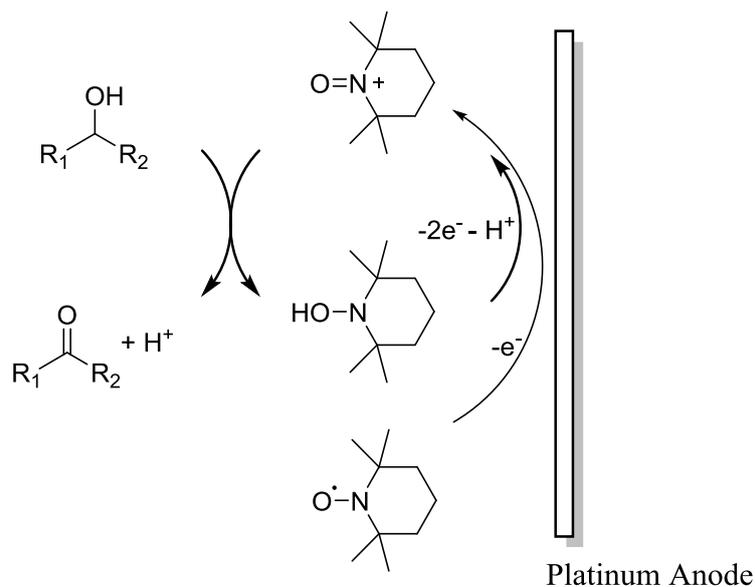


Scheme 1.14. Synthesis of diphenylcarbonate from phenol.

1.5. The use of other mediators in the electrochemical oxidation of alcohols

Not only ruthenium or palladium catalysts are used in the electrochemical mediated oxidation of alcohols. The electrochemical recycling of, for example, copper is reported for the selective oxidation of sugars where only one secondary alcohol is oxidized [60]. Copper acetate is used and Cu^{2+} is regenerated at the electrode to oxidize for example D-ribose. Only limited yields of the desired oxidized products are reported.

Also organic mediators are used in electrosynthesis applications. The most important classes are triaryl amines and 2,2,6,6-tetramethylpiperidinyl-1-oxyl radicals (TEMPO). The use of TEMPO for the electrochemical mediated oxidation of alcohols is well investigated [61]. The TEMPO radicals can be electrochemically oxidized at a relative low potential to the oxoammonium cations. This property can be used for oxidation reactions (Scheme 1.15) [62].



Scheme 1.15. TEMPO mediated oxidation of alcohols.

In acetonitrile, primary alcohols can be oxidized to the corresponding aldehydes by using this mediator. When a mixture of water and organic solvents is used, oxidation to the corresponding carboxylic acids is obtained. The selectivity of this mediator is investigated and it is reported that TEMPO can be used for the selective oxidation of glycerol to dihydroxyacetone. However, the reaction resulted in a yield of only 25 % [63].

To improve efficiency and increase turnover numbers, the use of TEMPO in a double mediator system with NaBr in a two-phase water-organic medium is reported. In this procedure a two-phase medium of water and dichloromethane is used, with the electrodes put in the aqueous phase. The electrochemical oxidation of bromide is then responsible for the oxidation of TEMPO to the oxoammonium cation at the interphase between the two phases, followed by the oxidation of the alcohol in the organic phase. Primary and secondary alcohols are oxidized to the corresponding aldehydes and ketones in good yields.

Modification of the electrode with TEMPO or TEMPO-based radicals, is also a strategy to improve the efficiency of this reaction [64]. Different types of modification strategies are possible, such as covalently attached TEMPO molecules to carbon based electrodes [65] or the combination of a gold electrode with TEMPO-coated gold nanoparticles. In the latter strategy, the TEMPO molecules are covalently attached to a binder with a thiol function which can react with the gold nano particles [66]. Another strategy is the usage of silica derivatized with TEMPO, which can form a thin film on an indium-tin-oxide electrode [67]. The main

problem with all the different techniques is the stability on the long term of the different electrodes made.

Not only TEMPO is tested as a radical mediator for the electrochemical oxidation of alcohols. Similar structures can be more stable. Recently the use of 4-acetamido-TEMPO (ACT) is reported as a more reactive alternative [68]. This compound showed a higher reactivity than TEMPO and other bicyclic nitroxyl derivatives for the electrochemical mediated oxidation of alcohols especially at higher pH.

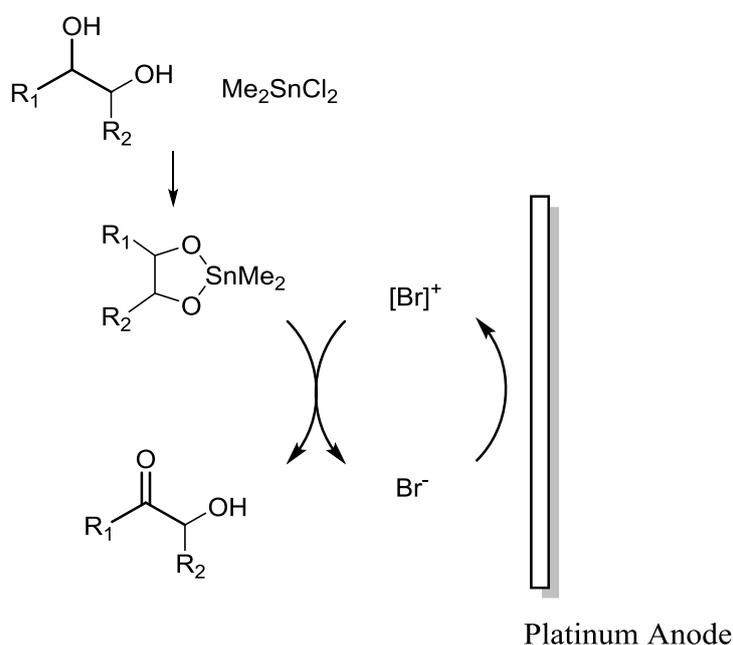
Also *N*-hydroxyphthalimide can be used as a mediator for the electrochemical oxidation of alcohols. The one electron oxidation in an alkaline acetonitrile solution generates a nitroxide radical, which is capable to oxidize the alcohol function. Both secondary and primary alcohols can be converted to the corresponding carbonyl compounds with activated alcohols giving the highest yields [69]. An interesting article is comparing different organocatalysts under similar conditions including TEMPO and *N*-hydroxyphthalimide for the electrochemical catalyzed oxidation of a lignin model compound (4-ethoxy-3-methoxyphenylglycerol- β -guaiacyl ether). *N*-hydroxyphthalimide proved to be the most efficient one for the selective oxidation of the secondary alcohol functionality [70].

Another example of an organic mediator for the electrochemical oxidation of alcohols reported is thioanisole [71]. This compound is first oxidized at the electrode surface and further reacting with secondary alcohols to form ketones. A remarkable feature is that the optimal solvent system is a mixture of acetonitrile and a small amount of 2,2,2-trifluoroethanol. The exact role of the 2,2,2-trifluoroethanol is not yet clear but higher yields are obtained by its addition to the reaction mixture.

Besides organic mediators also halogenides can be used as mediator in organic synthesis. The example of chloride species used for the generation of ruthenium tetroxide in a biphasic system for the oxidation of alcohols has been already given (page 14). Additionally, the direct oxidation of alcohols by the generated iodonium (I^+) via the electrochemical oxidation of iodide at the electrode surface is reported [72]. Potassium iodide can be used as the iodide source in a water, organic solvent mixture. Primary alcohols are converted to esters,

secondary alcohols to the corresponding ketones [73]. Drawback is the large amount of charge needed to obtain reasonable yields, illustrating the low efficiency of this system.

In combination with organotin compounds, bromide can oxidize alcohols [74]. This strategy is especially useful for the selective oxidation of vicinal diols. In methanol at zero degrees, Me_2SnCl_2 as tin catalyst and Et_4Br as halogen source are used for the oxidation of different diols to the ketohydroxy group (Scheme 1.16) [75].



Scheme 1.16. Bromide mediated oxidation of diols with organotin catalyst.

First, the organotin compound binds with the diol to form an acetal based complex. At the anode an oxidized bromo species (Br^+) is generated, which is capable of oxidizing the complex into the ketohydroxy compound. In this manner, the oxidation of the bromide at the anode becomes a crucial step in this oxidation procedure. Later this method was expanded to its use in water as a more environmentally friendly solvent. More specific 1.2 equivalents of KBr was used as bromide source and the reaction was kept in dark to obtain the highest yield of ketohydroxy compound [76]. It was also found that the organotin catalyst can be replaced by boronic acids, being safer compounds than the organotin catalysts [77]. A similar reaction scheme is presented where $\text{MeB}(\text{OH})_2$ is able to form esters with the diol. This complex is then oxidized by an oxidized bromo species generated at the anode.

To conclude, nitrate anions can be of interest for alcohol oxidation [78]. In a biphasic system of chloroform and water, the electrodes are placed in the aqueous phase. To the acidic aqueous solution, sodium nitrate is added and under galvanostatic conditions the nitrate anion is oxidized to a nitrate radical capable of oxidizing benzylic alcohols at the interphase region. The nitrate radical can be regenerated at the anode. Benzylic alcohols are oxidized to aldehydes and ketones using this method.

1.6. References

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Chapter 2

Experimental setup and methods

2.1. Three electrode system

Standard electrochemical experiments require a three electrode setup connected to a potentiostat (Figure 2.1). These three electrodes are the working electrode (WE), the counter electrode (CE) and the reference electrode (RE). In this system the potential is measured between the working and the reference electrode. The reference electrode has a stable and known potential, which should not be changed during an experiment. Therefore, no current can flow between the working and the reference electrode. Instead the current flows between the working electrode and the counter electrode.

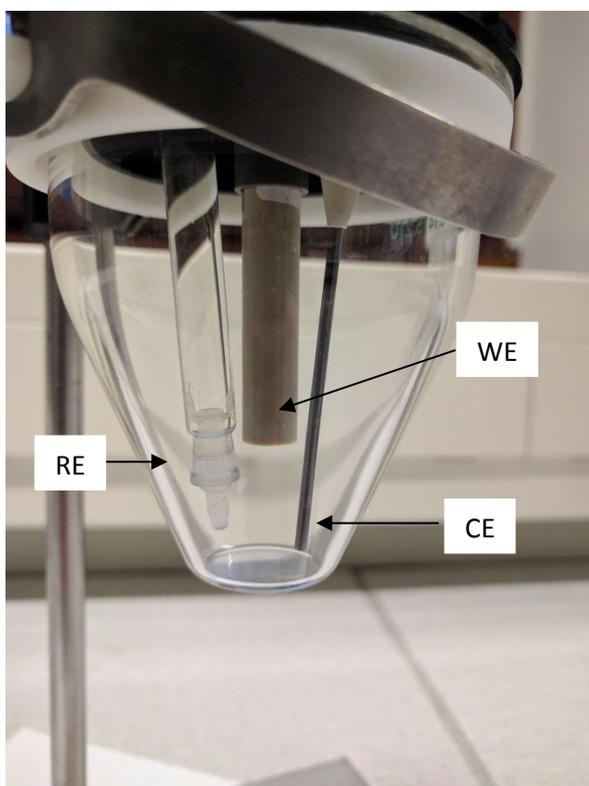


Figure 2.1. Three electrode setup with indication of the working electrode (WE), reference electrode (RE) and counter electrode (CE).

It is the reaction occurring at the working electrode that is of interest, while what happens at the counter electrode is not of interest and cannot be studied. The surface of the counter electrode is normally substantially larger than the surface of the working electrode. In this

manner, a current through the cell results in a lower current density at the counter electrode than the current density at the working electrode. Fluctuations at the counter electrode that can disturb the measured signal are thus avoided and the larger surface of the counter electrode will result in a more homogeneous distribution of the current over the working electrode.

Another important feature of this setup are 'small A/V conditions', meaning that the surface of the working electrode (A) is small compared to the volume of the electrolyte solution (V). The currents measured or applied at the working electrode are in comparison so small that they have no influence on the concentrations in the solution. The so-called bulk solution is not altered during these measurements by the applied potentials.

Commonly, the reaction occurring at the counter electrode is the reduction or the oxidation of the solvent or the electrolyte. Often a platinum sheet is used, platinum is inert and can be kept clean and pure. Oxide layers are not formed easily on Pt, these could possibly lead to an unacceptable resistance in the cell. Also carbon electrodes such as glassy carbon rods can be used as counter electrode.

The working electrode is commonly a planar disk electrode (Figure 2.2). Metal disks of gold or platinum can be used. Glassy carbon disk electrodes are also common.

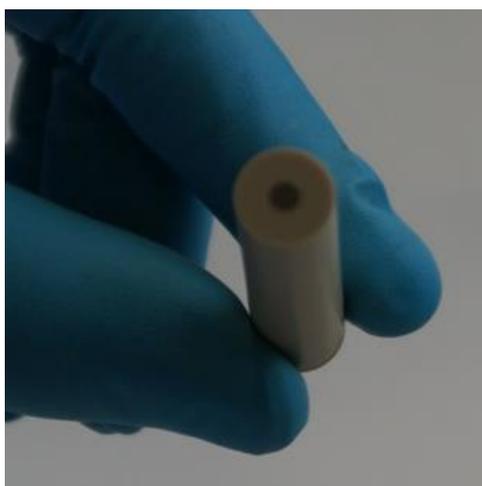


Figure 2.2. Platinum disk electrode (Metrohm).

The reference electrode is normally the most complicated electrode in this setup and so also the most fragile part. The two most used reference electrode systems are the Ag/AgCl reference and the standard calomel reference (SCE). The Ag/AgCl reference electrode is composed of a silver wire partially covered with AgCl paste and normally immersed in saturated KCl solution. This reference system has a potential difference of 197 mV versus the standard hydrogen electrode. The standard calomel electrode consists of mercury paste surrounded by Hg_2Cl_2 dispersed in a saturated KCl solution. This reference system has a potential difference of 242 mV versus the standard hydrogen electrode.

The potentiostat is the machine that controls these electrodes. In theory the potentiostat controls the potential at the working electrode in comparison with the reference electrode. As no current can go through the reference electrode, the current must flow between working and counter electrode. The potentiostat keeps control of the cell if the cell changes.

In practice we can evaluate the electronic circuit to see how a potentiostat works. The potentiostat actually controls the potential at the counter electrode in comparison of the reference electrode and this is checked with the potential at the working electrode, the working electrode itself is at ground. Knowing this, this actually emphasizes the importance of the counter electrode. In case of problems, it is important to check for example for undesired resistances created at the counter electrode. An important feature of a potentiostat is its compliance voltage, which determines between which range the machine can keep control of the cell. A potentiostat cannot infinitely keep control of the cell. This is especially the case when there is in some way a large resistance build-up or present in the cell between the electrodes. It is the compliance voltage that determines till which potential the potentiostat can keep up. If the resistance becomes too high, the desired potential cannot be reached and the potentiostat will give the message of a voltage overload. The potentiostats of Metrohm, that are used during this PhD, will flash a red light with V ovl to set attention to this specific situation.

2.2. Cyclic voltammetry

Cyclic voltammetry experiments are one of the basic measurements used in electrochemical analytical measurements, which can unravel crucial information on the redox behavior of the components in solution or of the components adsorbed on the surface. For this type of experiments, a standard three-electrode setup connected to a potentiostat is necessary. In a cyclic voltammetry experiment, the electrochemical behavior of system is studied in a potential region by varying the potential linearly at a constant rate. At a certain potential the direction of the scan is then reversed and the potential is scanned back to the starting point. During the experiment the potential is gradually changed in function of the time and the current is measured. The potentials changes, according to the direction and the scan rate set at the beginning of the experiment. In Figure 2.3 the applied potential in function of the time is presented.

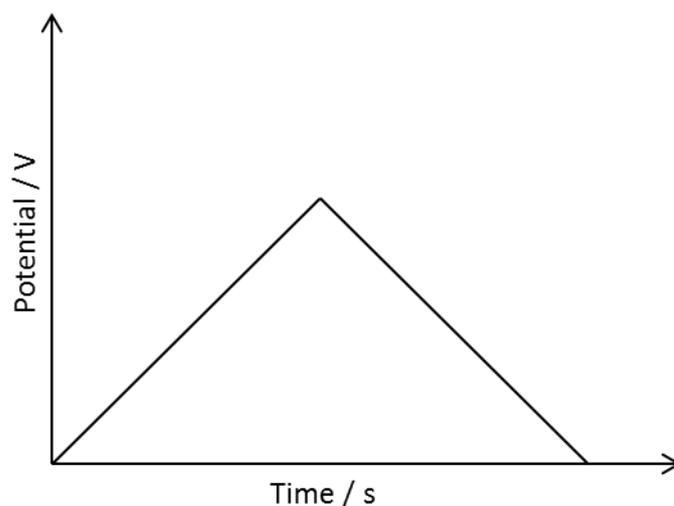


Figure 2.3. Cyclic voltammetry plot potential in function of time.

A typical way to visualize this type of experiment is a graph with the current in function of potential (Figure 2.4). When a positive current is detected, oxidation is occurring at that potential. When a negative current is detected, a reduction is occurring at that respective

potential. By taking a cyclic voltammogram of a system, the potentials at which oxidation or reduction are happening are immediately visualized and it can easily be detected which processes are connected to each other or not.

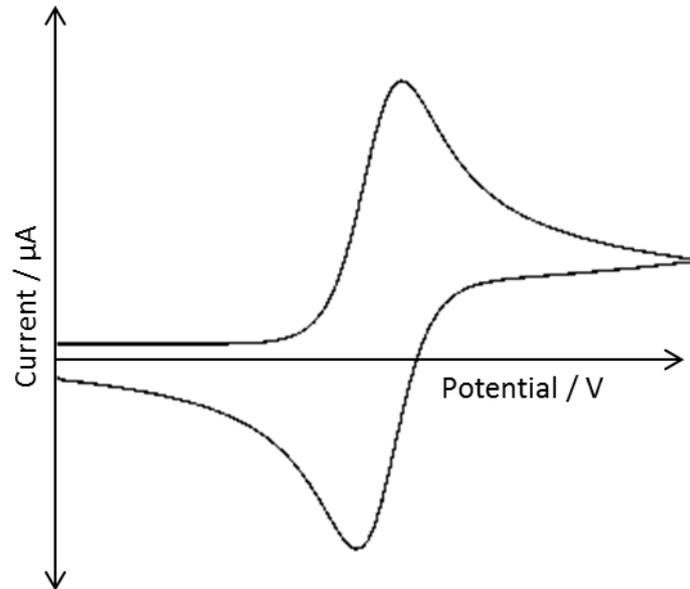


Figure 2.4. Cyclic voltammetry plot current in function of potential.

If we assume a reaction where the electron transfer is fast, then the reaction rate and the current is determined by the transport of molecules to the electrode surface. In this situation the reaction is controlled by mass-transfer. The flux of the molecules can now be given by the Nernst-Planck equation (Equation 2.1) [1]. With $J(x)$ the flux of the molecule at distance x of the electrode surface, D the diffusion coefficient, $\partial C(x)/\partial x$ the concentration gradient, $\partial \phi(x)/\partial x$ the potential gradient, Z the charge of the molecule, C the concentration, F the Faraday constant, R the gas constant, T the temperature and $v(x)$ the rate of convection.

$$J(x) = -D \frac{\partial C(x)}{\partial x} - \frac{ZF}{RT} D C \frac{\partial \phi(x)}{\partial x} + C v(x) \quad \text{Equation 2.1}$$

In this equation we can see a term for the diffusion, a term for the migration and a term for convection. During a normal cyclic voltammetry experiment we can remove the migration and

convection factors of this equation. The transport of molecules to the electrode is occurring by diffusion now.

The peak current of a perfect reversible system can be described by using the Randles –Sevcik equation (Equation 2.2) derived from Fick's laws of diffusion [1]. With n the number of electrons, F the Faraday constant, R the gas constant, T the temperature, A the surface area of the electrode, D the diffusion constant, v the scan rate and C the concentration. We can see that the peak current is dependent of the concentration and the square root of the scan rate (v) for a species in solution.

$$I_p = 0.4463 n^{3/2} F^{3/2} R^{-1/2} T^{-1/2} A D^{1/2} v^{1/2} C \quad \text{Equation 2.2}$$

The setup used for cyclic voltammetry during this PhD consisted of a three electrode setup, using a Potentiostat/Galvanostat PGSTAT 101 from Metrohm, connected with a PC provided with NOVA 1.10 software. The electrodes used are a platinum working electrode of 2 mm diameter (Metrohm, the Netherlands) or a glassy carbon working electrode of 3 mm diameter, a platinum sheet counter electrode and a bridged Ag/AgCl reference electrode with 2 M LiCl ethanol solution as inner solution and as a bridge solution 0.1 M Bu₄NBF₄ dissolved in the appropriate solvent. All potentials mentioned in the results are relative to this reference electrode unless stated otherwise. The reference electrode has a voltage difference of +150 mV versus a standard hydrogen electrode (SHE) and the voltage difference versus the ferrocene redox couple (Fc⁺/Fc) is -500 mV. The working electrode was pretreated by mechanical polishing. It was subjected to sequential polishing for 10 minutes with a cloth covered with alumina powder of 1 and 0.05 μm particle size (SPI supplies, USA). Afterwards the electrode surface was rinsed thoroughly with deionized water and cleaned in an ultrasonic bath containing deionized water for 2 minutes to remove any adherent Al₂O₃ particles. Next the electrode was rinsed with acetone and dried. Solutions of 0.1 M Bu₄NBF₄ dissolved in the appropriate solvent were freshly made and purged with nitrogen gas for 10 minutes to remove oxygen before each measurement.

2.3. Rotating disk electrode

In a rotating disk electrode setup, the working electrode (similar type as for cyclic voltammetry) is put on a rotator which makes it possible to rotate the electrode at different rotation speeds. There is connection from the electrode surface to the axis of the rotator and the electrochemical signal is passed through a sliding contact on the side of the axis to the wire that makes connection to the potentiostat.

By rotating the electrode a flow of the bulk solution is generated directly towards the surface of the electrode. A constant rotation generates a stable hydrodynamic layer at the electrode surface and generates a constant supply of new substrates that are actually sucked to the electrode surface and spread around sideways.

The Nernst-Planck equation can now be solved for this particular situation [1]. The hydrodynamic layer at the electrode remains constant for a specific rotation rate of the electrode. When the substrate is scanned over a certain potential range, at the oxidation potential of the substrate the current keeps on rising till the limiting current is achieved. Here the current remains constant for an increasing overpotential. The limiting current (I_l) is given by the Levich equation (Equation 2.3).

$$I_l = 0.620 n F A D^{2/3} \nu^{-1/6} \omega^{1/2} C \quad \text{Equation 2.3}$$

with n the number of electrons, F the Faraday constant, A surface of the electrode, D the dissociation constant, ν the kinematic viscosity of the solvent, ω the rotation rate and C the concentration. It can be observed that the limiting current is dependent on the square root of the rotation rate of the electrode. When plotting the limiting current in function of the rotation rate, fundamental information on the electrochemical reaction can be obtained for instance to calculate the diffusion coefficient.

The setup used for rotating disk measurements during this PhD is similar as the one for cyclic voltammetry with the addition of a controlled speed rotator with a liquid mercury contact from Metrohm.

2.4. Electrolysis

Electrolysis is in essence the conversion of electrical energy in chemical energy to produce or convert molecules either by oxidation or reduction reactions. An important difference with the techniques described before is the different ratio of electrode area, A , to solution volume, V . During an electrolysis one is trying to change or synthesize as much product as possible and therefore large A/V conditions are a necessity. Compared to cyclic voltammetric experiments, different electrodes are needed for this type of experiments. During this PhD a carbon electrode is used, more specific a reticulated vitreous carbon electrode (RVC). This is a similar material as glassy carbon but is constructed as a foam based material with an increased surface area (Figure 2.5).



Figure 2.5. Reticulated vitreous carbon (RVC) electrode (basi, USA).

An electrolysis experiment can be performed under controlled-current condition or under controlled-potential condition. When controlled-current is used, this means that at the start point of the experiment the level of the current is determined and is kept constant during the electrolysis. The potential of the working electrode can change during electrolysis and depends on the presence of substrates (still) available at the surface of the electrode. For a constant positive current, the working electrode will oxidize the substrate which has the lowest oxidation potential to reach the current. When the concentration of this substrate is decreased, the potential will get higher till the oxidation potential of the next substrate is reached followed by its oxidation. This will continue as long as the electrolysis takes place. An

advantage of this setup is the use of only two electrodes, without a reference electrode (if it is not important to know at which potential the working electrode is situated). This is simplifying the setup, however a control of the potential during the electrolysis is no longer possible which might cause side reactions when higher potentials are reached during the electrolysis. The alternative is to work under controlled-potential conditions in which the potential at the working electrode is determined and kept constant during the time of the electrolysis. The current is measured in function of time. In this way a much more controlled electrolysis is obtained. Less side reactions can be expected by choosing the proper potential at which the desired reaction takes place. A three electrode system is needed for this type of experiment making the design of an electrolysis cell more complicated.

Another important feature of an electrolysis experiment is the use of a divided or an undivided cell. For an undivided cell, both working and counter electrode are immersed in the same solution. When a divided cell is used, the working electrode and the counter electrode are separated from each other and can be immersed in a different solution to obtain a different electrochemical reaction at each electrode. For example, if we look at the electrochemical oxidation of alcohols using a divided cell. The starting alcohol, the formed products but also the used catalyst and mediator cannot come into contact with the cathode. In this way no unwanted process can take place at this electrode and therefore, increasing the selectivity of the system. The anode and the cathode are separated from each other with the membrane. In this way the oxidation of the alcohol with the electrochemical reoxidation of the mediator can take place in the anodic part. This will not be influenced by the reduction of protons, which is simultaneously occurring at the cathodic part of the cell. A schematic overview of a divided cell can be seen in Figure 2.6.

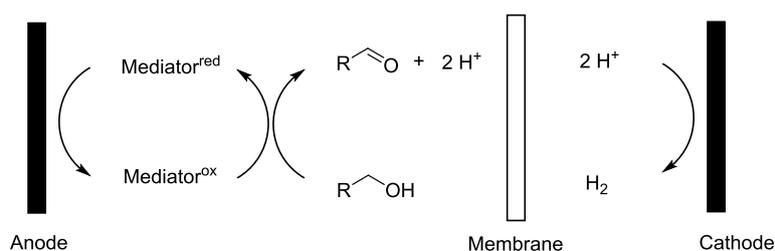


Figure 2.6. Schematic overview of a divided electrolysis cell.

Important is that both half cells have to be connected to each other, there must be good conductivity between the two half cells. The resistance over this connection cannot be too high in order to be able to apply the potential desired. This is actually determined by the compliance voltage of the potentiostat used, as mentioned before. So the two half cells have to be separated from each other but still good conductivity has to be present. To achieve this, a proper separator has to be used. Different types of separators can be used such as sintered (or fritted) glass disks, ion-exchange membranes or porous ceramics.

The setup used for electrolysis experiments during this PhD consisted of a homemade airtight electrolysis cell (Figure 2.7). The cell could be put under an inert atmosphere to exclude any interference of atmospheric oxygen. The working electrode used is a reticulated vitreous carbon (RVC) electrode (basi) with a surface area of $10.5 \text{ cm}^2/\text{cm}^3$. A bridged Ag/AgCl reference electrode with 2 M LiCl ethanol solution as inner solution and as a bridge solution 0.1 M Bu_4NBF_4 dissolved in the appropriate solvent was used. The counter electrode was a platinum rod electrode.

For both cell types, the undivided and the divided cell, experiments were conducted using this setup.

For the divided cell the counter electrode was put in a divided glass cell separated from the anodic part by a ceramic frit. In the divided part a reduction has to take place easily so that there is no overload occurring. The reduction of protons to hydrogen gas is favorable and acetic acid is added to the divided part to facilitate this reduction.

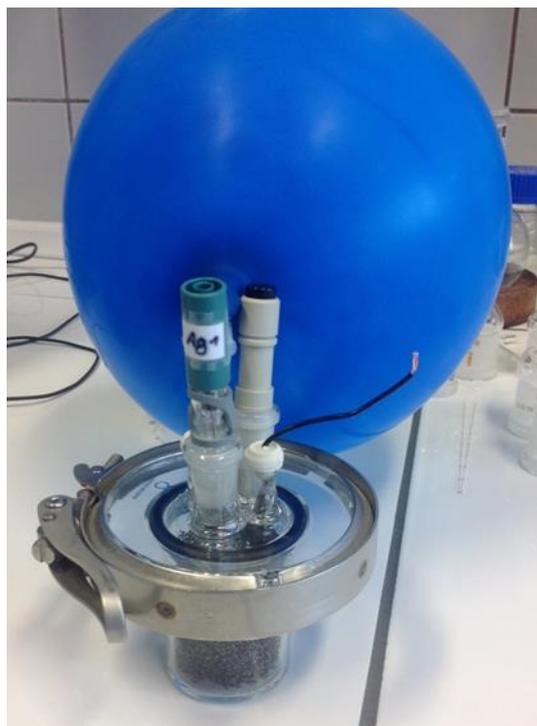


Figure 2.7. Homemade airtight electrolysis cell under argon atmosphere.

When doing electrolysis experiments, an important and rather time-consuming part is the work-up after electrolysis. During this PhD, electrolysis reactions were commonly performed in high boiling organic solvents such as *N,N*-dimethylformamide (DMF) or DMSO with an electrolyte, normally Bu_4NBF_4 . The products of interest had to be separated out of this solution. The general strategy included an extraction with ether. In this process the desired aldehydes and ketones can be separated from the mixture of water, the polar organic solvent and the electrolyte. To obtain the pure reaction products an additional purification using column chromatography was performed. Characterization of the products is achieved by using NMR.

Distillation

In a distillation it is possible to separate volatile products from the less volatile products. The reaction vessel is heated till a temperature high enough to evaporate the products of interest and leaving the other molecules behind in the flask. The mixture is separated by selective evaporation followed by condensation.

This approach was followed for the oxidation of butanol to butanal with the aid of the TPAP catalyst. Butanol, butanal and acetonitrile (the solvent) can be distilled from the electrolyte

and catalysts used. In this way, the ratio alcohol / aldehyde formed during the electrolysis could be monitored. Drawback of this method is the fact that non-volatile products are not separated from the electrolyte.

Extraction

During an extraction an organic layer and an aqueous layer are well mixed together. Next, the flask is put down to rest and the two layers are separated from each other with the organic products dissolved in the organic layer and the more polar products dissolved in the aqueous layer.

This was the standard separation technique used after each electrolysis with DMF or DMSO, as these solvent have a high boiling temperature. To separate the organic products such as the starting alcohol and carbonyl compounds formed, an extraction was performed. Water has been added to the reaction mixture and extracted with *tert*-butylmethylether. The compounds of interest are obtained in the organic ether layer.

Column chromatography

To purify the products obtained by extraction and to obtain the isolated products, it was necessary to perform column chromatography. In this procedure a column of silica gel was used and the mixture of products was separated by running through the column with a heptane/ ethylacetate mixture as eluent. After this procedure, a separation of alcohol and ketone was possible and all other impurities were removed. The result of this procedure has led to a pure compound.

2.5. References

- [1] A. J. Bard, L. R. Faulkner, *Electrochemical Methods: Fundamentals and Applications*, 2nd Edition, Wiley, **2001**

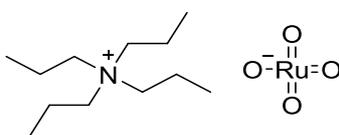
Chapter 3

The electrochemistry of tetrapropylammonium perruthenate

Based on: J. Lybaert, B.U.W. Maes, K. Abbaspour Tehrani and K. De Wael, The electrochemistry of tetrapropylammonium perruthenate, its role in the oxidation of primary alcohols and its potential for electrochemical recycling, *Electrochimica Acta* **2015**, 182, 693-698

3.1. Introduction

In organic chemistry, perruthenate anion is traditionally used for the selective conversion of alcohols into aldehydes. The synthesis of the tetrapropylammonium salt of the anion (tetrapropylammonium perruthenate; TPAP) by Ley and coworkers made it soluble in organic solvents and available for oxidation reactions (Scheme 3.1) [1]. It did become a popular reagent as it combines some desirable properties, namely air stability, commercial availability, performance at room temperature and high chemoselectivity.



Scheme 3.1. Tetrapropylammonium perruthenate.

As ruthenium is a rather expensive transition metal and in the strive towards more sustainability, catalytic oxidation methods have been developed using catalytic amounts of TPAP in combination with *N*-methyilmorpholine *N*-oxide (NMO) as a stoichiometric oxidant [2]. Commonly, dichloromethane or acetonitrile or a combination of these two solvents is used with the addition of powdered 4 Å molecular sieves to remove water formed during the reaction. Recent advances with the TPAP/NMO method has made the oxidation of primary alcohols to carboxylic acids possible [3]. Here 10 equivalents of NMO are added, the excess of NMO facilitates the formation of an aldehyde hydrate, which is a necessary step in the controlled oxidation of aldehydes to carboxylic acids.

Within the same search for more environmentally friendly methods, it has been found that oxygen as well can be used as a stoichiometric oxidant to oxidize alcohols in combination with catalytic amounts of TPAP [4,5]. Furthermore, it has been shown that TPAP can be used as a heterogeneous catalyst with NMO or oxygen as a stoichiometric oxidant. Most of the suggested approaches consist of an ionic bond between the perruthenate anion and a heterogeneous quaternary ammonium cation, for example the polystyrene supported perruthenate [6], the mesoporous silicate MCM-41 with immobilized perruthenate [7] or the alkyl-imidazolium-based periodic mesoporous organosilica with supported perruthenate [8]. Finally, a sol-gel encapsulated TPAP [9] strategy is also reported.

Despite the fact that the perruthenate anion is an important catalyst in organic synthesis, its electrochemical behavior in organic solvents has never been studied before. A study of the catalyst in joint reaction with the oxidation of alcohols might be interesting to see if strategies can be found to make electrochemical recycling of the oxidant possible.

The perruthenate anion (RuO_4^-) is the active part of TPAP and the formal oxidation state of ruthenium in the perruthenate anion is +7 (Ru^{VII}). This anion has already been studied electrochemically in water but without taking into account the presence of alcohols [10]. In this study, different ruthenium-oxy species were observed: ruthenium tetroxide (RuO_4), the ruthenate anion (RuO_4^{2-}) and ruthenium oxide (RuO_2), with an oxidation state of respectively +8 (Ru^{VIII}), +6 (Ru^{VI}) and +4 (Ru^{IV}). A few methods have already been developed, making use of the electrochemical recycling of ruthenium-oxy species for the catalytic oxidation of alcohols, but all focusing on RuO_2 as mentioned before.

In this chapter, the results of an in-depth investigation of the electrochemical behavior of the perruthenate anion in a non-aqueous neutral solvent are presented. Additionally, the oxidation reaction of *n*-butanol in the presence of TPAP has been electrochemically elucidated by performing potentiostatic experiments and by recycling of the spent catalyst under mild conditions.

3.2. Results and discussion

3.2.1. Electrochemical screening of TPAP

An electrochemical study of TPAP in a non-aqueous solvent has been performed by using cyclic voltammetry. The use of both dichloromethane and acetonitrile were tested because these are the solvents used for a classical TPAP/NMO oxidation. Dichloromethane was found not to be useful to perform cyclic voltammetry on TPAP as no reproducible redox reactions could be obtained. The redox processes observed are not stable as a function of scan number.

On the other hand, the use of acetonitrile was successful and reproducible peaks could be obtained. The metal coordinating properties of acetonitrile could probably account for this different behavior [11]. Other advantages of acetonitrile are its higher conductivity and higher

boiling point, so less evaporation occurs under a nitrogen flow. Figure 3.1 represents the current-potential behavior of 1 mM TPAP in acetonitrile with 0.1 M Bu_4NBF_4 as electrolyte and with a scan rate of 100 mVs^{-1} . A scan of the platinum electrode in a solution of acetonitrile without TPAP is also shown and in this case no redox processes are observed. In the presence of TPAP four different redox processes can be distinguished. At ca. 0.9 V a first anodic peak I_a can be observed, upon reversal of the scan direction a cathodic peak I_c appears around 0.85 V. Towards more negative potentials a new cathodic process II_c is observed around -1.0 V and upon reversal an anodic wave II_a is detected around -0.5 V.

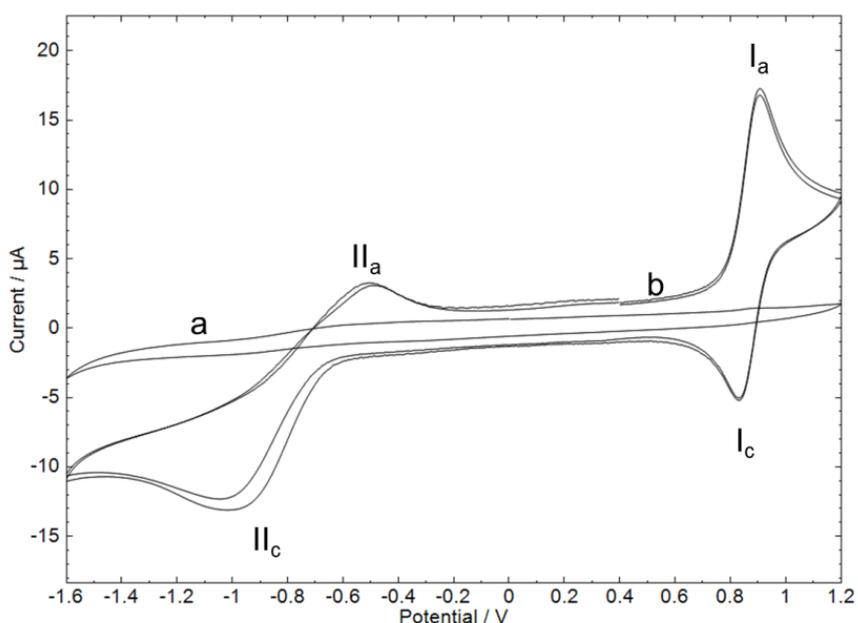


Figure 3.1. Cyclic voltammograms obtained at a Pt electrode in a 0.1 M Bu_4NBF_4 acetonitrile solution (a) containing 1 mM TPAP (scans 2 and 5) (b) with a scan rate of 100 mVs^{-1} .

In order to investigate the nature and the reversibility of the redox couple I, the dependency of the peak currents of I_a and I_c on the scan rate is investigated (Figure 3.2).

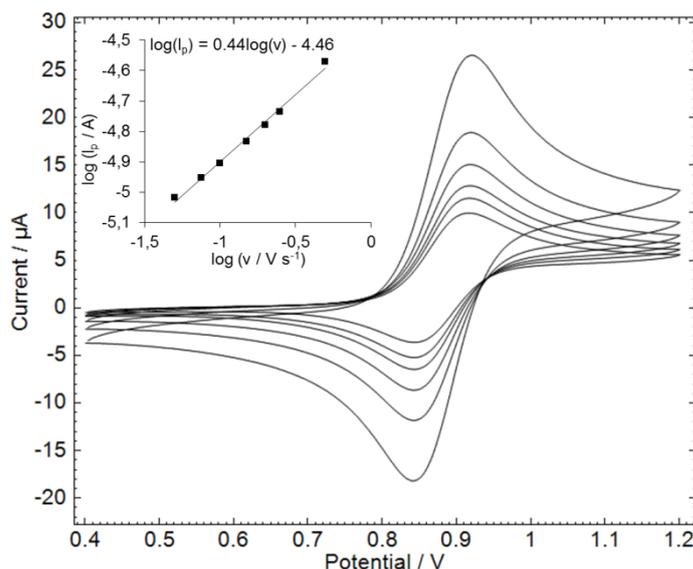


Figure 3.2. Cyclic voltammograms of 1 mM TPAP in 0.1 M Bu₄NBF₄ acetonitrile solution at a Pt electrode with different scan rates: 50; 75; 100; 150; 250 and 500 mVs⁻¹. Inset: log I_p versus log v.

A linear relationship was found between the peak current (I_p) and the square root of the scan rate (v). A slope of circa 0.5 was found between $\log I_p$ and $\log v$, the inset of Figure 3.2 represents this relationship for I_a , following the Randles–Sevcik formula. Additionally, it was observed that the peak potential (E_p) remains constant for different scan rates. These results correspond to a reversible diffusion controlled reaction of TPAP [12]. The value for $E_{p,1/2}$, i.e. 0.85 V, agrees well with the potential obtained by Lam et al. for the transition between RuO₄⁻ and RuO₄ in a NaOH solution [10].

To calculate the number of electrons taking part in the redox process, the difference between E_p and the half-peak potential ($E_{p,1/2}$) was calculated, theoretically this value should be 56.5 mV divided by the amount of electrons involved [12]. A calculated value of 59.2 mV indicates a reversible one-electron process. Therefore, it is clear that the reversible peaks of process I are caused by the transition between RuO₄⁻ and RuO₄ (Equation 3.1).



To determine the diffusion coefficient of the perruthenate anion, cyclic voltammetry experiments using a rotating disk were performed (Figure 3.3).

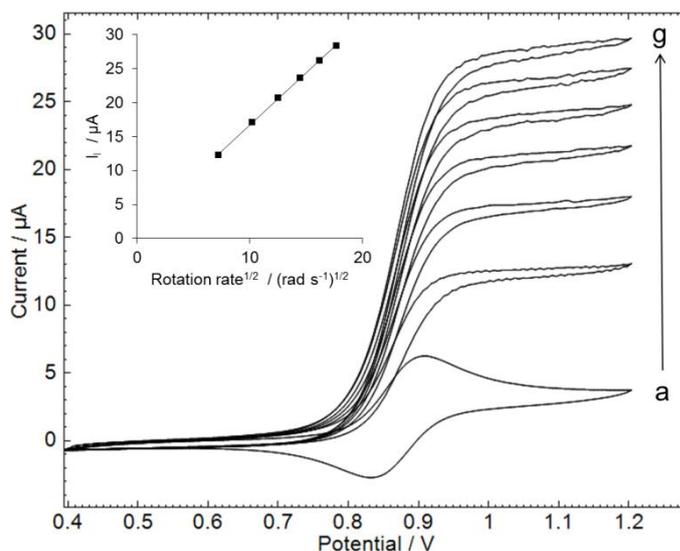


Figure 3.3. Cyclic voltammograms of 0.5 mM TPAP in a 0.1 M Bu_4NBF_4 acetonitrile solution at a Pt electrode with different rotation speeds: 0 (a); 500 (b); 1000 (c); 1500 (d); 2000 (e); 2500 (f) and 3000 (g) rpm. Inset: I_l versus $(\omega)^{1/2}$.

A linear relationship between the square root of the rotation speed (ω) and the limiting current (I_l) is observed, confirming that the $\text{Ru}^{\text{VII}}/\text{Ru}^{\text{VIII}}$ transition is mass-transfer controlled. To the best of our knowledge, for the first time the diffusion coefficient of the perruthenate anion could be experimentally obtained by using the Levich equation [12], giving a calculated diffusion coefficient $D = 1.72 \cdot 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

When focusing on II_c (see Figure 3.1) the reduction of the perruthenate anion is examined. No reversible peaks are detected but instead a broad reduction process is observed. Most likely the reduction of RuO_4^- to RuO_2 is occurring here. RuO_2 is not soluble in acetonitrile and, during our experiments, a layer was deposited on the electrode surface, especially when multiple scans were taken or when a rotating disk electrode was used. Similar observations were made by using glassy carbon electrodes.

To identify the product formed, the deposits on the electrode surface were further electrochemically investigated by entrapping the deposit in a thin nafion film. The modified electrode was scanned in a 0.5 M NaOH solution and a similar redox behavior was observed

as for commercial $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ (with protective nafion film) deposited on an electrode surface (Figure 4).

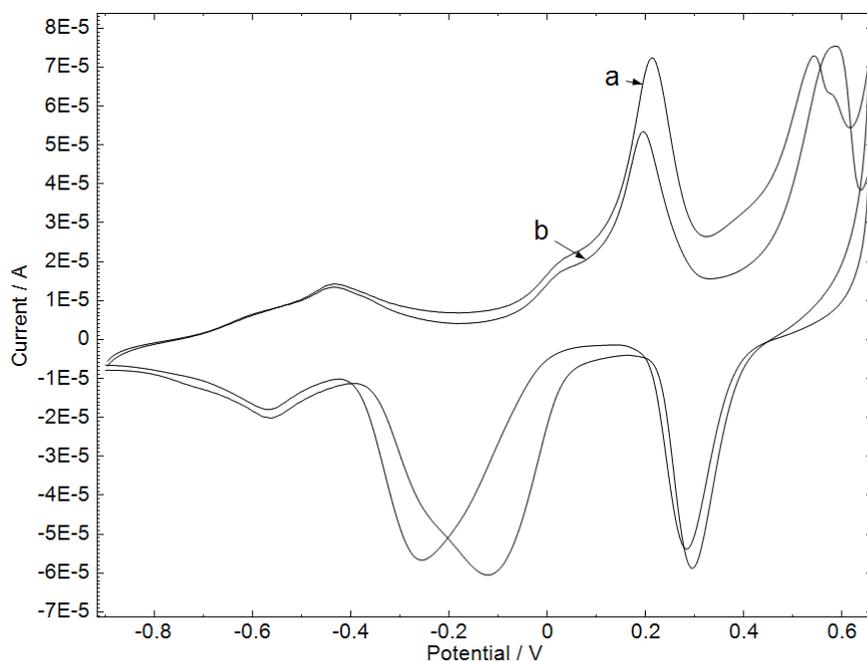


Figure 3.4. Cyclic voltammograms with a scan rate of 100 mVs^{-1} obtained in a 0.5 M NaOH solution versus a standard calomel electrode of a covered glassy carbon working electrode, **a:** working electrode obtained, after cycling 20 scans in a 1 mM TPAP electrolyte solution between 0.0 V and -1.5 V , covered by $2.5 \mu\text{L}$ of a 1 wt \% Nafion ionomer solution; **b:** commercial $\text{RuO}_2 \cdot x\text{H}_2\text{O}$, 10 mg of $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ was dispersed in 5 mL of distilled water and subjected to ultrasonification for 15 minutes. Next $5 \mu\text{L}$ of this dispersion was put on freshly polished working electrode and dried. Next the electrodes were covered by $2.5 \mu\text{L}$ of a 1 wt \% Nafion ionomer solution.

Additionally, the modified electrodes (both with unknown deposit and with commercial $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ as deposit) were also tested in a $0.5 \text{ M H}_2\text{SO}_4$ solution, here a broad peak around 0.4 V versus standard calomel electrode was detected (Figure 3.5) unraveling the redox chemistry of RuO_2 [13].

These results indicate the formation of ruthenium oxide or a mixture with hydrous ruthenium oxides during the potential cycling in TPAP. It is clear that the presence of Ru^{6+} and Ru^{5+} could not be electrochemically identified.

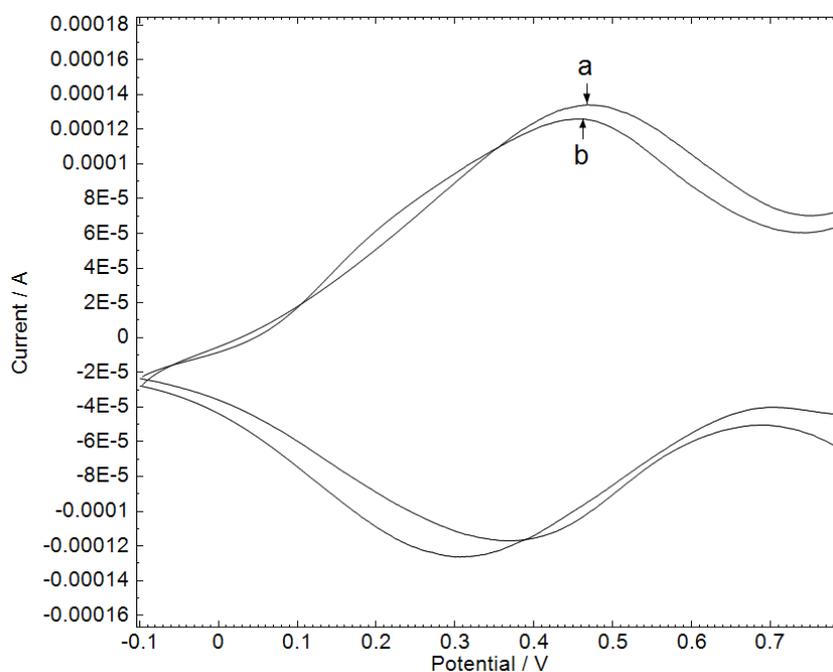


Figure 3.5. Cyclic voltammograms with a scan rate of 100 mVs^{-1} obtained in a $0.5 \text{ M H}_2\text{SO}_4$ solution versus a standard calomel electrode of a covered glassy carbon working electrode, **a:** working electrode obtained, after cycling 20 scans in a 1 mM TPAP electrolyte solution between 0.0 V and -1.5 V , covered by $2.5 \mu\text{L}$ of a $1 \text{ wt } \%$ Nafion ionomer solution; **b:** commercial $\text{RuO}_2 \cdot x\text{H}_2\text{O}$, 10 mg of $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ was dispersed in 5 mL of distilled water and subjected to ultrasonication for 15 minutes . Next $5 \mu\text{L}$ of this dispersion was put on freshly polished working electrode and dried. Next the electrodes were covered by $2.5 \mu\text{L}$ of a $1 \text{ wt } \%$ Nafion ionomer solution.

3.2.2. Alcohol oxidation by TPAP

Initially cyclic voltammetry was used to observe the effect of adding *n*-butanol to a TPAP solution. Not unexpectedly, when doing multiple scans, the formation of a solid on the electrode hampered the analysis. The mechanism of the stoichiometric reaction between

TPAP and alcohol (no electrolysis) has been studied before in organic solvents [14,15] and inspired by these investigations we propose the following mechanism:



The perruthenate anion is a two-electron oxidant and oxidizes *n*-butanol to *n*-butanal. The reduction proceeds in multiple steps and the final reduced ruthenium species is RuO₂. The formation of RuO₂ indeed was confirmed by UV-VIS (vide infra).

To investigate this mechanism and to see what are the possibilities for recycling the perruthenate ions or other catalytic ruthenium species during the oxidation of the alcohol, potentiostatic experiments were performed. These experiments were done with a platinum rotating disk electrode under constant potential to record the current as a function of time (Figure 3.6). The potential applied can have an effect on the different ruthenium intermediates mentioned in the mechanism above. The potential was set at 0.7 V, because the formation of RuO₄ does not yet occur at this potential as can be seen from the cyclic voltammetry scans (Figure 3.1). In the case when only *n*-butanol is added to the electrolyte solution (Figure 3.6, curve a), no direct oxidation is expected and indeed no faradaic oxidation current can be observed. When only TPAP is added to the electrolyte solution (Figure 3.6, curve b), a similar phenomenon occurs, and almost no faradaic oxidation current can be witnessed. When both TPAP and *n*-butanol are added (Figure 3.6, curve c), a steep rise of the current is detected. In this experiment the reagents are added step by step, first TPAP is added after 150 seconds and in a next step, after 370 seconds, *n*-butanol is added resulting in an increase of the current.

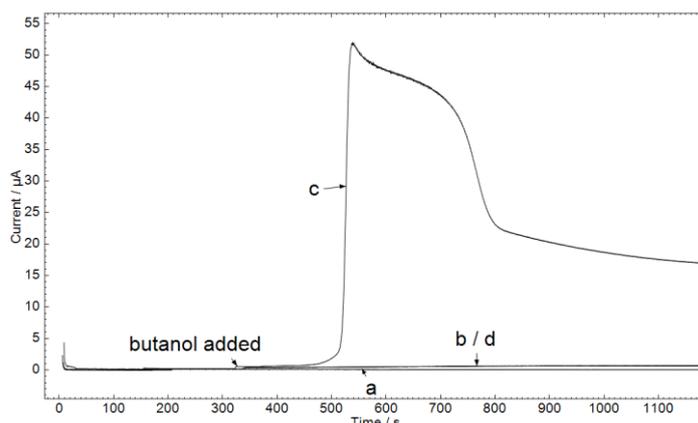


Figure 3.6. Oxidation current response of different species under potentiostatic conditions at 0.7 V with rotating disk Pt electrode (2000 rpm), 20 mM *n*-butanol in an electrolyte solution (a); 2 mM TPAP in an electrolyte solution (b); 20 mM *n*-butanol + 2 mM TPAP in an electrolyte solution (c) and 20 mM *tert*-butanol + 2 mM TPAP in an electrolyte solution (d).

This rise of the current is a clear evidence that now reoxidation of the spent TPAP is occurring. Unfortunately the exact nature of the species generated at the electrode surface cannot be determined within this set of experiments. As a control experiment *tert*-butanol was added to a TPAP solution under potentiostatic conditions following the same procedure (Figure 3.6, curve d). *Tert*-butanol cannot be oxidized by TPAP and so no reoxidation of spent TPAP is expected at the electrode surface. Although *tert*-butanol cannot be oxidized by TPAP, the formation of a complex where *tert*-butanol acts as a ligand is possible. From Figure 3.6 it is clear that indeed no rise of the current is observed. This observation rules out that the current rise is caused by the oxidation of this complex.

It is also observed from Figure 3.6 that the oxidation current drops after ca 300 seconds. The reason for this is unclear at the moment but the formation of a deposit on the electrode (such as RuO₂) and the formation of inert catalyst species might be the cause. The formation of RuO₂ in solution could be confirmed by UV-VIS measurements [15] after the potentiostatic experiment (Figure 3.7). When using a glassy carbon working electrode similar results as in Figure 3.6 could be observed. No different behavior could be seen when varying the electrode material.

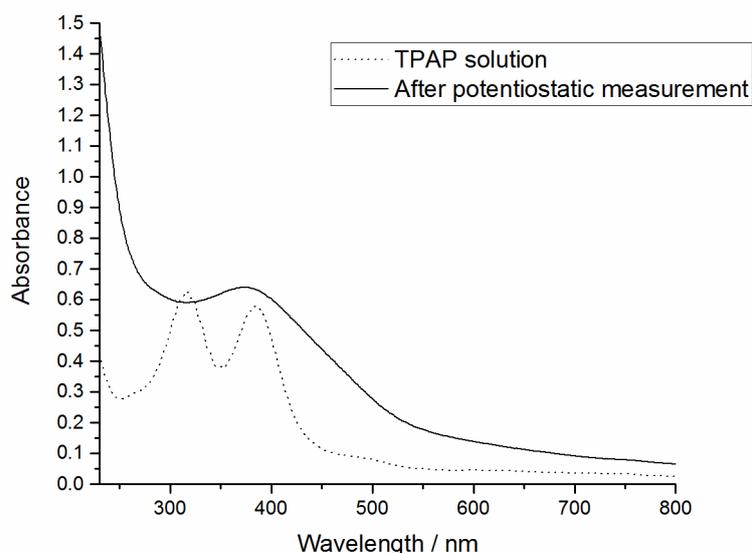


Figure 3.7. UV-VIS spectra of a 2 mM *n*-butanol + 0.2 mM TPAP + 0.01 M Bu₄NBF₄ acetonitrile solution after potentiostatic experiment at 0.7 V (solid line); of a 0.2 mM TPAP + 0.01 M Bu₄NBF₄ acetonitrile solution (dotted line).

Also the formation of the deposit on the electrode could be visible seen. During a potentiostatic experiment of a 20 mM *n*-butanol + 2 mM TPAP in an electrolyte solution with a Pt rotating (2000 rpm) disk electrode, the measurement was paused at different times and the working electrode removed from the solution. The electrode was cleaned, put back in the solution and the measurement was continued (Figure 3.8). After each cleaning a rise of the current could be observed but immediately followed by a decrease again.

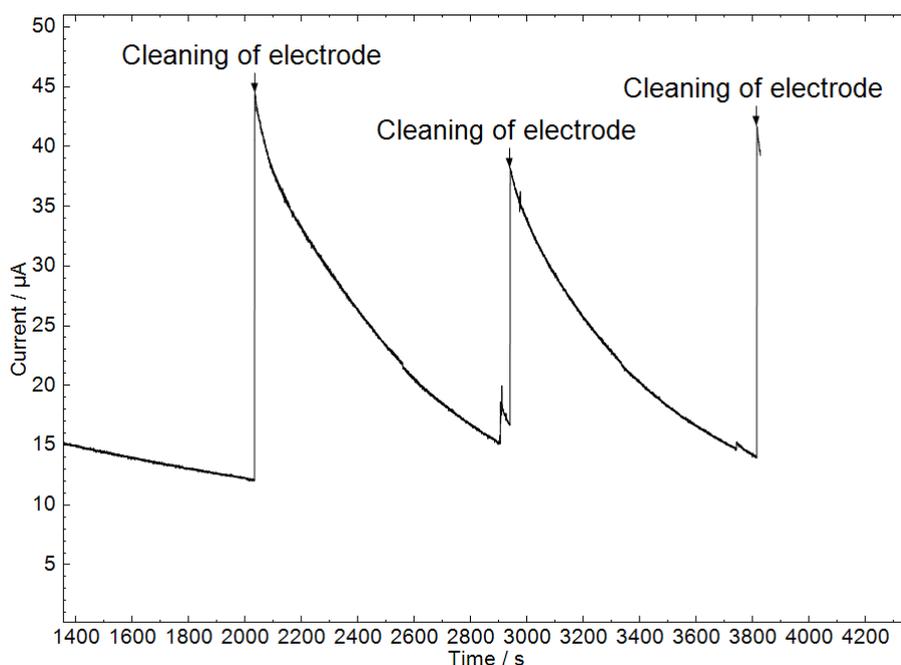


Figure 3.8. Oxidation current response under potentiostatic conditions at 0.7 V of a 20 mM *n*-butanol + 2 mM TPAP in an electrolyte solution with a rotating (2000 rpm) Pt disk electrode which was cleaned at the positions mentioned in the figure.

Next the influence of applying higher potentials on the oxidation current is examined by following the same stepwise procedure. At potentials higher than 0.8 V, the perruthenate anion is oxidized at the electrode surface with formation of ruthenium tetroxide. In Figure 3.9 the potentiostatic response of TPAP at 1.1 V and the addition of *n*-butanol are shown. In this experiment TPAP was added after 180 seconds (Figure 3.9, a), then rotation was initiated at 300 seconds (Figure 3.9, b). The current increase observed is caused by the oxidation of the perruthenate anion to ruthenium tetroxide. Around 330 seconds, *n*-butanol is added to the solution (Figure 3.9, c), followed by a drop of the current which is caused by the reaction of perruthenate with *n*-butanol in the bulk solution. Although the RuO_4 , produced in the previous step, is also able to oxidize *n*-butanol [11], its influence is negligible because of the very low concentration compared to the bulk concentration of perruthenate. The concentration of the perruthenate at the electrode surface is decreasing as it is consumed by the alcohol. This is followed by a new rise of the current, caused by reoxidation of the spent TPAP. The current is then at a similar level as with a potential of 0.7 V. This indicates that a higher potential does not have a large influence on the reoxidation of the spent TPAP.

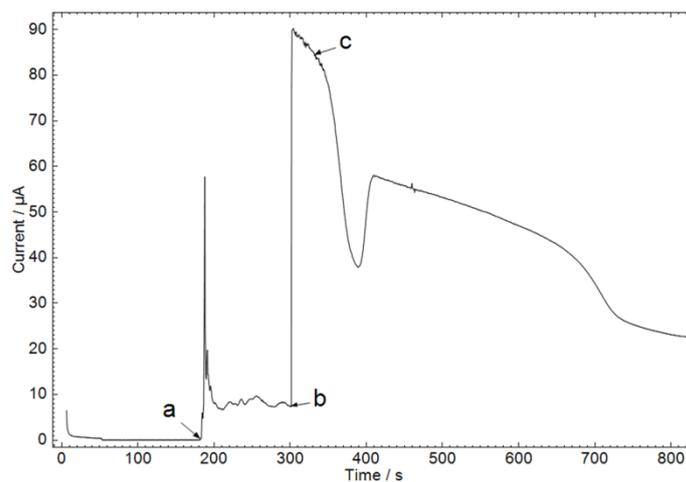


Figure 3.9. Oxidation current response at 1.1 V under potentiostatic conditions with rotating disk Pt electrode: after 180 s 2 mM TPAP is added to the electrolyte/acetonitrile solution (a), rotation (2000 rpm) is initiated after 300 s (b) and 20 mM *n*-butanol is added (c).

To get an overview of the potentiostatic response at different potentials, experiments were performed over a broad potential range. In Figure 3.10 the potentiostatic response for TPAP and *n*-butanol is shown at different potentials. The time of *n*-butanol addition is set at 0 s. Consequently, at 0 s, 2 mM TPAP, 20 mM *n*-butanol and 0.1 M electrolyte are present in the acetonitrile solution (under constant rotation).

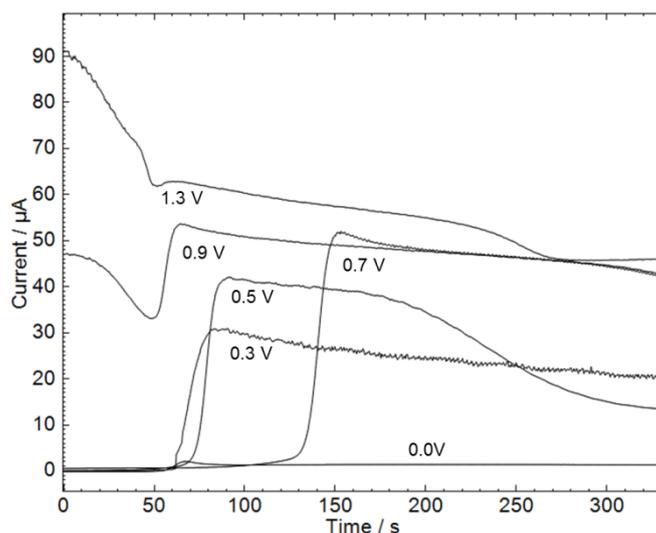


Figure 3.10. Oxidation current response at different potentials for 2 mM TPAP + 20 mM *n*-butanol added at 0 s in an electrolyte solution with rotating disk Pt electrode at 2000 rpm.

When applying a potential below 0.8 V, it is clear that initially no oxidation current is observed at 0 s as no oxidation reaction of TPAP might occur (Figure 3.10). When raising the potential from 0.3 to 0.5 and 0.7 V, a gradual rise in the current height can be detected. When looking at higher potentials than 0.8 V, an oxidation current (Ru^{VI} to Ru^{VIII}) is present from the start onwards. Due to *n*-butanol oxidation with TPAP, a decrease of the current is detected until a steady state situation is reached. The value for this steady state current is similar to the value obtained in the 0.7 V experiment. It can be concluded that a potential of 0.7 V is sufficient to reoxidize the spent TPAP. No significant influence of oxidation to Ru^{VIII} at higher potentials is observed.

3.2.3. Electrolysis experiments with *n*-butanol

For the oxidation of *n*-butanol on a larger scale, an airtight homemade electrolysis cell was used with a reticulated vitreous carbon (RVC) working electrode, which has a high surface area. The cell was placed under an inert argon atmosphere to exclude the interference of atmospheric oxygen. A constant potential was applied of 0.7 V or 1.3 V to a solution of *n*-butanol and TPAP in electrolyte solution for 5 hours. Next, the resulting mixture was distilled to obtain a solution of the volatile reaction products and remaining starting alcohol in acetonitrile. This distillate was analyzed by means of GC-MS and separated peaks of *n*-butanol and *n*-butanal were detected. In case no potential was applied a 5/95 ratio of butanal/butanol was observed, while at 1.3 V this ratio changed in favour of butanal (34/66 : butanal/butanol). Obviously, when no potential is applied, only the stoichiometric oxidation of *n*-butanol can take place, using the 0.1 equivalents of TPAP present and giving rise to a maximum of 10% conversion of *n*-butanol (Figure 3.11).

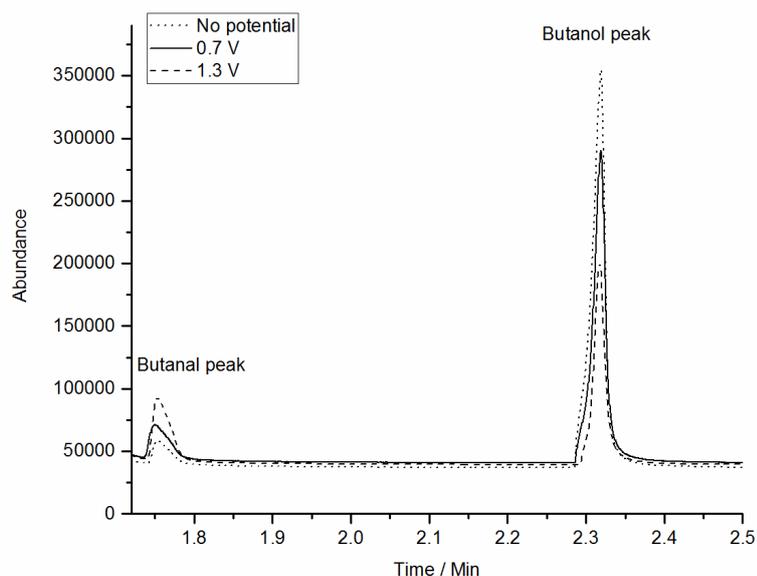


Figure 3.11. GC-MS of the distillate obtained after electrolysis of a 0.1 M Bu_4NBF_4 acetonitrile solution with 2 mM TPAP and 20 mM of *n*-butanol under nitrogen atmosphere.

The highest conversion of *n*-butanol into *n*-butanal was obtained by applying a potential of 1.3 V, indicating that on a larger scale the electrosynthesis benefits from these higher oxidation potential values. At this higher potential the conversion of *n*-butanol increased from 5 % to 34%, which shows that reoxidation of the spent TPAP is possible and is able to further oxidize the alcohol.

3.2.4. Electrolysis experiments with benzyl alcohol

After the first positive results with the butanol oxidations, we expanded our scope and started to investigate the oxidation of benzyl alcohol (1). With this alcohol it would be easier to separate and quantify how much yield is obtained. In this way the optimization of the electrolysis could be performed and it is investigated if a practical oxidation method could be obtained.

When a constant potential was applied this was not sufficient to oxidize all the alcohol present, the main product detected was still the alcohol (Table 3.1, Entry 1) although the current was dropped and no extra oxidation was happening.

Inspired by the approach of Torii et al. [16] we tried a different potential profile and started with a switching potential, where the potential is switched between 1.3 V and -0.55 V. This switching of potential is designed to remove any deposits formed on the electrode surface. The formation of these deposits was already seen during the potentiostatic experiments as mentioned before. By applying a different potential the surface can be cleaned in an electrochemical way.

When this switching of potentials is applied it is immediately clear that the current obtained remains higher during a longer time (Figure 3.12). Now a longer electrolysis time can now be applied and still oxidation of the alcohols can be obtained.

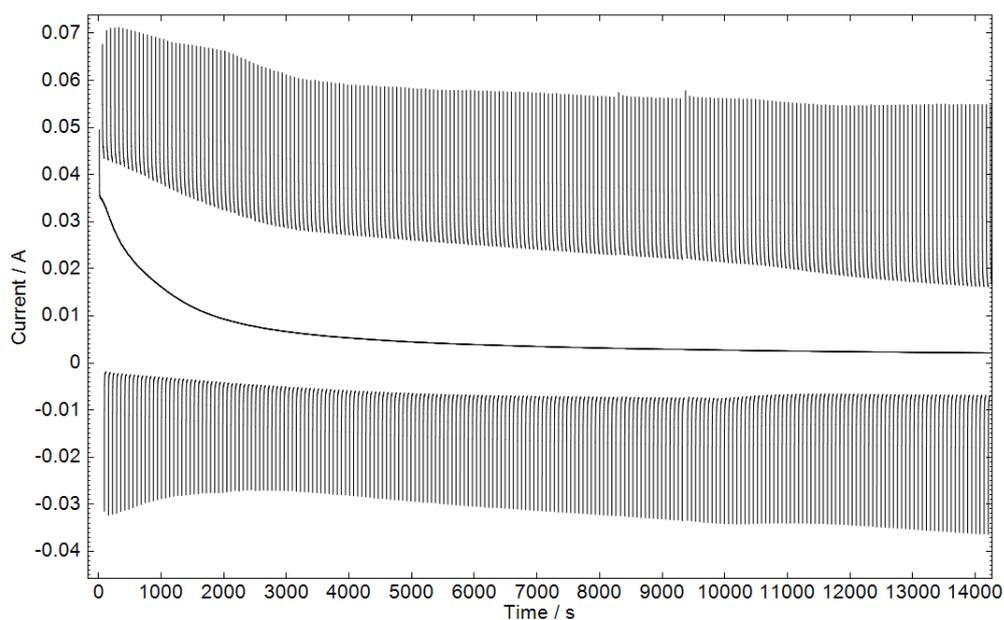
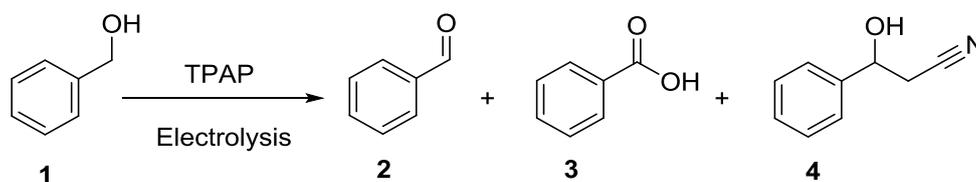


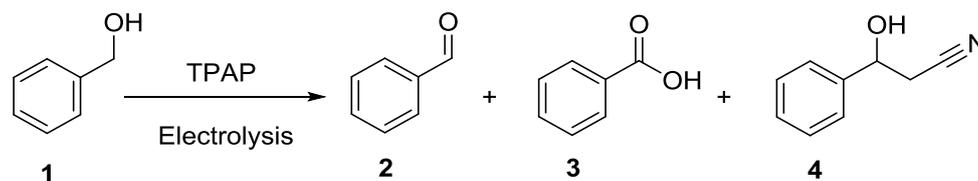
Figure 3.12. Electrolysis, comparison constant potential and switching potential. Current versus Time for electrolysis reaction with the following conditions: 1 mmol benzyl alcohol with 0.06 equivalents of TPAP in 14 mL CH₃CN with 0.1 M Bu₄NBF₄ at room temperature and constant potential of 1.3 V or switching potential of 1.3 V and -0.55 V.

From Table 3.1 it is clear that longer electrolysis time is necessary to obtain a full conversion of the alcohol (Table 3.1, Entry 2 + 3). After work up different products could be detected, the expected benzaldehyde (2) but also the further oxidation to benzoic acid (3) and surprisingly the addition product between acetonitrile and benzaldehyde namely 3-hydroxy-3-phenylpropionitrile (4). It is also clear that although full reaction of the alcohol is achieved, the yield of the different products detected is quite low and do not fully explain what has happened with the starting product.



Scheme 3.2. Products detected after benzyl alcohol oxidation. Reaction conditions: 1 mmol benzyl alcohol with 0.06 equivalents of TPAP in 14 mL CH₃CN with 0.1 M Bu₄NBF₄ at room temperature and switching potential of 1.3 V and -0.55 V.

To improve the yield and the conversion to the aldehyde or acid it was reasoned that the addition of a base could be beneficial so a reaction was performed with the addition of potassium carbonate (Table 3.1, Entry 4). Remarkably a higher yield of the benzoic acid was detected but remains still relatively low. It was reasoned that the addition of some water (Table 3.1, Entry 5) could benefit the formation of the acid since for the oxidation of the aldehyde to the acid the formation of an aldehyde hydrate is necessary. This was not beneficial for the reaction, even more when 1 mL of water was added to the reaction mixture the conversion of the alcohol was lower and no full conversion of the alcohol could be detected (Table 3.1, Entry 6). Probably the addition of too much water is harmful for the catalyst and leads to its loss of reactivity.

Table 3.1. Oxidation of benzyl alcohol with electrochemical regeneration of the TPAP catalyst.

Entry ^a	Potential [V]	Time [h]	Yield 2 [%] ^b	Yield 3 [%] ^b	Yield 4 [%] ^b	Conversion [%] ^b
1	1.3	5	6	3	16	38
2	1.3 and -0.55	5	12	2	13	44
3	1.3 and -0.55	49	2	9	3	100
4 ^c	1.3 and -0.55	49	1	19	5	100
5 ^d	1.3 and -0.55	50	2	14	2	100
6 ^e	1.3 and -0.55	51	11	8	2	66

^a) Reaction conditions: 1 mmol benzyl alcohol with 0.06 equivalents of TPAP in 14 mL CH₃CN with 0.1 M Bu₄NBF₄ at room temperature.

^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^c) With addition of 4 equivalents of K₂CO₃.

^d) With addition of 4 equivalents of K₂CO₃ and 4 equivalents of H₂O.

^e) With addition of 4 equivalents of K₂CO₃ and 1 ml of H₂O.

As the formation of 3-hydroxy-3-phenylpropionitrile, the addition product of acetonitrile and benzaldehyde, is the main side product detected the use of other solvents was tested. Dichloromethane (DCM) (Table 3.2, Entry 2), *N,N*-dimethylformamide (DMF) (Table 3.2, Entry 3) and tetrahydrofuran (THF) (Table 3.2, Entry 4) were all tried, but with all the solvents used no full conversion of benzyl alcohol was detected. Another effort was made with an ionic liquid namely 1-Butyl-3-methylimidazolium tetrafluoroborate (BMIMBF₄), the use of ionic liquids is beneficial in sustainable electrochemistry. These are molten salts, so they have a high conductivity necessary for electrochemistry unlike organic solvents where the addition of an electrolyte is always necessary. Another general property is their high boiling point, which improves the safety as no vapors of unhealthy chemicals can be spread when using it as a solvent. Unfortunately also with the use of the ionic liquid no full conversion of the alcohol

could be detected (Table 3.2, Entry 5). Acetonitrile was found as the most active solvent for the electrochemical of benzyl alcohol with recycling of TPAP as a catalyst.

Table 3.2. Oxidation of benzyl alcohol with electrochemical regeneration of the TPAP catalyst in different solvents.

Entry	Time [h]	Yield 2 [%] ^b	Yield 3 [%] ^b	Yield 4 [%] ^b	Conversion [%] ^b	
1	49	2	9	3	100	CH ₃ CN
2	24	6	0	0	53	DCM
3	43	7	1	0	73	DMF
4	23	6	3	0	46	THF
5 ^c	48	2	2	0	38	BMIMBF ₄

^a) Reaction conditions: 1 mmol benzyl alcohol with 0.06 equivalents of TPAP in 14 mL solvent with 0.1 M Bu₄NBF₄ at room temperature with a switching potential between 1.3 V and -0.55 V.

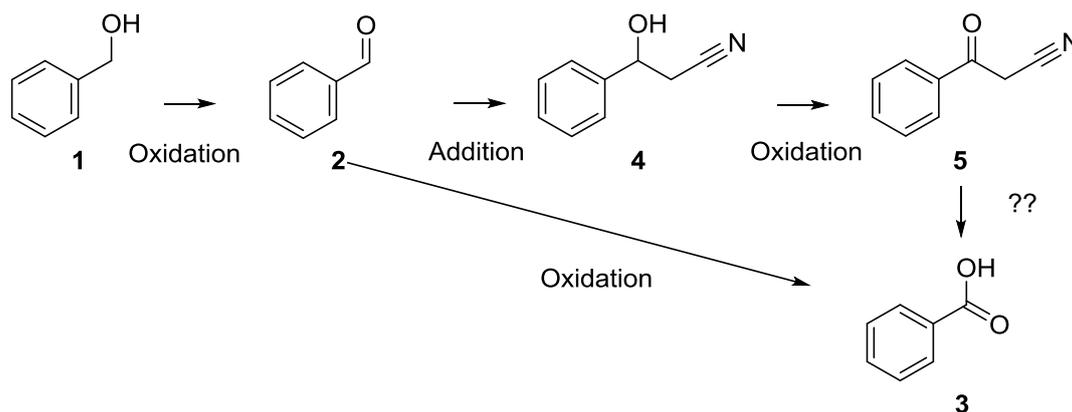
^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^c) Without the addition of 0.1 M Bu₄NBF₄.

Further research was conducted to see what causes the formation of 4 and what is the stability of this product under the circumstances used. It might be possible that further oxidation of the alcohol functionality to benzoylacetone (5) can occur under the reaction conditions used. An experiment was performed using 3-hydroxy-3-phenylpropionitrile as starting material in electrolysis with TPAP as catalyst. Current was detected, so the product seems to be active under the reaction conditions used and to our surprise after reaction no oxidation product (5) could be detected. Some starting material was recovered and also benzoic acid was detected. Next benzoylacetone was tested under the reaction conditions used and a direct oxidation of the product was detected without the addition of TPAP. Benzoic acid was the only product detected after electrolysis but only in relative low yield. Also benzoic acid was tested under the same circumstances, no current was detected and the acid was mostly recovered unchanged after the electrolysis. As expected, benzoic acid is not active under the circumstances.

After these sets of experiments we have determined a possible route that can partially explain the relatively low yield obtained during the electrolysis experiments. First the alcohol gets

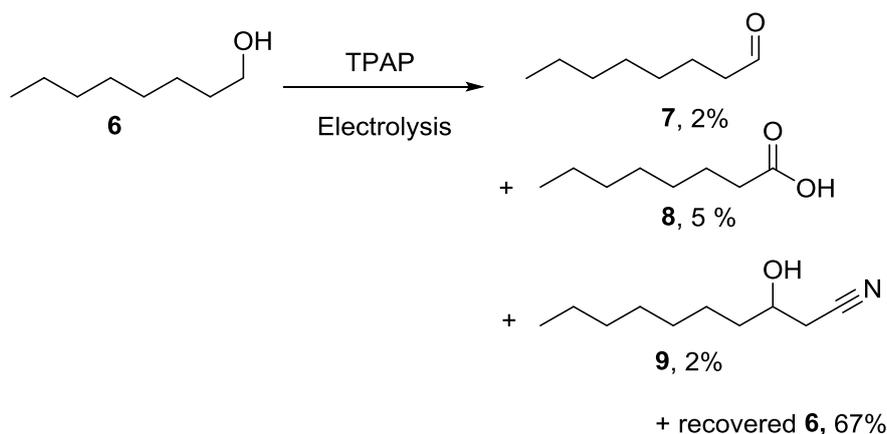
oxidized to benzaldehyde followed by the addition of acetonitrile. Next, this addition product can also be oxidized but the benzoylacetonitrile formed here is not stable at the potentials used and is partially oxidized to benzoic acid with the formation of some other unidentified products or polymers. This partially explains the low yield of products detected and the formation of benzoic acid under the circumstances necessary to electrochemically recycle TPAP for the oxidation of benzyl alcohol.



Scheme 3.3. Degradation during electrolysis of benzyl alcohol.

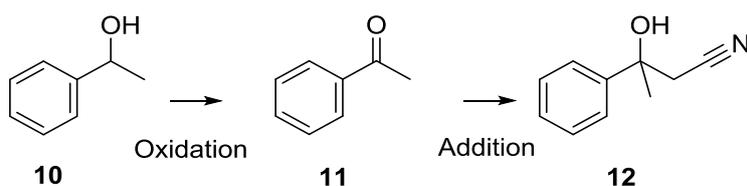
3.2.5. Electrolysis experiments with other alcohols

Also an aliphatic primary alcohol, namely 1-octanol (**6**) was tested using the same reaction conditions but this alcohol seemed less reactive and unaffected alcohol was the main product detected after work up. The reaction products detected were 1-octanal (**7**), octanoic acid (**8**) and the addition product with acetonitrile 3-hydroxydecanenitrile (**9**). So 1-octanol is less reactive but similar reaction products as with benzyl alcohol could be found.



Scheme 3.4. Electrolysis experiment with 1-octanol.

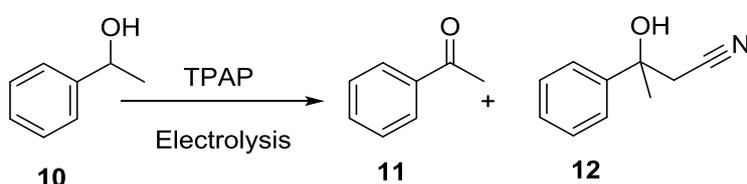
The oxidation of a benzylic secondary alcohol was also tested. An advantage is that no overoxidation to the acid is possible and if the addition product with acetonitrile is formed, this product cannot be oxidized further. An electrolysis under similar reaction conditions was tested and acetophenone (**11**) was detected with a reasonable yield together with the addition product with acetonitrile, 3-hydroxy-3-phenylbutanenitrile (**12**), as a minor side product. Unfortunately no complete conversion of the alcohol could be obtained as before with benzyl alcohol despite the same length of electrolysis time and an observed drop of the current during the electrolysis.



Scheme 3.5. Reaction occurring during electrolysis of 1-phenylethanol.

To avoid the formation of 12, DMF was tested (Table 3.3, Entry 2) as a solvent but here the reaction did not seem to have the same effectiveness as 1-phenylethanol was the main component recovered after work up. Also the stability of acetophenone was tested (Table 3.3, Entry 3) under the reaction circumstances used and the starting material was mainly recovered together with the addition product 3-hydroxy-3-phenylbutanenitrile.

Table 3.3. Oxidation of 1-phenylethanol with electrochemical regeneration of the TPAP catalyst.



Entry ^a	Time [h]	Yield 11 [%] ^b	Yield 12 [%] ^b	Conversion [%] ^b
1	45	49	10	75
2 ^c	51	2	0	52
3 ^d	49	58	7	42

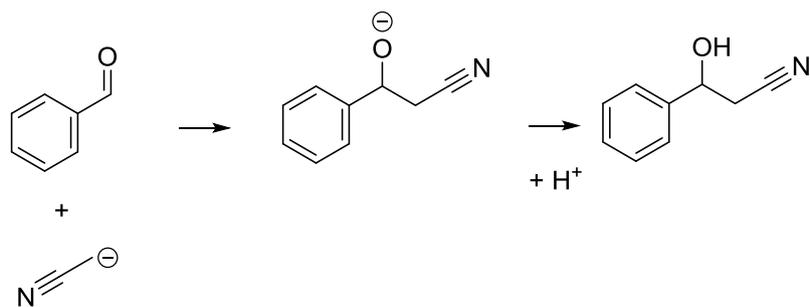
^a) Reaction conditions: 1 mmol 1-phenylethanol with 0.06 equivalents of TPAP and 4 equivalents of K₂CO₃ in 14 mL solvent with 0.1 M Bu₄NBF₄ at room temperature with a switching potential between 1.3 V and -0.55 V.

^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^c) DMF as solvent instead of CH₃CN

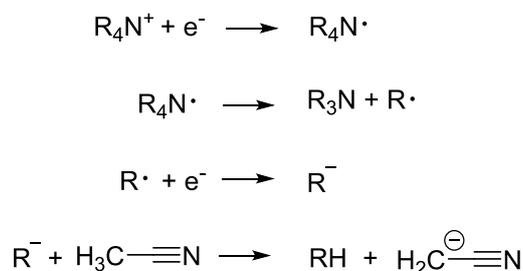
^d) 1 mmol Acetophenone instead of 1-phenylethanol.

The formation of the addition product of the ketone or aldehyde formed with acetonitrile is a reaction which was not anticipated. The formation of this product is not fully known yet but a possible logic route would be the nucleophilic attack of an acetonitrile anion on the carbonyl function (Scheme 3.6).



Scheme 3.6. Nucleophilic addition of acetonitrile anion to benzaldehyde.

Question then is how the deprotonation of acetonitrile takes place. Normally it requires more than stoichiometric quantities of strong bases to deprotonate alkylnitriles. Hypothetically, the cyanomethyl anion can be electrogenerated in our procedures. The electrochemical reduction to create the cyanomethyl anion is also known and it can be produced by direct electrolysis under galvanostatic control in a solution of tetraethylammonium tetrafluoroborate in acetonitrile. It can be used as a base in a large number of organic reactions such as the addition reaction with carbonyl compounds for the synthesis of β -hydroxynitriles [17]. The reaction scheme explaining the formation of the cyanomethyl anion does not involve a straightforward reduction of acetonitrile. It is actually the reduction of the ammonium compound that can form a carbanion as can be seen in scheme 6. This carbanion is a strong base and is capable of deprotonating the solvent, more specific acetonitrile (present in excess) which in an next step forms the cyanomethyl anion which can initiate the addition reaction on the carbonyl compound [18]. In literature this reaction takes place at galvanostatic conditions at the cathode so the exact potential is unknown. Under our electrolysis conditions the exact potential of the cathode is also unknown but the detection of similar addition products might point to the fact that similar reactions occur during the electrolysis experiments.



Scheme 3.7. Possible electrogeneration of cyanomethyl anion.

3.3. Conclusions

An extensive electrochemical analysis of the TPAP catalyst is performed in an acetonitrile solution. The electrochemical reversible redox couple between the perruthenate anion and ruthenium tetroxide could be fully described and interestingly a diffusion coefficient was calculated for the perruthenate anion using the Levich equation, giving a value of $D = 1.72 \cdot 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

Via potentiostatic experiments the interaction between TPAP and a primary alcohol, *n*-butanol, was elucidated. Interestingly, an oxidation current has been observed, indicating the conversion of the alcohol in interaction with the catalyst. The oxidation current reflects the reoxidation of spent TPAP inducing the conversion of the alcohol. By using GC-MS, it has been shown that *n*-butanol can be oxidized into *n*-butanal via the reoxidation of spent TPAP.

The electrolysis of alcohols using this reoxidation of spent TPAP was further examined with other alcohols. With benzyl alcohol it was shown that electrolysis time could be extended by using a switching potential profile. The most active solvent tested was acetonitrile. Not only the expected oxidation products, benzaldehyde and benzoic acid, were detected but also the addition product between benzaldehyde and acetonitrile. It was shown that this product could be further oxidized to benzoylacetonitrile, which is not stable under the conditions selected during the electrolysis and probably is polymerized by the potentials used. Also the electrolysis of 1-octanol and 1-phenylethanol was examined. Although the reactivity decreased, the corresponding products could be obtained.

3.4. Abbreviations

TPAP	Tetrapropylammonium perruthenate
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
GC-MS	Gas chromatography – Mass spectroscopy
D	Dissociation constant
DCM	Dichloromethane
DMF	<i>N,N</i> -Dimethylformamide
THF	Tetrahydrofuran
[BMIM][BF ₄]	1-butyl-3-methylimidazolium tetrafluoroborate

3.5. Experimental

3.5.1. General information

GC-MS samples were analyzed on an Agilent 7890A gas chromatograph connected via splitter to both a quadrupole MS and a FID detector. The instrument was equipped with a fused silica capillary column (OPTIMA 5MS Accent – 0.25 μ M, 30 m, 0.25 mm ID – manufactured by Machery-Nagel). The column had a silarylene stationary phase with ultra-low bleeding and a polarity similar to 5 % diphenyl/95 % dimethylpolysiloxane (i.e. non-polar) and a maximum temperature of 340°C (isothermal).

The ^1H NMR spectra were recorded on a Bruker Avance II 400 spectrometer with TMS as the internal standard. All coupling constants are given in Hertz and the chemical shifts are given in ppm. Multiplicity is indicated using the following abbreviations: b for broad, d for doublet, t for triplet, q for quintet, m for multiplet and s for singlet.

3.5.2. General procedures

All electrochemical measurements were performed by using a Potentiostat/Galvanostat PGSTAT 101 from Metrohm, connected with a PC provided with NOVA 1.10 software.

A typical cyclic voltammetry experiment was performed using a three-electrode cell with a platinum working electrode of 2 mm diameter (Metrohm, the Netherlands) or a glassy carbon working electrode of 3 mm diameter, a platinum sheet counter electrode and a bridged Ag/AgCl reference electrode with 2 M LiCl ethanol solution as inner solution and acetonitrile as bridge solution. The working electrode was pretreated by mechanical polishing. It was subjected to sequential polishing with a cloth covered with alumina powder of 1 and 0.05 μ m particle size (SPI supplies, USA) for 10 minutes to remove any adherent Al_2O_3 particles. The electrode surface was rinsed thoroughly with deionized water and cleaned in an ultrasonic bath containing deionized water for 2 minutes. Next the electrode was rinsed with acetone and dried. Solutions of 0.1 M Bu_4NBF_4 in acetonitrile were freshly made and purged with nitrogen gas for 10 minutes to remove oxygen before each measurement. Rotating disk measurements were measured with a controlled speed rotator (Metrohm, the Netherlands).

A typical potentiostatic experiment was done as follows, a cell was filled with a freshly prepared solution of 0.1 M Bu₄NBF₄ in CH₃CN (20 mL), electrodes were added and nitrogen gas was purged for 10 minutes. Then, a constant potential was applied and after 200 seconds TPAP (14 mg, 0.04 mmol) was added, after 300 seconds the rotation was initiated (2000 rpm) and finally after 350 seconds *n*-butanol (37 μL, 0.4 mmol) was added.

Electrolysis experiments were performed in a homemade airtight electrolysis cell. The working electrode used is a reticulated vitreous carbon (RVC) electrode with a surface area of 10.5 cm²/cm³. A typical electrolysis experiment was done as follows, the cell was filled with a freshly prepared solution of 0.1 M Bu₄NBF₄ in CH₃CN (30 mL), electrodes were added and nitrogen gas was purged for 10 minutes. Next TPAP (21 mg, 0.06 mmol) and the alcohol (0.6 mmol) were added and the cell was put under an argon atmosphere. For the electrolysis experiments with *n*-butanol a constant potential (or no potential) was applied under stirring for 5 hours at room temperature. The resulting mixture was distilled and samples were taken from the distillate for analysis with gas chromatography–mass spectrometry (GC-MS). For the electrolysis experiments with other alcohols, typically a switching potential between 1.3 V and -0.55 V was applied, where each potential was kept constant for 30 seconds. Next stirring was applied for the appropriate time at room temperature. Afterwards the resulting solution was concentrated under reduced pressure and 20 mL of a 0.5 M HCl solution was added. The resulting mixture was extracted with diethylether (3 times 20 mL). Next the organic layer was dried with MgSO₄ filtered and evaporated. The resulting solution was examined with NMR.

3.6. References

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Chapter 4

Cooperative electrocatalytic and chemoselective alcohol oxidation by Shvo's catalyst

Based on: J. Lybaert, S. Trashin, B.U.W. Maes, K. De Wael and K. Abbaspour Tehrani

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4.1. Introduction

The Shvo complex (Scheme 4.1, compound 1) is a versatile ruthenium catalyst used in organic synthesis. The discovery in the middle eighties of its unique stable dimer structure by Shvo and coworkers [1] was the beginning of a search to the borders of his applicability and the exact mechanism of the reactions in which the catalyst is involved. Because of the dimer structure, it has the possibility to dissociate in two different monomer forms, one (compound 2) can be used for reduction reactions while the other (compound 3) for oxidation reactions. They can convert into each other by the loss or addition of hydrogen gas. The dissociation is the key to the broad applicability of the complex [2], for example it can be used for the oxidation of alcohols to ketones [3], the oxidation of amines into imines [4], the alkylation of amines with amines [5], the hydrogenation of ketones and alkenes [6]. In combination with lipases Shvo's catalyst has been used for the dynamic kinetic resolution of secondary alcohols [7].

Nowadays the interest of making efficient reactions more environmentally friendly is of unremitting importance. In the framework of alcohol oxidation reactions the use of molecular oxygen as the final hydrogen acceptor is the natural solution and low-cost alternative for toxic chemicals or catalyst materials [8]. In combination with the Shvo's complex, an aerobic oxidation of secondary alcohols has been observed by Bäckvall and coworkers [9]. More specific, a biomimetic coupled catalytic system, in which the alcohol is oxidized by the Shvo's complex was employed. The reduced Shvo's complex in his turn gets oxidized by benzoquinone, followed by an oxidation of the in situ formed hydroquinone via a cobalt-salen complex. Finally, this cobalt complex is oxidized by oxygen (Scheme 4.1) [9]. Similarly the oxidation of amines to imines is possible using the same catalyst system [4]. In a later stage, the complexity of the system could be reduced by linking the hydroquinone and the cobalt complex in one compound resulting in high yields of ketones [10].

Despite the green properties of molecular oxygen as an oxidant, it has some drawbacks, the solubility is low in organic solvents and there is always a risk in mixing extra oxygen with hot organic solvents, especially in the context of upscaling. The limiting oxygen concentration (determining the flammability) of organic solvents is rather low and therefore in industry it

involves strict safety rules when performing reactions in organic solvents under oxygen atmosphere. The chance of ignition is avoided at all time by operating well below the limiting oxygen concentration. For example it has been shown that the limiting oxygen concentration is below 10% (vol. percent) for toluene at 100 °C at normal pressure [11]. This is more or less half the concentration of oxygen present in ambient air. To overcome the drawback of using oxygen as a stoichiometric oxidant, an interesting alternative is the use of electrochemistry for the conversion of alcohols to ketones or aldehydes [12].

So far no literature is available on the combination of Shvo's complex and electrocatalysis. In an electrocatalytic oxidation reaction, a mediator will be oxidized at the surface of the electrode at a low potential followed by the oxidation of the target molecule [13]. Ruthenium oxides can be used as a mediator. For example RuO₂ can be directly oxidized at the electrode surface to a Ru⁷⁺ species in an alkaline acetonitrile/water mixture, followed by the Ru⁷⁺ promoted oxidation of alcohols [14]. Alternatively, the popular perruthenate anion [15] or TEMPO [16] can be used as mediators for the oxidation of alcohols. Another possible mediator is benzoquinone, together with palladium acetate as a catalyst, it can be used for a Heck-type reaction between an arene and an alkene in acetic acid [17], for an electro-oxidative homocoupling between arylboronic acids or arylboronates [18] and for the oxidation of alcohols [19]. Aldehydes and ketones could be obtained in moderate yields using this method. Drawbacks are the necessity to add equivalent amounts of base and eventual catalyst decomposition because of redox active intermediates at the potentials necessary to oxidize the hydroquinone.

Inspired by all these approaches, a combination of the Shvo's complex and the electrochemical oxidation of hydroquinone is examined and proposed as a new environmentally friendly method for high yield conversion of secondary alcohols into ketones. With this method the applicability of quinones as mediators for the regeneration of the redox catalyst in organic-electrochemical synthesis of ketones will be extended. Also the chemoselectivity of the method is addressed, especially for diols. The selective oxidation of vicinal diols directly to α -hydroxy ketones is of utmost importance in the development of atom-economical reactions [20]. The chemoselective oxidation of diols is for example possible with a cationic palladium catalyst in combination with air [21] or RuCl₃ as a catalyst in combination with buffered oxone [22]. Interesting is also the electrocatalytic method where a carbon supported platinum electrode is modified with bismuth to get a direct selective oxidation of glycerol at the electrode surface [23]. Also the use of TEMPO as a mediator is reported for the selective oxidation of glycerol but only in 25% yield [24]. Only very recently, Pd-supported nanoparticles have been applied as catalysts for a non-selective glycerol electro-oxidation in an aqueous NaOH solution [25]. A selective electrochemical oxidation of diols under mild conditions and in high yield is now presented.

4.2. Electrochemical study

The critical reaction at the anode surface (Scheme 4.1) is the oxidation of hydroquinone to 1,4-benzoquinone. In the cathodic compartment acetic acid is added in order to reduce the protons to H₂ at the platinum electrode. To avoid pressure build-up by the hydrogen gas, the cathodic part of the divided cell is left open under atmospheric pressure. Since 2,6-dimethoxy-1,4-benzoquinone was one of the most active benzoquinones for the oxidation of the Shvo complex [9], this compound was selected as a mediator for the following reactions. Another advantage is the lower oxidation potential of 2,6-dimethoxyhydroquinone compared to hydroquinone. The electrochemical behavior of 2,6-dimethoxyhydroquinone was screened in different solvents in order to identify the most stable redox process at the lowest oxidation potential (Table 4.1). Dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) gave the best results. The oxidation in these solvents occurs at a potential of ca. 0.55 V (Table 4.1, Entry 1 and 2). It is known that the alkalinity of these two solvents is able to lower the oxidation potential of hydroquinones [26].

Table 4.1. Oxidation peak potential of 2,6-dimethoxyhydroquinone in different solvents^a.

Entry	Solvent	Oxidation peak potential (V) ^b
1	<i>N,N</i> -Dimethylformamide	0.6
2	Dimethyl sulfoxide	0.5
3	Sulfolane	1.0
4	1,1,1,3,3,3-Hexafluoro-2-propanol	1.2
5	2-methyltetrahydrofuran	1.1
6	Dimethylcarbonate	1.0
7	<i>n</i> -butylacetate	> 1.4
8	Acetonitrile	0.8
9	Propionitrile	0.9

^a) In an 0.1 M Bu₄NBF₄ solution at 20°C with glassy carbon (GC) working electrode.

^b) Versus an Ag/AgCl reference electrode

Next step aiming at the use of the Shvo complex in an electrochemical synthesis procedure, an electrochemical study of its redox behavior has been performed using cyclic voltammetry. Figure 4.1 represents the current-potential response of the gradual addition of the Shvo complex to a DMF solution at a glassy carbon (GC) working electrode in the presence of 0.1 M of Bu₄NBF₄ as supporting electrolyte. With the addition of the Shvo complex, different redox processes appear in the cyclic voltammogram and a linear relationship between the peak current and the concentration of the catalyst can be detected for different processes.

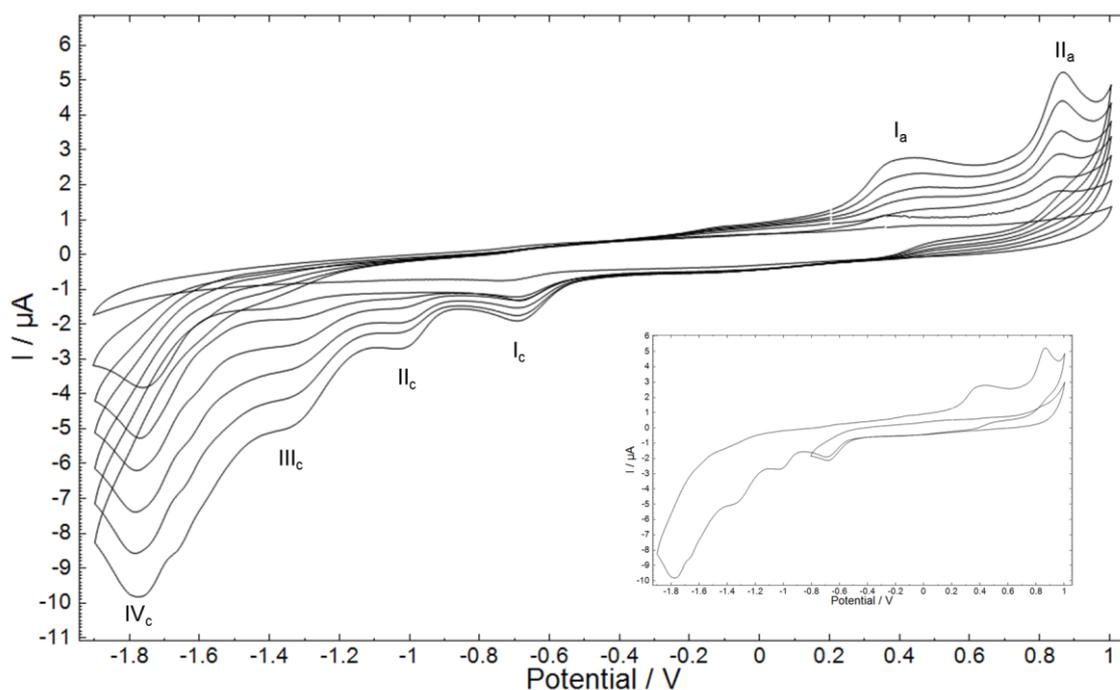


Figure 4.1. Cyclic voltammograms obtained at GC electrode in an 0.1 M Bu_4NBF_4 DMF solution, gradual addition of Shvo complex (concentrations: 0.0 mM; 0.11 mM; 0.12 mM; 0.31 mM; 0.39 mM; 0.47 mM; 0.54 mM) with scan rate 100 mVs^{-1} ; inset: different potential of scan reversal.

A first cathodic peak can be detected around -0.7 V (I_c), linked to the presence of traces of oxygen left in the solution. At -1.0 V , -1.3 V and -1.8 V (II_c , III_c and IV_c) three reduction processes of the Shvo complex are observed. When scanning to more positive potentials two anodic processes appear (I_a and II_a). The relationship between the reduction and oxidation processes is well illustrated when changing the potential window (inset Figure 4.1). When the scan direction is reversed at -0.8 V no anodic peak is observed, making clear that the oxidation peaks (I_a and II_a) are caused by the oxidation of reduced species formed at a potential lower than -0.8 V , i.e. the processes II_c and III_c . An investigation of the electrochemical behavior showed that the ligand of the dimer (compound 1) or the ligands of its dissociation product (compound 2 and 3) are responsible for the detected redox processes in the potential window of interest as can be seen in Figure 4.2. The ligand of the oxidized form (compound 3) has a tetraphenylcyclopentadienone ring as a ligand which electrochemical behavior is well known [27].

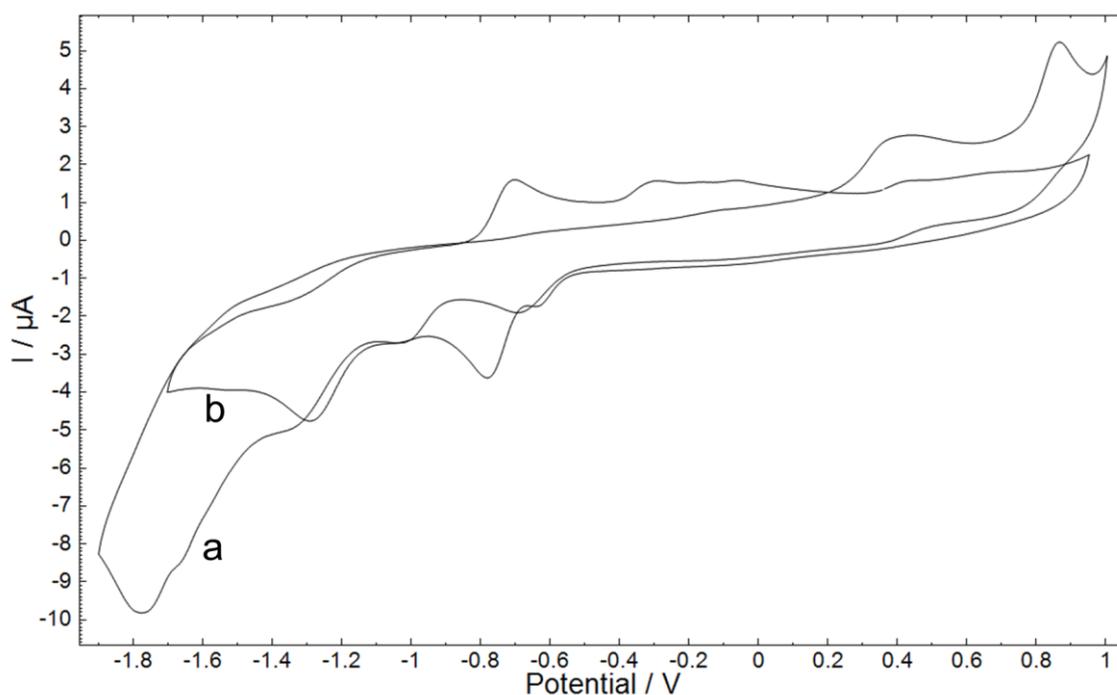


Figure 4.2. Cyclic voltammograms of 0.75 mM Shvo catalyst in an 0.1 M Bu_4NBF_4 DMF solution (a) and voltammograms of 0.82 mM tetraphenylcyclopentadienone in an 0.1 M Bu_4NBF_4 DMF solution (b).

Aiming at the use of the Shvo's complex in an electrochemical synthesis procedure, the redox behavior of the complex has been further investigated using cyclic voltammetry. The Shvo's complex was examined in a DMF solution at a glassy carbon (GC) working electrode in the presence of 0.1 M of Bu_4NBF_4 as supporting electrolyte. Figure 4.3 represents the redox behavior of the Shvo catalyst at room temperature, no oxidation or reduction process is observed in a potential window from -0.4 V until 1 V (Figure 4.3, black curve). Higher potentials are avoided because the oxidation of the solvent may interfere with the catalytic cycle. At lower potentials starting around -0.7 V, different reduction processes of the catalyst, explained as redox chemistry of the ligand, can be detected so these potentials are avoided as well. The temperature of the Shvo catalyst solution was raised to 80 °C as a higher temperature is typically required for the reaction between the Shvo catalyst and the alcohol [28]. The higher temperature did not affect the current-potential behavior of the complex. In a next step an excess of 1-phenylethanol was added, allowing the Shvo catalyst to react with the alcohol turning the Shvo catalyst into its reduced form. However, no change in the current-potential behavior is observed (Figure 4.3, blue curve), since no direct oxidation of the reduced

form of the Shvo catalyst is possible in this potential range. Additionally, the alcohol cannot be oxidized in this potential window, as much higher overpotentials are needed [29]. It is clear that there is a need for a mediator such as a benzoquinone to facilitate the electrochemical regeneration of the Shvo catalyst.

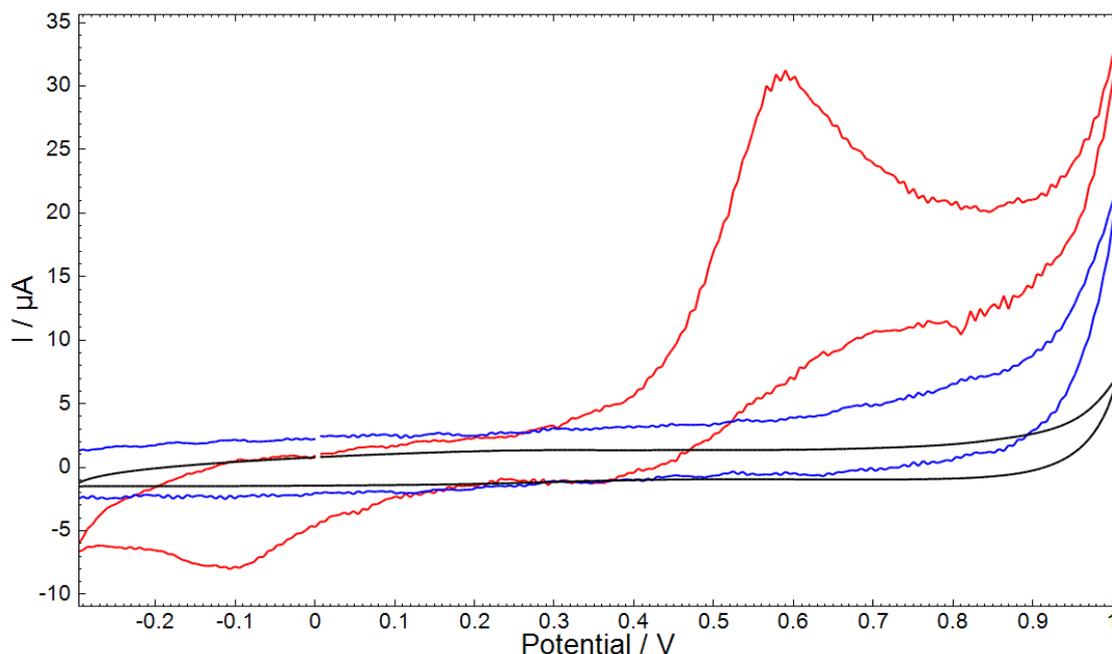


Figure 4.3. Cyclic voltammograms of 0.75 mM Shvo catalyst in an 0.1 M Bu_4NBF_4 DMF solution at 20 °C with a scan rate of 0.1 V/s (Black curve); at 80 °C with addition of 33 mM 1-phenylethanol (Blue curve); with addition of 1.1 mM 2,6-dimethoxybenzoquinone (Red curve).

When 2,6-dimethoxybenzoquinone is added to a solution containing alcohol and Shvo catalyst, an oxidation process at ca. 0.6 V appears, i.e. the oxidation peak of 2,6-dimethoxyhydroquinone to 2,6-dimethoxybenzoquinone. The formation of 2,6-dimethoxyhydroquinone observed by the oxidation peak in Figure 4.3 (red curve) is a strong indication for the Shvo's catalyst mediated oxidation of 1-phenylethanol. Even more, this catalytic cycle can now be implemented in an electrochemical setup for electrosynthesis conversion. In brief, the oxidation of the alcohol by the Shvo catalyst generates the hydrogenated form of the Shvo catalyst, which is oxidized by the 2,6-dimethoxybenzoquinone forming the 2,6-dimethoxyhydroquinone which in its turn is oxidized at the electrode surface at a potential of 0.6 V. This potential corresponds to the oxidation peak potential of the 2,6-

dimethoxyhydroquinone in DMF, as confirmed in Table 4.1. A control experiment was performed leaving the Shvo catalyst out of the catalytic cycle. No oxidation processes were detected in the range of -0.4 V until 1.0 V (similar as Figure 4.3, blue curve). Since no 2,6-dimethoxyhydroquinone is formed, this excludes the mechanism where a direct oxidation of the alcohol by the 2,6-dimethoxybenzoquinone occurs.

4.3. Electrochemical mediated oxidation of alcohols by the Shvo catalyst and 2,6-dimethoxybenzoquinone

Encouraged by the results of the cyclic voltammetry study, electrolysis experiments were performed. An airtight homemade electrolysis cell was used in combination with a working electrode with high surface area. Using this setup, the electrolysis was tested for the oxidation of the model alcohol 1-phenylethanol to acetophenone. Different catalyst loadings were tested and the addition of 5 mol% of Shvo catalyst and 25 mol% of 2,6-dimethoxybenzoquinone followed by a constant potential of 0.7 V for 6 hours at 80 °C is sufficient to give a yield of 82% of acetophenone (Figure 4.4). When using 1 mol% of Shvo catalyst in combination with 10 mol% of 2,6-dimethoxybenzoquinone the yield of the ketone dropped drastically to 25%. In the literature [2] Shvo catalyst promoted oxidations require loadings of 1%, which is rather low compared to the optimal catalyst loading of 5 mol% (10 mol% Ru) in the present study. Most Ru-catalyzed dehydrogenations take place in aromatic solvents at high temperatures, but in order to ensure the solubility of the electrolyte (Bu_4NBF_4) in the electrocatalytic oxidation DMF was used as the solvent. The higher catalyst loading may therefore be explained by a faster degradation of the Shvo complex in DMF. A qualitative rationalisation was made by means of IR spectroscopy of a solution of Shvo catalyst in 2-MeTHF. By adding DMF after 3.5 hours to this stable 2-MeTHF solution, the characteristic peaks for compound **2** [6] at 2036 cm^{-1} , 2005 cm^{-1} and 1976 cm^{-1} decreased.

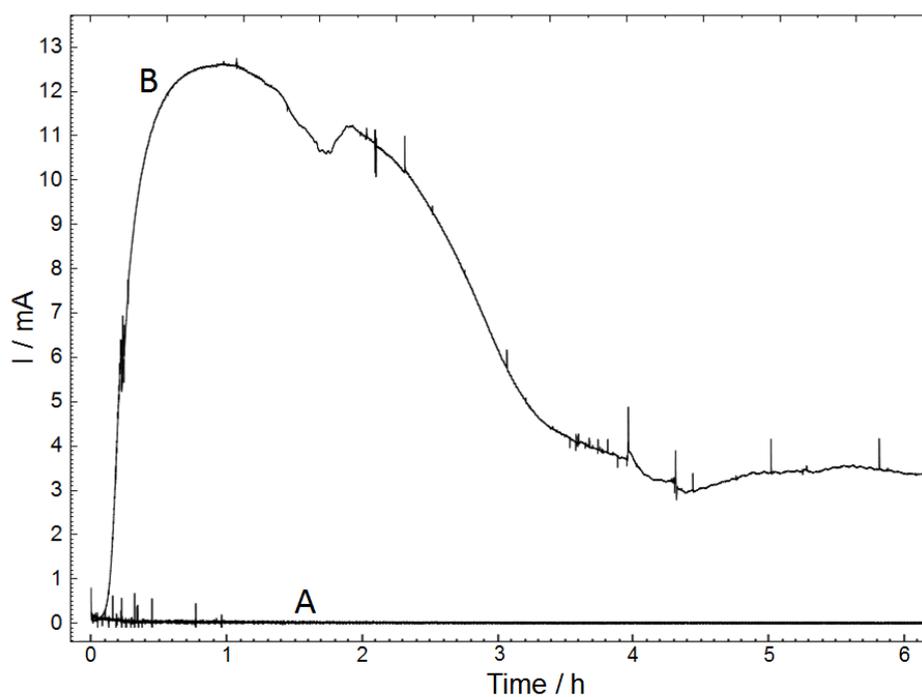
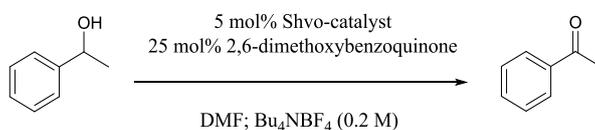


Figure 4.4. Current in function of time for electrolysis of 1-phenylethanol (0.7 mmol) in 0.2 M Bu_4NBF_4 DMF solution at 80 °C at a constant potential of 0.7 V (A); with Shvo catalyst (0.035 mmol) and 2,6-dimethoxybenzoquinone (0.175 mmol) (B).

After 6 hours of electrolysis, the current dropped steadily and hence also the efficiency of the electrolysis. By further electrolysis to a total reaction time of 24 hours (Table 4.2, entry 6) only a small increase of the yield to 88% was observed. This can be partially explained by electro-osmotic phenomena, a small part of the solution migrated during electrolysis through the frit into the compartment of the cathode, and so a small part of the alcohol becomes unavailable together with a small loss of catalyst.

Table 4.2. Oxidation of 1-phenylethanol with electrochemical regeneration of the Shvo catalyst via 2,6-dimethoxybenzoquinone.



Entry ^[a]	Potential [V]	Time [h]	Yield [%] ^[b]	Recovered alcohol [%] ^[b]	Selectivity [%]
1	0.7	0.5	30	65	86
2	0.7	1.5	56	38	90
3	0.7	4	72	21	91
4	0.7	6	82	11	92
5	0.7	7	84	10	93
6	0.7	24	88	5	93
7	No	7	25	61	64
8 ^[c]	0.7	16	0	94	0
9	0.8	7	78	9	86
10 ^[d]	0.7	7	81	7	87
11 ^[e]	0.7	7	70	16	83

^[a] Reaction conditions: 0.7 mmol 1-phenylethanol with 0.05 equivalents of Shvo complex and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMF with 0.2 M Bu₄NBF₄ at 80 °C with constant potential.

^[b] NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^[c] Without Shvo catalyst and 2,6-dimethoxybenzoquinone.

^[d] At 100 °C.

^[e] No acetic acid added to the cathodic compartment.

Control electrolysis experiments were performed in order to confirm the proposed oxidation mechanism (Scheme 4.1). When the electrolysis of 1-phenylethanol was performed without the Shvo catalyst, no current increase was observed and no oxidation of the alcohol could be detected (Table 4.2, entry 8). In case no potential was applied, only the stoichiometric oxidation of the alcohol could be detected (Table 4.2, entry 7), giving an expected yield of

acetophenone of 25%. An electrolysis experiment with a constant potential of 0.8 V was performed but no change of the yield could be observed (Table 4.2, entry 9). Also the influence of the temperature was examined by performing an experiment at 100 °C, again no significant influence on the yield was observed (Table 4.2, entry 10). When acetic acid in the cathodic part was omitted, the yield dropped from 82% to 70% (Table 4.2, entries 4 and 11).

In Figure 4.5 the progress of the oxidation of 1-phenylethanol has been plotted in function of the charge passed during the electrolysis. This makes clear that after adding 135 Coulombs of charge (approximately 7 hours of electrolysis) the effectiveness of the catalytic cycle drops. Extending the time of electrolysis does not much improve the yield of the reaction.

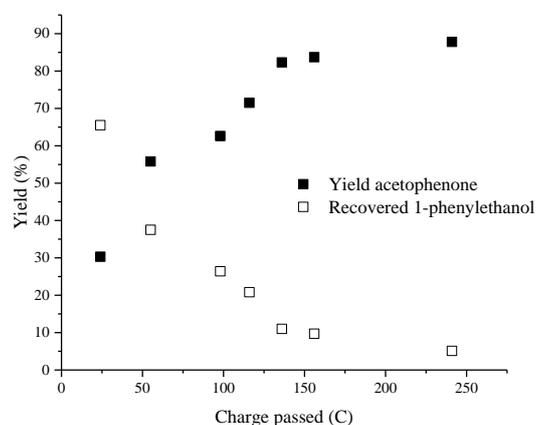
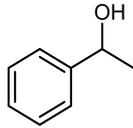
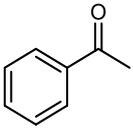
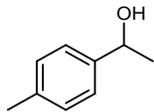
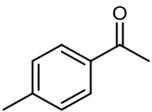
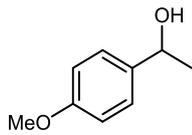
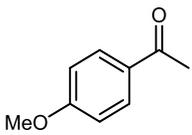
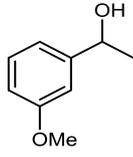
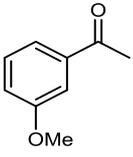
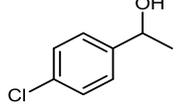
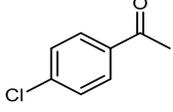
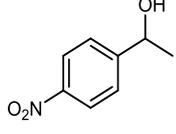
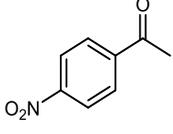


Figure 4.5. Yield of acetophenone in function of total charge passed during electrolysis; Reaction conditions: 0.7 mmol 1-phenylethanol with 0.035 mmol of Shvo complex and 0.175 mmol of 2,6-dimethxobenzoquinone in 14 mL DMF with 0.2 M Bu_4NBF_4 at 80 °C with a constant potential of 0.7 V. Yields are the average of two runs.

To study the substrate scope a variety of alcohols were electrolysed during 5 h at 0.7 V. Various secondary alcohols were oxidized to ketones with a sufficient yield. A range of substituted 1-phenylethanols gave good yields for methyl (Table 4.3, entry 2) and methoxy (Table 4.3, entries 3 and 4) derivatives. A more challenging oxidation was found with an electron withdrawing group at the para position, for example *para*-chloro and *para*-nitro (Table 4.3, entries 5 and 6) derivatives only gave moderate yields. The oxidation of allylic alcohols, 3-octene-2-ol and 1-cyclohexyl-2-buten-1-ol (Table 4.3, entries 9 and 10), also furnished the corresponding ketone in good yields. During this process the stereochemistry of the alkene

was conserved. Further, no ruthenium catalyzed isomerization of the allylic alcohols to the saturated ketone was observed under these conditions [30,31]. Most likely, the reason for this selectivity is the fact that the present system runs without any additional base [30]. Also more resistant aliphatic secondary alcohols were investigated and good yields of ketones were obtained for 2-nonanol, dicyclohexylmethanol and 4-*tert*-butylcyclohexanol (Table 4.3, entries 10, 11 and 12). The more sterically demanding neomenthol and L-menthol (Table 4.3, entries 13 and 14) were tested and a difference in reactivity was observed. The lower yield of the L-menthol oxidation is explained by the steric hindrance of the alcohol group. In L-menthol the alcohol function and the isopropyl group are both in an equatorial position (entry 14) whereas the alcohol group of neomenthol is in an axial position making it more easily accessible for the catalyst (entry 13).

Table 4.3. Oxidation of different secondary alcohols^[a].

Entry	Substrate	Product	Yield [%] ^[b]	Selectivity [%]
1			82 (75)	92
2			88 (77)	96
3			88 (81)	93
4			85 (83)	94
5			73 (71)	91
6			39	87

Entry	Substrate	Product	Yield [%] ^[b]	Selectivity [%]
7			84 (72)	85
8			86 (79)	90
9			82 (74)	89
10			83 (78)	85
11			83 (76)	90
12			83 (77)	92
13			82 (76)	88
14			24	75
15			52	93
16			14	26

^[a] Reaction conditions: 0.7 mmol alcohol with 0.05 equivalents of Shvo complex and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMF with 0.2 M Bu₄NBF₄ at 80 °C with constant potential of 0.7 V for 5 hours.

^[b] NMR yields were calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard. Between brackets, the yields after column chromatography are given.

After the successful oxidation of secondary alcohols, the same method was applied for primary alcohols. For benzyl alcohol (Table 4.3, entry 13) a moderate yield of 52% of the aldehyde was obtained. For 1-octanol (Table 4.3, entry 14) the current obtained during electrolysis was lower than with the previous oxidations and after work up it was clear that the yield of the aldehyde was much lower in comparison with the yield obtained for ketones.

4.4. Electrolysis of more complex alcohols

This result prompted us to investigate the oxidation of diols to see if a chemoselective oxidation of the secondary alcohol is possible. For the oxidation of 1,2-octanediol (Table 4.4, entry 1) the standard procedure resulted in a moderate yield of 62 % of the expected hydroxy ketone, proving that a chemoselective oxidation is possible. The starting diol is also recovered and no double oxidation of both alcohol functions could be observed.

Table 4.4. Oxidation of complex alcohols^[a].

Entry	Substrate	Product	Yield [%] ^[b]	Recovered starting substrate [%] ^[b]	Selectivity [%]
1			61 (49)	24	80
2			34	26	46
3			Unknown	Unknown	
4			n.d.	74	0
5			n.d.	79	0

^[a] Reaction conditions: 0.7 mmol alcohol with 0.05 equivalents of Shvo complex and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMF with 0.2 M Bu₄NBF₄ at 80 °C with constant potential of 0.7 V for 5 hours.

^[b] NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard. Between brackets, isolated yields.

Also other diols were tested but were less successful. This can already be detected during the measurement, a lower charge is obtained with the other diols in comparison with 1,2-octanediol. For 1-phenyl-1,2-ethanediol (Table 4.4, Entry 2) the charge was lower and also the yield of the ketone is relatively low. Some starting material was also detected, but no double oxidation of both alcohol functionalities could be detected. The economical interesting triol glycerol (Table 4.4, Entry 3) was also tested but, also here only a limited charge was obtained. An extra trouble with this product is its isolation from the reaction mixture. During an extraction both starting material and the expected product were not extracted to the ether or ethylacetate layer. It could not be made certain that the glycerol remained unaffected or till which extend oxidation had taken place. Next a more complex alcohol was tested, by trying to oxidize the amino acid threonine. First the boc protected threonine (Table 4.4, Entry 4) was tested, only a very limited charge was obtained and most of the starting material was recovered unaffected. The methyl ester variant of the boc protected threonine (Table 4.4, Entry 5) was also tried but a similar result was obtained and most of the starting material was recovered unaffected. It might be that the secondary amine of the amide function interacts with the Shvo complex. It is well known that amines can act as ligands for the Shvo complex. In this way there is occurring competition between the amine and the alcohol to react with the Shvo complex in the reaction mixture preventing an efficient oxidation of the alcohol functionality.

4.5. Electrolysis of amines

Also the oxidation of amines was tested using the same procedure. It was shown before that the Shvo catalyst could be used for the oxidation of secondary amines to the corresponding imines [4,32]. An important difference when we study the electrochemical mediated oxidation of alcohols in comparison with amines, is that the oxidation potential of amines is much lower in comparison with the oxidation potential of alcohols. Of course it depends on substituents so they span a certain potential range, but some examples are compared by Roth et al. [33]. They give a range between 0.3 V and 1.3 V versus standard calomel electrode for the oxidation potential of a series of different amines.

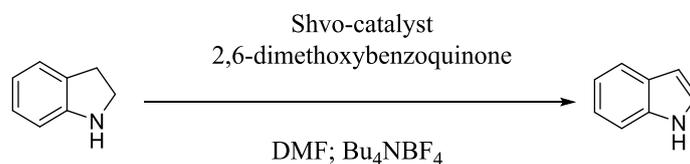
The electrochemical oxidation of indoline mediated by the Shvo catalyst was studied. Also here the oxidation peak of indoline is detected at relative low potential, the onset of the peak detected in cyclic voltammetry was reported to start at 0.7 V versus our reference electrode [34]. So this is at the limit in comparison with the oxidation potential of 2,6-dimethoxyhydroquinone in our system used.

First an electrolysis was tested with indoline under the standard conditions used but without the Shvo catalyst and the 2,6-dimethoxybenzoquinone present (Table 4.5, Entry 1). A current could be detected and the direct oxidation of indoline is possible at 0.7 V. After work up, it was clear that this was not an optimal procedure, as indole was found but only in relative low yield. Other products could not be identified, but from literature it is clear that polymerization is major side reaction that can occur by the direct oxidation of amines.

When an electrolysis is tried at the same potential with our catalytic system added, the yield of the detected indole was much higher (Table 4.5, Entry 2). To further improve the procedure for this amine, a lower potential of 0.6 V was tested and this resulted in an increase of the yield (Table 4.5, Entry 3). At this potential the direct oxidation of the indoline is suppressed and the main oxidation that takes place at the electrode surface is now the reoxidation of hydroquinone to benzoquinone.

To detect the influence of a direct oxidation of indoline at 0.6 V, an electrolysis was tested at this potential. The current was much lower than at 0.7 V, only a small charge could be obtained together with a low yield of indole and most of the indoline could be recovered unaffected (Table 4.5, Entry 4).

Table 4.5. Oxidation of indoline with electrochemical regeneration of the Shvo catalyst via 2,6-dimethoxybenzoquinone.



Entry ^{a)}	Potential [V]	Time [h]	Yield indole [%] ^{b)}	Recovered indoline [%]	Selectivity [%]
1 ^{c)}	0.7	5	17	3	18
2	0.7	5	64	0	64
3	0.6	5	72	7	77
4 ^{c)}	0.6	5	10	58	24

^{a)} Reaction conditions: 0.7 mmol indoline with 0.05 equivalents of Shvo complex and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMF with 0.2 M Bu₄NBF₄ at 80 °C with constant potential.

^{b)} NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard

^{c)} Without Shvo catalyst and 2,6-dimethoxybenzoquinone

After the successful oxidation of indoline (Table 4.6, Entry 1), the oxidation of similar molecules was tested. For the oxidation of tetrahydroquinoline (Table 4.6, Entry 2) also a good yield of quinoline was obtained. A longer reaction time of 8 hours was necessary to obtain the fully oxidized quinoline and no degradation of the process was seen during the prolonged reaction time.

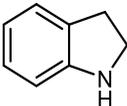
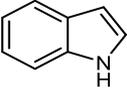
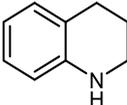
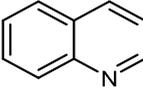
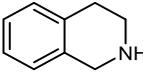
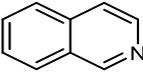
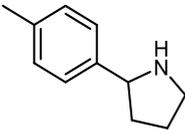
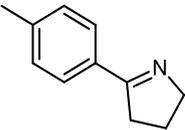
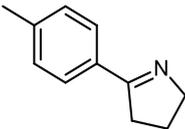
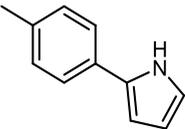
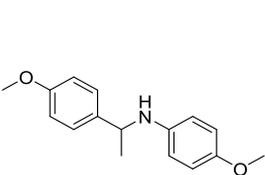
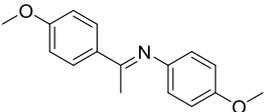
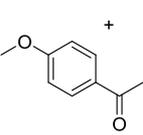
The oxidation of tetrahydroisoquinoline (Table 4.6, Entry 3) was also tested but here during the electrolysis almost no current was detected and after work up, most of the starting material was recovered unaffected.

The position of the nitrogen, directly connected to the benzylic system or not, seems to have an influence on the activation of the substrate for oxidation by the Shvo catalyst under the conditions used and this might explain the large difference between tetrahydroisoquinoline and tetrahydroquinoline.

Also the oxidation of a hydrogenated pyrrole was tested, namely 2-tolyl-tetrahydropyrrole (Table 6, Entry 4) also here only a small amount of oxidized product was found and most of

the starting material was recovered unaffected. It appears that the amine is not active enough to get oxidized, just as for tetrahydroisoquinoline. The tertiary amine 2-Tolyl-dihydropyrrole was also tested to see if oxidation to an aromatic pyrrole structure was possible but no current was detected during the electrolysis and most of the starting material was recovered unaffected.

Table 4.6. Oxidation of different secondary amines^[a].

Entry	Substrate	Product	Yield [%] ^[b]	Recovered starting substrate [%]
1			72 (69)	5
2 ^[c]			70 (68)	8
3			6	77
4 ^d			9	69
5 ^[d]			0	78
6		 + 	12 + 25	37

^[a] Reaction conditions: 0.7 mmol alcohol with 0.05 equivalents of Shvo complex and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMF with 0.2 M Bu₄NBF₄ at 80 °C with constant potential of 0.6 V for 5 hours.

^[b] NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard. Between brackets, isolated yields.

^[c] Reaction time of 8 hours

^[d] With a constant potential of 0.7 V

It is reported that the Shvo catalyst is capable of oxidizing secondary amines to imines without the generation of an aromatic system like for indoline and tetrahydroquinoline. So our oxidation system developed was tested on an example used by Bäckvall and coworkers [4,26], more specific *N*-methoxyphenyl-*N*-(1-methoxyphenylethyl)amine (Table 4.6, Entry 6). The electrolysis was tested, but only moderate current and charge could be obtained. After work up, a small amount of the expected imine was found but the main product was unaffected starting material. Surprisingly also some acetophenone was found and so it seems that the imine formed undergoes hydrolysis under our conditions used.

To conclude, smooth oxidation of active amines is obtained when it is accompanied with the formation of an aromatic system. This gives an extra driving force to obtain the oxidized product. For less active amines, no or only partially oxidized products could be obtained. In the conditions used it seems that the Shvo catalyst is not active enough to provide a smooth oxidation of the amines. An extra caution that has to be taken into account is that amines have a relative low electrochemical oxidation potential and a direct oxidation can be an important side reaction as the direct oxidation of amines is accompanied with the formation of dimers and polymers which are not the desired products.

4.6. Conclusions

The combination of the Shvo complex with 2,6-dimethoxybenzoquinone was tested as a possible mediator system for oxidation reactions. First an extensive electrochemical study of the different components was performed.

The oxidation of 2,6-dimethoxyhydroquinone to 2,6-dimethoxybenzoquinone was studied in different solvents in order to see which can be used for an efficient reoxidation at the electrode surface. Next, the Shvo complex was studied electrochemically and around the potential of interest no redox processes could be detected. This was followed by examining the influence of the temperature and the addition of an excess of alcohol. Next, 2,6-dimethoxybenzoquinone was added and the expected reoxidation peak of the hydroquinone to the benzoquinone was detected giving the first indicative proof that reoxidation is possible and a synthetic application can be made.

The electrolysis reaction using this mediator system was studied and an efficient synthetic method could be developed. Different secondary alcohols were tested. For the benzylic alcohols with electron donating substituents, good yield of the corresponding ketones were obtained. For the benzylic alcohols with electron withdrawing groups, only limited yields could be obtained. For aliphatic secondary alcohols, good yields of the corresponding ketones were also obtained. For primary alcohols, only limited yields of aldehydes were obtained especially for the aliphatic.

The oxidation of 1,2-diols was studied and a good yield for the selective oxidation of the secondary alcohol with 1,2-octanediol was obtained. Some protected threonines were also tested using the same procedure but unfortunately no oxidation of the alcohol could be detected.

To fully determine the scope of the procedure also the oxidation of amines was examined and here only an efficient oxidation of amines was achieved if it was combined by extending the aromatic system of the molecule.

To finalize, we have performed an in depth electrochemical study of the Shvo's complex and established a methodology for the cooperative electrocatalytic alcohol oxidation to ketones via the use of the Shvo catalyst in combination with a benzoquinone. In this way a new sustainable method is developed for the oxidation of secondary alcohols to ketones. Good to excellent yields for different ketones, aromatic as well as aliphatic, could be obtained.

4.7. Abbreviations

DMSO	Dimethyl sulfoxide
GC	Glassy carbon
DMF	<i>N,N</i> -Dimethylformamide
Boc	<i>tert</i> -butyloxycarbonyl
n.d.	Not detected

4.8. Experimental

4.8.1. General information

The ^1H NMR spectra were recorded on a Bruker Avance II 400 spectrometer with TMS as the internal standard. All coupling constants are given in Hertz and the chemical shifts are given in ppm. Multiplicity is indicated using the following abbreviations: b for broad, d for doublet, t for triplet, q for quintet, m for multiplet and s for singlet.

4.8.2. General procedure for the electrolysis reaction

A homemade airtight electrolysis cell was used equipped with a reticulated vitreous carbon (RVC) as working electrode (basi, USA), a bridged Ag/AgCl reference electrode with 2 M LiCl ethanol solution as inner solution and a 0.1 M Bu_4NBF_4 DMF as bridge solution was used and the counter electrode, a platinum rod electrode, was put in a divided cell separated from the anodic part by a ceramic frit. In a typical electrolysis experiment 4 mL of a 0.2 M Bu_4NBF_4 DMF solution was added to the divided part followed by the addition of 200 μL of acetic acid. In the anodic part Shvo complex (0.05 equivalent) and 2,6-dimethoxybenzoquinone (0.25 equivalent) was added to a 14 mL solution of 0.2 M Bu_4NBF_4 in DMF. The cell was closed and placed under an argon atmosphere. Stirring was started and the cell was put in an oil bath for heating, next a potential of 0.7 V was applied and finally the alcohol (0.7 mmol) was added. After the appropriate reaction time, the reaction mixture was cooled down and 30 mL of water was added. The resulting mixture was extracted with *tert*-butylmethylether (3 times 25 mL). The collected organic layer was washed with 15 mL of a 0.2 M HCl solution to further remove DMF. Next the organic layer was dried with MgSO_4 filtered and evaporated. The resulting solution was examined with NMR. Isolated products were obtained using column chromatography with heptane/ethylacetate (95/5) as eluent.

acetophenone

The general procedure for the electrolysis was followed with 1-phenylethanol as the alcohol. Giving an isolated yield of acetophenone of 75%.

^1H NMR (400 MHz, CDCl_3): δ = 2.59 (s, 3H, CH_3), 7.46 (m, 2H, $\text{CH}_{\text{arom. meta}}$), 7.54 (m, 1H, $\text{CH}_{\text{arom. para}}$), 7.94(d, 2H, $\text{CH}_{\text{arom. ortho}}$).

4-methyl-acetophenone

The general procedure for the electrolysis was followed with 1-(4-methylphenyl)ethanol as the alcohol. Giving an isolated yield of 4-methyl-acetophenone of 77%.

^1H NMR (400 MHz, CDCl_3): δ = 2.40 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.25 (d, 2H, $\text{CH}_{\text{arom. meta}}$), 7.85(d, 2H, $\text{CH}_{\text{arom. ortho}}$).

4-methoxyacetophenone

The general procedure for the electrolysis was followed with 1-(4-methoxyphenyl)ethanol as the alcohol. Giving an isolated yield of 4-methoxyacetophenone of 81%.

^1H NMR (400 MHz, CDCl_3): δ = 2.54 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.92 (d, 2H, $\text{CH}_{\text{arom. meta}}$), 7.93 (d, 2H, $\text{CH}_{\text{arom. ortho}}$).

3-methoxyacetophenone

The general procedure for the electrolysis was followed with 1-(3-methoxyphenyl)ethanol as the alcohol. Giving an isolated yield of 3-methoxyacetophenone of 81%.

^1H NMR (400 MHz, CDCl_3): δ = 2.59 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.10 (d, 1H, $\text{CH}_{\text{arom. para}}$), 7.36 (t, 1H, $\text{CH}_{\text{arom. meta}}$), 7.50(m, 2H, $\text{CH}_{\text{arom. ortho}}$).

4-chloroacetophenone

The general procedure for the electrolysis was followed with 1-(4-chlorophenyl)ethanol as the alcohol. Giving an isolated yield of 4-chloroacetophenone of 71%.

^1H NMR (400 MHz, CDCl_3): δ = 2.58 (s, 3H, CH_3), 7.42 (d, 2H, $\text{CH}_{\text{arom. meta}}$), 7.89 (d, 2H, $\text{CH}_{\text{arom. ortho}}$).

indanone

The general procedure for the electrolysis was followed with 1-indanol as the alcohol. Giving an isolated yield of indanone of 72%.

^1H NMR (400 MHz, CDCl_3): δ = 2.68 (t, 2H, CH_2), 3.14 (t, 2H, CH_2), 7.35 (t, 1H, CH), 7.48 (d, 1H, CH), 7.59 (t, 1H, CH), 7.75 (d, 1H, CH).

dicyclohexylketone

The general procedure for the electrolysis was followed with dicyclohexylmethanol as the alcohol. Giving an isolated yield of dicyclohexylketone of 78%.

^1H NMR (400 MHz, CDCl_3): δ = 1.31 (m, 10H, 5 x CH_2), 1.75 (m, 10H, 5 x CH_2), 2.49 (t, 2H, 2 x CH).

2-nonanone

The general procedure for the electrolysis was followed with 2-nonanol as the alcohol. Giving an isolated yield of 2-nonanone of 76%.

^1H NMR (400 MHz, CDCl_3): δ = 0.88 (t, 3H, CH_3), 1.28 (m, 8H, 4 x CH_2), 1.57 (q, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.41 (t, 2H, CH_2).

***tert*-butylcyclohexanone**

The general procedure for the electrolysis was followed with *tert*-butylcyclohexanol as the alcohol. Giving an isolated yield of *tert*-butylcyclohexanone of 77%.

^1H NMR (400 MHz, CDCl_3): δ = 0.92 (s, 9H, 3 x CH_3), 1.47 (m, 3H), 2.08 (m, 2H), 2.38 (m, 4H).

menthone

The general procedure for the electrolysis was followed with *neo*-menthol as the alcohol. Giving an isolated yield of menthone of 76%.

^1H NMR (400 MHz, CDCl_3): δ = 0.85 (d, 3H, CH_3), 0.90 (d, 3H, CH_3), 1.01 (d, 3H, CH_3), 1.37 (m, 2H, 2 x CH), 1.95 (m, 6H, 3 x CH_2), 2.35 (m, 1H, CH).

1-hydroxy-octan-2-one

The general procedure for the electrolysis was followed with 1,2-octanediol as the alcohol. Giving an isolated yield of 1-Hydroxy-octan-2-one of 49%.

^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, 3H, CH_3), 1.29 (m, 6H, 3 x CH_2), 1.61 (q, 2H, CH_2), 2.41 (t, 2H, CH_2), 3.20 (s, 1H, OH), 4.24 (s, 2H, CH_2).

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Chapter 5

Electrolysis of vicinal diols with the aid of neocuproine palladium catalysts

5.1. Introduction

Chemoselective oxidation reaction pathways aim to selectively oxidize an alcohol functionality in the presence of other alcohols. The oxidation of vicinal diols to the corresponding α -hydroxyketone functionality is of particular interest as this functionality is present in antitumor antibiotics such as kurasoin A and B [1] and in different natural products such as olivomycin A [2]. The α -hydroxyketone group also plays an important role in the modification of carbohydrates and other reaction schemes in general organic synthesis [3].

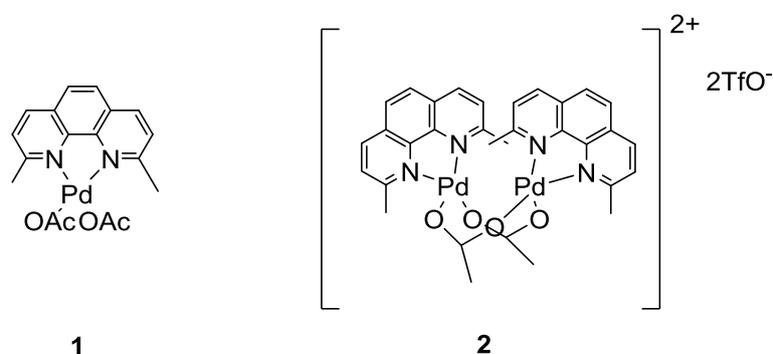
Different (non-electrochemical) methods have been proposed to achieve a chemoselective reaction of vicinal diols. For example, the use of peroxotungstophosphates in combination with hydrogen peroxide is reported to give a selective oxidation of different vicinal diols [4]. Also, the stoichiometric use of dioxiranes results in chemoselectivity [5]. Another oxidation pathway consists of NaBrO_3 in combination with NaHSO_3 and is described in literature to selectively oxidize cyclic vicinal diols to the corresponding hydroxyl ketones [6]. Focusing on catalytic systems using metal catalysts, the combination of RuCl_3 with buffered oxone as the stoichiometric oxidant is reported to oxidize different vicinal diols to the corresponding α -hydroxyketones [7]. Other examples of metal catalysts are the organotin compounds in combination with stoichiometric oxidants like Br_2 or N-iodosuccinimide (NIS) [8]. The organotin catalysts can also be replaced by boronic acids [9] or used in combination with electrochemical oxidized bromo species (Br^+) [8,9], as already explained in the general introduction (see page 23).

In general, catalysts for alcohol oxidation can be immobilized on (modified) electrode surfaces, for example a carbon supported platinum electrode modified with bismuth. Using such electrode, glycerol can be oxidized to dihydroxyacetone with high selectivity [10]. A second electrochemical approach includes TEMPO as a mediator and a similar selective oxidation of glycerol to dihydroxyacetone can be obtained by reoxidizing TEMPO at the electrode surface. However, only a yield of 25 % is reported [11].

Palladium catalysts have been investigated thoroughly for the aerobic non-electrochemical oxidation of alcohols. Catalysts such as for example a Palladium carbene catalysts [12] or cationic pyridine based palladium complexes [13] have been reported for selective oxidation

reactions with oxygen as stoichiometric oxidant. Another example of a palladium catalyst that can selectively oxidize vicinal diols is the cationic palladium complex using neocuproine as a ligand, developed by Waymouth et al. [14].

The beneficial use of neocuproine as a ligand for palladium catalysts was first investigated by Sheldon et al. [15]. They reasoned that the methyl groups on the 2 and 9 position of the phenanthroline ligand cause steric hindrance and thus prevent the formation of dimeric structures, resulting in a more active catalyst for oxidation reactions. The highest activity for the aerobic oxidation of alcohols was achieved by using the palladium catalyst neocuproinePd(OAc)₂ (Scheme 5.1, structure 1) which has a phenanthroline with two methyl groups substituents at the 2 and 9 position (neocuproine).



Scheme 5.1. Two neocuproine palladium catalysts: neocuproinePd(OAc)₂ (1) and [neocuproinePdOAc]₂[OTf]₂ (2).

Later, this catalyst was used as a basis for the synthesis of a new cationic palladium complex using neocuproine as a ligand [16]. It was reasoned that a cationic palladium complex with non-coordinating counter anions could increase the rate of aerobic alcohol oxidation. The dimeric acetate bridged [neocuproinePdOAc]₂[OTf]₂ (Scheme 5.1, structure 2) was synthesized by comproportionation of neocuproinePd(OAc)₂ and the ditriflate analogue neocuproinePd(MeCN)₂(OTf)₂. Catalyst 2 proved to have faster initial rates for the aerobic oxidation of alcohols at room temperature. In comparison, catalyst 1 needs 80 degrees Celsius for an efficient conversion [15].

Interestingly, catalyst 2 allowed the selective oxidization of polyols [14]. More specific, in vicinal diols only the secondary alcohol is oxidized to the corresponding α -hydroxyketone. Also glycerol can be selectively oxidized to the corresponding dihydroxyacetone under mild conditions [17]. In these approaches either oxygen or p-benzoquinone is used as the stoichiometric oxidant. Additionally, it was communicated that catalyst 2 may convert unprotected pyranosyl glucosides to the corresponding ketosaccharides. In this conversion reaction, the catalyst can discriminate between different secondary hydroxyl groups. The secondary hydroxyl group at the C3 position will only be oxidized to the ketone by using 2,6-dichlorobenzoquinone as a stoichiometric oxidant [18].

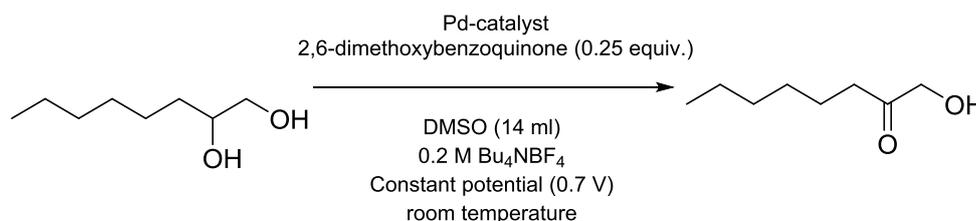
The drawback of using oxygen as the stoichiometric oxidant in combination with catalyst 2 is the fact that it may lead to the oxidation of the neocuproine ligand and the corresponding loss of reactivity over time [16]. To avoid this effect, other catalysts have been synthesized. Waymouth et al. reported on a catalyst having a trifluoromethyl substituted phenanthroline ligand instead of neocuproine and studied its oxidation potential of 2-heptanol [19]. The results were not convincing. Although the turnover number of this catalyst doubled and no ligand oxidation was observed, the initial rate, however, was 3.7 times lower compared to catalyst 2. Furthermore, the ligand is much more difficult to synthesize. Recently, a deuteration of the methyl substituents in the neocuproine ligand was suggested to obtain a more resistant ligand against oxidation [20].

In this chapter, an electrocatalytic approach by using catalyst 1 and 2 is suggested. By working in an inert gas atmosphere, the possible degradation of the catalyst by oxygen is prevented. Secondly, electrochemical recycling avoids the use of a stoichiometric amount (or excess) of the oxidant, making this approach a more sustainable alternative. In an electrocatalytic oxidation reaction, a mediator gets oxidized at the electrode surface at a low potential followed by the oxidation of the target molecule [21]. Mediators of interest are benzoquinones as it is known that the reduced species (hydroquinones) can easily be reoxidized at relative low potentials [22-26]. The selective oxidation of vicinal diols directly to α -hydroxy ketones is of utmost importance when looking for an atom-economical reaction. For the first time, palladium catalysts with neocuproine ligands are combined with the electrochemical recycling of benzoquinones. A selective electrochemical oxidation of diols under mild conditions and high yield is now presented.

5.2. Testing different palladium catalysts for the oxidation of 1,2-octanediol

A first set of experiments was performed to evaluate the usability/reactivity of different palladium precursors for the selective oxidation of 1,2-octanediol, in combination with the electrochemical recycling of 2,6-dimethoxybenzoquinone. During the constant potential electrolysis (electrolysis cell equipped with a reticulated vitreous carbon (RVC) as working electrode), a current could be obtained and selective oxidation to the hydroxy ketone was observed.

Table 5.1. Oxidation of 1,2-octanediol with different palladium catalysts with electrochemical recycling of 2,6-dimethoxybenzoquinone.



Entry ^{a)}	Palladium Catalyst	Time [h]	Yield [%] ^{b)}	Recovered alcohol [%] ^{b)}	Selectivity [%]	Charge [Coulomb]
1	neocuproinePd(OAc) ₂	7	49	34	74	70
2 ^{c)}	[neocuproinePdOAc] ₂ [OTf] ₂	5	53	36	83	74
3	NeocuproinePd(CH ₃ CN) ₂ (OTf) ₂	5	40	48	77	58
4	Pd(OAc) ₂	5	5	90	50	4

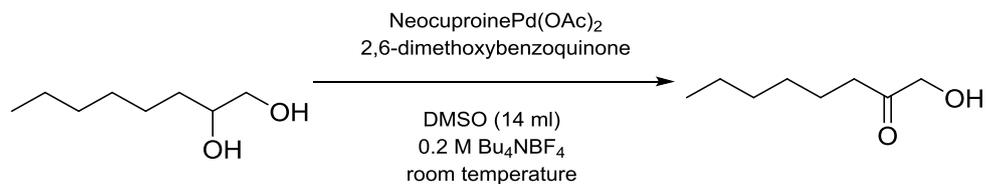
^{a)} Reaction conditions: 0.7 mmol alcohol with 0.05 equivalents of palladium catalyst and 0.25 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMSO with 0.2 M Bu₄NBF₄ at room temperature with constant potential of 0.7 V under argon atmosphere.

^{b)} NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^{c)} With 0.025 equivalents of (neocuproinePdOAc)₂(OTf)₂

The different palladium catalysts could convert the alcohol into the hydroxyl ketone during the electrolysis procedure. All three neocuproine ligated palladium catalysts gave a similar yield, as can be seen in Table 5.1. Only the palladium acetate (Table 5.1, entry 4) was observed being inactive, as only a very low current was detected during the electrolysis. Next, both catalysts 1 and 2 were further tested in different solvents (DMSO, DMF and acetonitrile). It was observed that DMSO is the solvent leading to the highest conversion. In DMF catalyst 1 seems to be inactive while catalyst 2 has limited activity. In acetonitrile both catalysts seemed to be inactive.

Currently, only the aerobic oxidation of alcohols with this specific catalyst is reported at 80 degrees Celsius with the addition of a base and only [neocuproinePdOAc]₂[OTf]₂ (catalyst 2) is reported to be active at room temperature in combination with an excess of 2,6-dimethoxybenzoquinone. Based on these reported reactions, an efficient electrochemical conversion at room temperature was expected only for catalyst 2. Simultaneously, the question was raised whether catalyst 1 could also be reactive at room temperature with an excess of 2,6-dimethoxybenzoquinone (without electrolysis). For this reason, different stoichiometric oxidations of 1,2-octanediol were performed with 2,6-dimethoxybenzoquinone and neocuproinePd(OAc)₂ at room temperature.

Table 5.2. Stoichiometric oxidation of 1,2-octanediol with 2,6-dimethoxybenzoquinone.

Entry ^a	Equivalent Benzoquinone	Time [h]	Potential	Yield [%] ^b	Recovered alcohol [%] ^b
1 ^c	3 equiv.	6	No potential	4	95
2	3 equiv.	6	No potential	11	87
3 ^d	3 equiv.	7	No potential	13	83
4	0.6 equiv.	8	No potential	9	87

^a) Reaction conditions: 0.7 mmol alcohol with 0.1 equivalents of neocuproinePd(OAc)₂ and x equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMSO with 0.2 M Bu₄NBF₄ at room temperature under argon atmosphere.

^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

^c) Without 0.2 M Bu₄NBF₄

^d) With 3 equivalents of *p*-benzoquinone instead of 2,6-dimethoxybenzoquinone.

In literature, reoxidation of catalyst 2 is performed with *p*-benzoquinone instead of 2,6-dimethoxybenzoquinone as mediator. Therefore, a similar reaction was also tested with three equivalents of *p*-benzoquinone (Table 5.2, entry 3). However, no difference was observed between both mediators.

The oxidation reaction of 1,2-octanediol was further tested with three equivalents or 0.6 equivalents of 2,6-dimethoxybenzoquinone. In both cases only the stoichiometric oxidation of 1,2-octanediol was observed.

As a conclusion, based on the comparison between electrolysis (Table 5.1) and stoichiometric oxidation (Table 5.2) of 1,2-octanediol, the electrochemistry clearly aids the facile conversion with high yield of the desired alcohol at room temperature in the presence of both catalyst 1 or catalyst 2.

To further examine the reactions responsible for the electrochemical oxidation of the alcohol, cyclic voltammetric experiments were performed. First, neocuproinePd(OAc)₂ was added to a DMSO electrolyte solution and scanned between the potentials of interest during the electrolysis. No redox peaks could be detected in a potential window from 0 to 1.0 V (Figure 5.1). At ca 1 V a Pd feature occurs. Therefore, this potential was further avoided to retain the activity of the catalyst. Next, an excess of 1,2-octanediol is added to the solution and scanned in the same potential range. No redox processes were observed. Finally, the addition of 2,6-dimethoxybenzoquinone to the solution resulted in the detection of a redox peak around 0.6 V, which is explained as the oxidation of 2,6-dimethoxyhydroquinone. This reoxidation phenomenon explains the current monitored during the electrolysis experiment. A peculiar observation is the fact that the peak height is not in correlation with the concentration of the benzoquinone added elucidating a slow reoxidation process of the mediator.

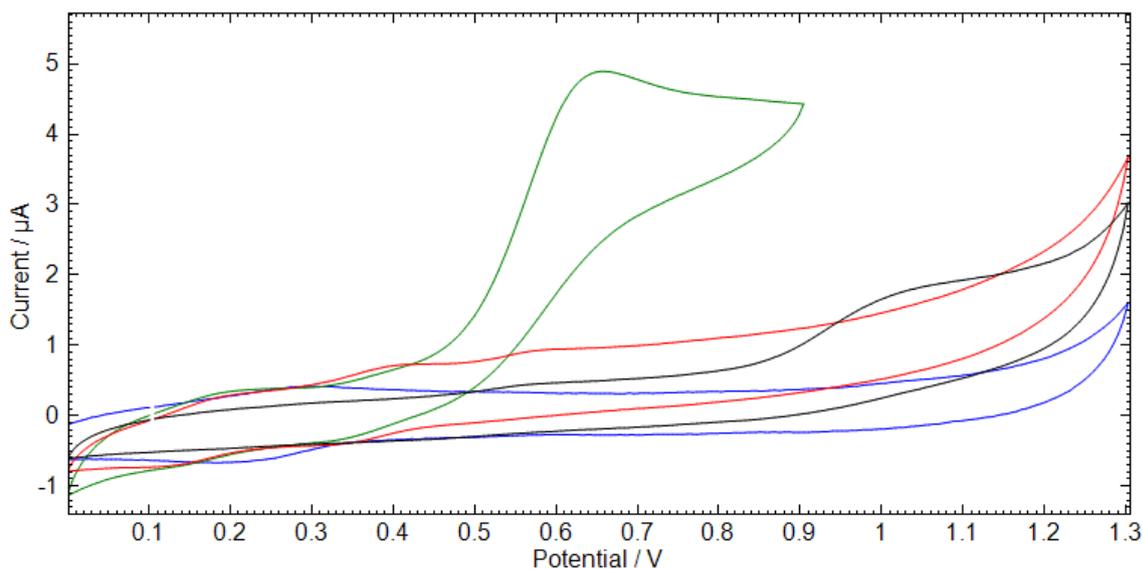


Figure 5.1. Cyclic voltammograms with a scan rate of 100 mVs^{-1} of an $0.1 \text{ M Bu}_4\text{NBF}_4$ DMSO solution at 20°C (blue); with addition of $0.9 \text{ mM neocuproinePd(OAc)}_2$ (black); with addition of $50 \text{ mM 1,2-octanediol}$ (red); with addition of $8.9 \text{ mM 2,6-dimethoxybenzoquinone}$ (green).

With $[\text{neocuproinePdOAc}]_2[\text{OTf}]_2$ a similar experiment is conducted, resulting in a peak current which is ten times higher for the oxidation of 2,6-dimethoxyhydroquinone (Figure 5.2). A much more efficient reoxidation process of the mediator is thus taking place. Although the cyclic voltammetric experiments reveal differences for the two catalysts on a short time scale, a similar result (yield) is obtained during an electrolysis (ca seven hours) experiment under similar conditions. Probably, catalyst 1 has only a slower activation in the starting phase but at longer times a similar conversion is obtained. Faster initial rates with catalyst 2 were also observed in aerobic oxidation processes [16].

Since a similar yield is obtained during electrolysis, there is no advantage in using catalyst 2, being much more expensive and having a time-consuming synthesis. Therefore, it was decided to further explore and optimize the electrolysis procedure using catalyst 1, the precursor of catalyst 2.

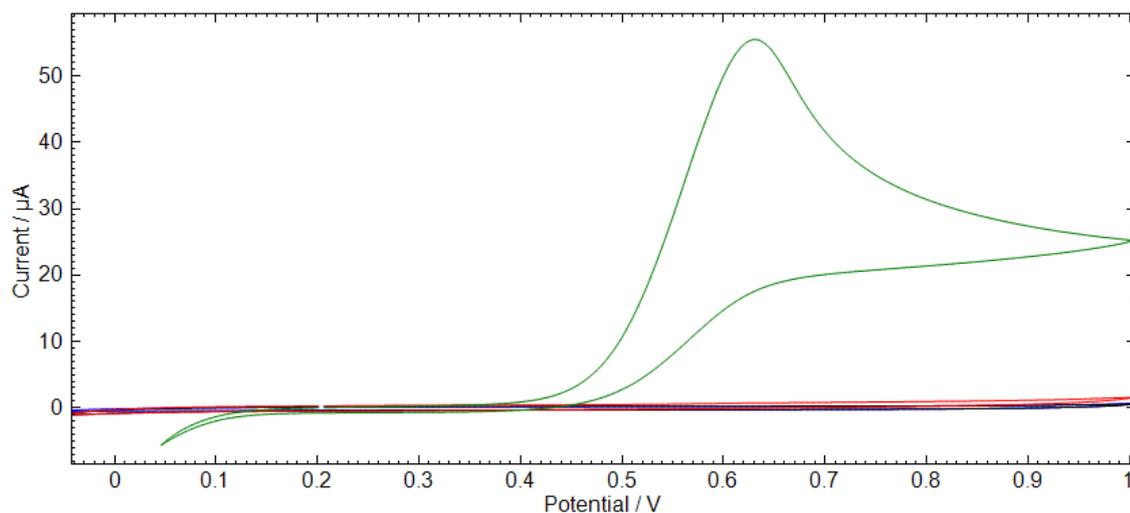
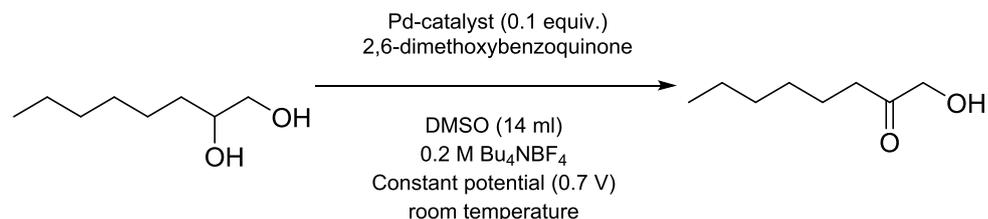


Figure 5.2. Cyclic voltammograms with a scan rate of 100 mVs^{-1} of an $0.1 \text{ M Bu}_4\text{NBF}_4$ DMSO solution at 20° C (blue); with addition of $0.9 \text{ mM [neocuproinePd(OAc)}_2\text{[OTf]}_2$ (black); with addition of $50 \text{ mM 1,2-octanediol}$ (red); with addition of $8.9 \text{ mM 2,6-dimethoxybenzoquinone}$ (green).

5.3. Optimization of the electrolysis with NeocuproinePd(OAc)₂ as a catalyst

It has been shown in Table 5.1 that the electrolysis, combining neocuproinePd(OAc)₂ and 2,6-dimethoxybenzoquinone, results in the selective oxidation of 1,2-octanediol into the hydroxyl ketone. A conversion of ca 50% could be obtained. To optimize the reaction conditions during the electrolysis, different concentrations of 2,6-dimethoxybenzoquinone were added to examine the influence on the alcohol conversion.

Table 5.3. Optimization of the electrolysis reaction of 1,2-octanediol.

Entry	Equivalent Benzoquinone	Equivalent of catalyst 1	Yield [%]	Recovered alcohol [%]	Selectivity [%]	Charge [Coulomb]
1	0 equiv.	0.1 equiv.	21	73	78	9
2	0.25 equiv.	0.1 equiv.	63	26	85	68
3 ^a	0.25 equiv.	0.1 equiv.	65	24	86	66
4	0.40 equiv.	0.1 equiv.	76	9	84	88
5	0.60 equiv.	0.1 equiv.	85	2	87	108
6	0.60 equiv.	0.01 equiv.	22	70	73	26
7	0.60 equiv.	0.05 equiv.	71	22	91	95
8 ^b	0.40 equiv.	0.1 equiv.	71	11	80	98
9 ^c	0.25 equiv.	0.1 equiv.	1	97	33	6
10 ^d	0.25 equiv.	0.1 equiv.	6	90	60	6

^a) With 0.25 equivalents of *p*-benzoquinone instead of 2,6-dimethoxybenzoquinone, with a potential of 0.9 V instead of 0.7 V.

^b) Electrolysis at 40 degrees Celsius.

^c) With the addition of 0.1 M of Bu₄NOAc.

^d) With the addition of 2 equivalents of Et₃N.

From Table 5.3, it is clear that the addition of 2,6-dimethoxybenzoquinone is crucial to obtain an efficient oxidation reaction. The higher the concentration of benzoquinone, the more efficient the palladium catalyst can be reoxidized. As a result, the formed hydroquinone can be more efficiently oxidized at the electrode surface, proven by a higher charge obtained during the electrolysis. The optimized reaction conditions take place with 0.6 equivalents of 2,6-dimethoxybenzoquinone added, as a quasi-full conversion of the alcohol to the hydroxy ketone is detected with a high selectivity (Table 5.3, entry 5).

Next, the influence of the concentration of the palladium catalyst on the conversion was examined. Lowering the concentration of the palladium catalyst results in a lower yield and hence in a lower charge. Enough palladium catalyst should be present to obtain an efficient oxidation reaction. From Table 5.3 (entry 5-7) it is clear that 0.1 equivalents are needed to obtain an optimal conversion, ca. 85%. Remarkable the highest selectivity was already obtained with 0.05 equivalents of palladium catalyst present.

Additionally, the influence of the nature of the mediator (benzoquinone) was investigated. An electrolysis reaction was performed using p-benzoquinone instead of 2,6-dimethoxybenzoquinone (Table 5.3, entry 3). As the oxidation potential of p-hydroquinone is shifted over +0.2 V compared to the one of 2,6-dimethoxyhydroquinone, a constant potential of 0.9 V instead of 0.7 V was applied. Comparable yields and efficiencies were found using these two types of quinones. Further optimization was conducted and also the influence of temperature was examined (Table 5.3, entry 8). A similar yield was obtained at 40 degrees Celsius compared to a reaction at room temperature. No benefits are therefore gained in using higher temperature.

The addition of a base was also examined, as it is known from literature that a high concentration of acetate is crucial to reoxidize the palladium catalyst in stoichiometric conversions using oxygen as stoichiometric oxidant. To our surprise, by adding 0.1 M of acetate (Table 5.3, entry 9) no electrolysis current could be detected and no oxidation of the 1,2-octanediol was observed. It was noticed that the addition of acetate anions is making the palladium catalyst inactive. Also, the addition of trimethylamine was tested instead of acetate (Table 5.3, entry 10). Again, no current could be detected and only a small amount of the hydroxy ketone was formed.

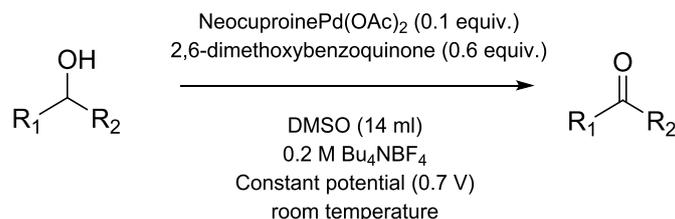
The optimized procedure using 0.1 equivalents of catalyst 1 and 0.6 equivalents of 2,6-dimethoxybenzoquinone at room temperature under a constant potential of 0.7 V for 8 hours was expanded to different alcohols, firstly to elucidate the difference in conversion between diols and singular alcohols. A primary and secondary aliphatic alcohol, 1-octanol (Table 5.4, entry 2) and 2-nonanol (Table 5.4, entry 3), were tested. Only an electrolysis current could be detected with 1-octanol, no current was detected with 2-nonanol. After work up, the aldehyde octanal was detected as a reaction product of the oxidation of 1-octanol and for the

electrolysis of 2-nonanol the starting alcohol was mainly recovered. A test was also performed with 1-nonanol (Table 5.4, entry 4) and again oxidation of the alcohol took place with formation of the aldehyde nonanal in reasonable yield. As a conclusion, the neocuproine catalyst seems to be capable of catalyzing the oxidation of both, vicinal diols (chemoselective) and primary aliphatic alcohols.

Next, a primary and secondary benzylic alcohol were tested. A similar behavior was observed as with the oxidation of aliphatic alcohols. For benzyl alcohol (Table 5.4, entry 6), benzaldehyde was found as the oxidation product in a reasonable yield. In contrast, for 1-phenylethanol (Table 5.4, entry 5) no electrolysis could be detected. The starting alcohol was mostly recovered unaffected.

When looking at the selectivity of the reactions, there is a remarkable difference between the primary and the secondary alcohols. Although the yields of the ketone formation is limited, it shows a higher selectivity than the oxidation of primary alcohols to aldehydes. This points to a slow but selective oxidation of the secondary alcohols.

Comparing the results of the singular alcohols with 1,2-octanediol, the diol shows a better reactivity during the electrolysis (higher charge-yield). The presence of the two alcohol functions seems to enhance the activation by catalyst 1, as an easier complexation is possible between the catalyst and the diol.

Table 5.4. Oxidation of singular alcohols.

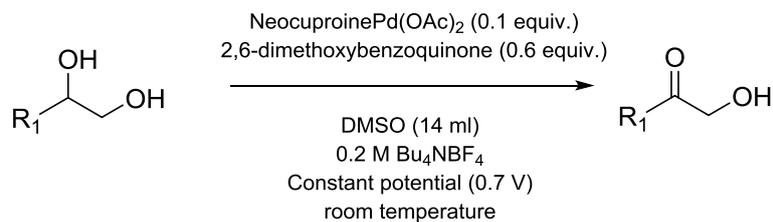
Entry ^a	Alcohol	Yield [%] ^b	Recovered alcohol [%] ^b	Charge [Coulomb]	Selectivity [%]
1	1,2-octanediol	85	2	108	87
2	1-octanol	64	16	86	76
3	2-nonanol	8	90	3	80
4	1-nonanol	60	17	99	72
5	1-phenylethanol	10	85	2	67
6	benzylalcohol	60	25	72	80

^a) Reaction conditions: 0.7 mmol alcohol with 0.1 equivalents of neocuproinePd(OAc)₂ and 0.6 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMSO with 0.2 M Bu₄NBF₄ at room temperature with constant potential of 0.7 V for 8 hours under argon atmosphere.

^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

To further expand the scope of the suggested procedure, different diols were tested. Electrolysis of 1,2-hexanediol was performed (Table 5.5, entry 2) and a selective oxidation of the secondary alcohol was detected in a comparable yield as with 1,2-octanediol. Similar results were obtained with 1,2-decanediol (Table 5.5, entry 3).

By testing cyclohexanediol, the influence of two vicinal secondary alcohols instead of one primary and one secondary is studied. Using the standard electrolysis procedure also these alcohols were selectively oxidized to the hydroxy ketone. Similar yields of hydroxyl ketone were obtained starting from cis-cyclohexanediol and from trans-cyclohexanediol, illustrating that there is no preference for a certain configuration of the alcohol functionalities on the cyclohexane structure.

Table 5.5. Oxidation of diols.

Entry ^a	Alcohol	Yield [%] ^b	Recovered alcohol [%] ^b	Charge [Coulomb]	Selectivity [%]
1	1,2-octanediol	85	2	108	87
2	1,2-hexanediol	79	n.d.	95	79
3	1,2-decanediol	88	3	101	91
4	Cis-cyclohexanediol	57	n.d.	106	57
5	Trans-cyclohexanediol	58	n. d.	91	58

^a) Reaction conditions: 0.7 mmol alcohol with 0.1 equivalents of neocuproinePd(OAc)₂ and 0.6 equivalents of 2,6-dimethoxybenzoquinone in 14 mL DMSO with 0.2 M Bu₄NBF₄ at room temperature with constant potential of 0.7 V for 8 hours under argon atmosphere.

^b) NMR yields calculated after extraction with the addition of 1,3,5-trimethoxybenzene as an internal standard.

5.4. Conclusions

Neocuproine palladium based catalysts are of interest for the oxidation of vicinal diols in an electrolysis setup based on the electrochemical reoxidation of benzoquinone mediators.

The use of electrolysis in organic synthesis is an interesting pathway to obtain more green and sustainable synthesis procedures. Electricity and in essence electrons are used as a reagent and when combined with sustainably generated electricity, good alternatives for chemical oxidants can be found.

The remarkable activity of the palladium catalyst neocuproinePd(OAc)₂ in the electrolysis procedure provides an interesting alternative for the selective oxidation of vicinal alcohols at room temperature. Because of the reactivity of neocuproinePd(OAc)₂ at room temperature, the cumbersome synthesis of more complicated palladium based catalysts is avoided while providing a similar reactivity using the same procedure.

The electrolysis procedure was evaluated and optimized by focusing on different singular and vicinal diols. For singular alcohols, only the primary alcohols could be oxidized. For the vicinal diols, all tested compounds were active and a selective oxidation with good yield was obtained using the suggested electrolysis procedure.

5.5. Abbreviations

OAc	Acetate
OTf	Triflate
DMSO	Dimethyl sulfoxide
C	Coulomb
DMF	<i>N,N</i> -Dimethylformamide
n.d.	Not detected

5.6. Experimental

5.6.1 General information

The ^1H NMR spectra were recorded on a Bruker Avance II 400 spectrometer with TMS as the internal standard. All coupling constants are given in Hertz and the chemical shifts are given in ppm. Multiplicity is indicated using the following abbreviations: b for broad, d for doublet, t for triplet, q for quintet, m for multiplet and s for singlet.

5.6.2 Synthesis of the catalysts

Synthesis of neocuproinePd(OAc)₂ (catalyst 1)

A solution of neocuproine (5.5 mmol, 1.25 g) in anhydrous CH_2Cl_2 (20 mL) was added to a solution of Pd(OAc)₂ (5.0 mmol, 1.12 g) in anhydrous toluene (100 mL) at room temperature under nitrogen. The mixture was stirred overnight and heptane was added to precipitate the complex. A yellow solid was filtered off, washed with acetone and dried under vacuum; yield: 1.78 g (4.0 mmol, 80%).

Synthesis of neocuproinePd(CH₃CN)₂(OTf)₂

To a slurry of catalyst 1 (0.221 g, 0.511 mmol) in acetonitrile (1.0 mL) was added a solution of triflic acid in acetonitrile (0.33 M, 3.8 mL, 2.5 equiv). The solution was stirred briefly and then precipitated with diethyl ether to give a yellow solid. This solid was isolated by centrifugation, precipitated two more times from acetonitrile using diethyl ether, and dried under vacuum to give a light yellow solid (0.090 g). Additional triflic acid (0.33 M, 1.0 mL) was added to the original supernatant, followed by brief stirring and precipitation with diethyl ether. The resulting yellow solid was subjected to the same workup as described above to give additional product (0.021 g). The pure solids were combined (0.111 g, 0.160 mmol, 31% yield).

Synthesis of [neocuproinePdOAc]₂[OTf]₂ (catalyst 2)

To a 25 mL round-bottom flask with a stirring bar was added catalyst 1 (0.0400 g, 0.0924 mmol), neocuproinePd(CH₃CN)₂(OTf)₂ (0.0642 g, 0.0924 mmol), and acetonitrile (10.0 mL). The resulting mixture was stirred until all solids dissolved and then precipitated with diethyl ether to give an orange solid. This solid was isolated by centrifugation, washed with diethyl ether, and dried under vacuum to give 1 as an orange solid (0.0589 g, 0.0563 mmol, 61% yield).

5.6.3 General procedure for the electrolysis reaction

A homemade airtight electrolysis cell was used equipped with a reticulated vitreous carbon (RVC) as working electrode (basi, USA), a bridged Ag/AgCl reference electrode with 2 M LiCl ethanol solution as inner solution and a 0.1 M Bu₄NBF₄ DMSO as bridge solution was used and the counter electrode, a platinum rod electrode, was put in a divided cell separated from the anodic part by a ceramic frit. In a typical electrolysis experiment 4 mL of a 0.2 M Bu₄NBF₄ DMSO solution was added to the divided part followed by the addition of 200 μL of acetic acid. In the anodic part neocuproinePd(OAc)₂ (0.1 equivalent), 2,6-dimethoxybenzoquinone (0.6 equivalent) and the alcohol (0.7 mmol) was added to a 14 mL solution of 0.2 M Bu₄NBF₄ in DMSO. The cell was closed and put under an argon atmosphere. Stirring was started, next a potential of 0.7 V was applied. After the appropriate reaction time 30 mL of water was added to the reaction mixture. The resulting mixture was extracted with *tert*-butylmethylether (3 times 25 mL). The collected organic layer was washed with 15 mL of water to further remove DMSO. Next the organic layer was dried with MgSO₄ filtered and evaporated. The resulting solution was examined with NMR. Isolated products were obtained using column chromatography with heptane/ethylacetate (7/3) as eluent.

1-hydroxy-octan-2-one

The general procedure for the electrolysis was followed with 1,2-octanediol as the alcohol. Giving an isolated yield of 1-hydroxy-octan-2-one of 81%.

^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, 3H, CH_3), 1.29 (m, 6H, 3 x CH_2), 1.61 (q, 2H, CH_2), 2.41 (t, 2H, CH_2), 3.20 (s, 1H, OH), 4.24 (s, 2H, CH_2).

1-hydroxy-hexan-2-one

The general procedure for the electrolysis was followed with 1,2-hexanediol as the alcohol. Giving an isolated yield of 1-hydroxy-hexan-2-one of 75%.

^1H NMR (400 MHz, CDCl_3): δ = 0.92 (t, 3H, CH_3), 1.35 (m, 2H, 1 x CH_2), 1.61 (q, 2H, CH_2), 2.41 (t, 2H, CH_2), 3.20 (s, 1H, OH), 4.24 (s, 2H, CH_2).

1-hydroxy-decan-2-one

The general procedure for the electrolysis was followed with 1,2-decanediol as the alcohol. Giving an isolated yield of 1-hydroxy-decan-2-one of 85%.

^1H NMR (400 MHz, CDCl_3): δ = 0.88 (t, 3H, CH_3), 1.28 (m, 10H, 5 x CH_2), 1.62 (q, 2H, CH_2), 2.39 (t, 2H, CH_2), 3.26 (s, 1H, OH), 4.22 (s, 2H, CH_2).

octanal

The general procedure for the electrolysis was followed with 1-octanol as the alcohol. Giving an isolated yield of octanal of 59%.

^1H NMR (400 MHz, CDCl_3): δ = 0.88 (t, 3H, CH_3), 1.30 (m, 8H, 4 x CH_2), 1.63 (q, 2H, CH_2), 2.41 (d x t, 2H, CH_2), 9.75 (t, 1H, CH).

nonanal

The general procedure for the electrolysis was followed with 1-nonanol as the alcohol. Giving an isolated yield of nonanal of 57%.

^1H NMR (400 MHz, CDCl_3): δ = 0.88 (t, 3H, CH_3), 1.29 (m, 10H, 5 x CH_2), 1.62 (q, 2H, CH_2), 2.41 (d x t, 2H, CH_2), 9.75 (t, 1H, CH).

benzaldehyde

The general procedure for the electrolysis was followed with benzyl alcohol as the alcohol. Giving an isolated yield of benzaldehyde of 56%.

^1H NMR (400 MHz, CDCl_3): δ = 7.52 (d, 2H, $\text{CH}_{\text{arom.meta}}$), 7.61 (t, 1H, $\text{CH}_{\text{arom.para}}$), 7.85 (d, 2H, $\text{CH}_{\text{arom.ortho}}$), 9.99 (s, 1H, CH).

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Summary

When looking at alternative organic synthesis procedures, an interesting approach is to make use of electrolysis reactions, as they have the potential to be a more environmentally friendly alternative to the current methods applied. In this research, we aimed to develop alternative procedures for the oxidation of the alcohol functionality into aldehydes and ketones. Our strategy was to replace stoichiometric oxidants by electricity during an electrolysis process, in combination with different metal catalysts.

First, the popular tetrapropylammonium perruthenate (TPAP) catalyst was examined. An extensive electrochemical analysis of the TPAP catalyst was performed in an acetonitrile solution. The electrochemical reversible redox couple between the perruthenate anion and ruthenium tetroxide could be described. Using potentiostatic experiments, the interaction between TPAP and a primary alcohol, n-butanol, was elucidated. Interestingly, an oxidation current was observed, indicating the conversion of the alcohol in interaction with the catalyst. This was further examined by the electrolysis of alcohols using the reoxidation of the spent TPAP. During the electrolysis experiments, reoxidation of the spent TPAP could be obtained. However, there were no conditions under which an efficient oxidation of alcohols was obtained. A reaction between the formed aldehyde and the solvent could be detected and, subsequently, a mixture of different products was obtained. Only limited or low yields for the desired carbonyl compounds were achieved.

In the second strategy an additional mediator, namely a benzoquinone was used, which was oxidized at the electrode surface during the electrolysis experiments. After an extensive electrochemical study of the different components, the combination of the Shvo complex with 2,6-dimethoxybenzoquinone was investigated as a possible mediator system for oxidation reactions. The electrolysis reaction using this mediator system was studied and an efficient synthetic method could be developed. Different secondary alcohols were tested. A good yield of the corresponding ketones was obtained for the benzylic alcohols containing electron

donating substituents. In contrast, only limited yields could be obtained for the benzylic alcohols containing electron withdrawing groups. Good yields of the corresponding ketones were achieved for aliphatic secondary alcohols, while for primary alcohols, only limited yields of aldehydes were obtained with the aliphatic alcohols in particular. In addition, the oxidation of 1,2-diols was studied and a good yield was obtained for the selective oxidation of the secondary alcohol with 1,2-octanediol. Considering the success of this procedure using a metal catalyst in combination with the electrochemical oxidation of hydroquinones at the electrode surface, the use of this method was expanded in combination with a different metal catalyst.

Thirdly, the use of neocuproine palladium catalysts was tested for the oxidation of vicinal diols. It was observed that these catalysts were able to oxidize vicinal alcohols in combination with the electrochemical reoxidation of the benzoquinone mediators. The palladium catalyst, neocuproinePd(OAc)₂, used in the electrolysis procedure, provides an interesting alternative to the selective oxidation of vicinal alcohols at room temperature. The electrolysis procedure was evaluated and optimized, and then used to test different singular and vicinal diols. It was found that for singular alcohols only the primary alcohols were active using the same electrolysis procedure. All the vicinal diols were active and a selective oxidation was obtained using the standard electrolysis procedure.

To summarize, the procedure using a neocuproine palladium catalyst was successful for alcohol oxidation, next to the procedure using the Shvo catalyst. The system with the Shvo catalyst was optimized for the oxidation of secondary alcohols, while the neocuproinePd(OAc)₂ catalyst is promising for the oxidation of both primary alcohols and vicinal diols at room temperature.

Samenvatting

Wanneer we kijken naar de verschillende mogelijkheden om organische synthese reacties uit te voeren, is een interessante optie het gebruik van elektrolyse processen. Dit type reacties heeft het potentieel om een duurzaam alternatief te zijn. Tijdens dit doctoraat hebben we gezocht naar alternatieve procedures voor het oxideren van de alcohol functionaliteit met vorming van ketonen of aldehydes. Onderzoek is verricht naar het vervangen van stoichiometrische oxidanten die momenteel gebruikt worden in combinatie met verschillende metaal katalysatoren. Het gebruik van elektriciteit tijdens elektrolyse processen kan gebruikt worden om deze oxidanten te vervangen en op die manier het gebruik van toxische producten te vermijden en het afval dat ze voort brengen te reduceren.

De eerste ruthenium katalysator die onderzocht werd tijdens dit doctoraat, is de populaire tetrapropylammonium perruthenate (TPAP) katalysator. Een uitgebreide elektrochemische studie van TPAP in een acetonitrile oplossing werd uitgevoerd. Op deze manier kon het reversibele redox koppel, het perruthenate anion en ruthenium tetraoxide, beschreven worden. Om de interactie tussen TPAP en *n*-butanol te bestuderen werden potentiostatische metingen uitgevoerd. Daarbij werd een oxidatiestroom gedetecteerd, die er op wijst dat heroxidatie van het verbruikt TPAP op een elektrochemische wijze mogelijk is. Vervolgens werd dit verder onderzocht via elektrolyse experimenten, maar er konden geen gunstige condities gevonden worden waarbij een efficiënte oxidatie van het alcohol werd bekomen. Tevens traden zijreacties op met als voorbeeld de reactie tussen het gevormde aldehyde en het solvent. Via elektrolyse was het aldus enkel mogelijk om de gewenste carbonyl verbindingen te bekomen in een geringe opbrengst.

In een tweede strategie werd het gebruik van een geschikte mediator verkend. Hierbij wordt de mediator aan het elektrodeoppervlak geheroxideerd bij een relatief lage potentiaal waardoor tevens de selectiviteit kan worden bevorderd.

Na een uitgebreide elektrochemische studie van de Shvo katalysator en de mediator 2,6-dimethoxyquinone afzonderlijk werd het potentieel van de combinatie van beide componenten voor alcohol oxidatie bestudeerd. Vervolgens werden elektrolyse reacties uitgevoerd en een efficiënte procedure kon op punt worden gesteld. Diverse secundaire alcoholen konden met deze strategie succesvol geoxideerd worden naar het overeenkomstige keton. De omzetting van de benzyliche alcoholen met elektron gevende substituenten vond plaats met een hoge opbrengst. Voor benzyliche alcoholen met elektron zuigende substituenten konden slechtst beperkte omzettingen bekomen worden. Alifatische secundaire alcoholen werden eveneens vlot omgezet, in tegenstelling tot de omzetting van primaire alcoholen. Ten slotte, werd tevens de omzetting van 1,2-diolen bestudeerd en werd een selectieve oxidatie van het secundaire alcohol waargenomen.

In een derde deel van het werk werden neocuproïne palladium katalysatoren getest voor de oxidatie van vicinale diolen. Op deze manier kon het principe van de elektrochemische heroxidatie van de benzoquinone mediators verder worden geëxploreerd. De palladium katalysator neocuproïnePd(OAc)₂ kon gebruikt worden in een elektrolyse opstelling en geeft zo een interessant alternatief voor de selectieve oxidatie van vicinale alcoholen op kamertemperatuur. Na optimalisatie van de procedure werden verschillende enkelvoudige alcoholen en vicinale alcoholen getest. Van de enkelvoudige alcoholen bleken enkel de primaire alcoholen actief te zijn met deze methode, terwijl voor de vicinale diolen al de geteste moleculen selectief geoxideerd konden worden met vorming van het overeenkomstige hydroxyketon. Op deze manier is deze methode een mooie aanvulling op de procedure met de Shvo katalysator. De Shvo katalysator is geschikt voor de oxidatie van secundaire alcoholen terwijl de neocuproïnePd(OAc)₂ katalysator kan gebruikt worden voor de oxidatie van primaire alcoholen en vicinale diolen op kamer temperatuur.

Critical remarks and outlook

To conclude, a critical revision of the different systems investigated is now provided, along with a critical overview of the results obtained and suggestions for future work.

Main focus was the strive for sustainable synthesis of chemicals meanwhile unravelling the opportunities that electrosynthesis provides to achieve this objective. The importance of sustainability cannot be underestimated and is a never ceasing concern in our society. It is a process that keeps on evolving. Thinking and rethinking every aspect in our society is necessary and should be guided by improving sustainability. For the synthesis of drugs and special fine chemicals the same focus should be present and kept present in the future. Another driving force is the use of electricity in synthesis procedures as a reagent, which in its core is sustainable. Of course electricity can be generated in different ways, it is important to realize that efforts need to be prolonged in this field to improve sustainability. Research in this area will pay off in the near future.

During this PhD new approaches were developed and investigated for the oxidation of alcohols, a fundamental transformation in organic synthesis which will remain an area of interest.

Certain catalyst systems were investigated to determine their suitability in an electrochemical approach. The results obtained provide fundamental insight to critically select catalyst systems for electrolysis of organic compounds. The methods presented should be further investigated and improved, certainly if one is aiming to develop an industrial process.

The selectivity of the reaction was one of the main criteria in selecting the catalysts and improving the procedures. The tetrapropylammonium perruthenate (TPAP) catalyst did not show good selectivity. The electrochemical recycling of this catalyst did not prove to be

appropriate for selective alcohol oxidation. This lack of selectivity can be explained by the high potential needed for the alcohol conversion.

Therefore, a different strategy was used for the other catalysts. An additional mediator was introduced, namely 2,6-dimethoxybenzoquinone, which can be reoxidized at the electrode surface at lower potentials. Using this strategy, the selectivity of the procedure improved.

Selectivity and efficiency are main focusses to develop improved procedures. So it is expected that new catalysts or catalyst systems will be discovered in the future. This can be achieved for example by changing ligands or functionalizing ligands to improve or specify the properties of the catalyst. Also, a variation in the type of metal in catalysts is a promising approach. There is an ongoing interest in developing efficient and selective catalysts using cheap and abundant metals such as iron. These catalysts have to be efficiently regenerated to truly be a catalyst. Of course one of the most suggested sustainable ways to do, is with the aid of oxygen. But as already argued in this PhD, electricity can be seen as an interesting alternative.

Therefore, the examination of new or improved mediator systems will be an interesting research area. During this PhD we found that the benzoquinone/hydroquinone couple is an interesting mediator couple which should be further explored. The combination of a catalyst (which is efficient and selective for the desired transformation of the target molecule) in combination with the electrochemical recycling of hydroquinones to benzoquinones (which is selective and occurring at relative low potential) is a concept that can be extended and improved in the future. Interesting research pathways might be to improve the benzoquinone by functionalization, to lower the oxidation potential but retaining its catalyst reoxidation potential.

To evaluate whether a certain procedure is applicable for use in real production or industrial processes, different parameters must be checked and will have to be satisfied for a process to be deemed useable. Specifically for electrosynthesis applications, one of the most important parameters evaluated is the current density that can be obtained or used in the electrochemical cell. Most industrial-scale electrochemical cells use a simplified two electrode setup in combination with the application of a constant current. An investigation of this specific setup was not undertaken in the research for this thesis. As the focus of the research was on finding reactions that are very selective, a constant potential method was always used. In this setup, there is more control over the reactions taking place, which allows the

determination of whether or not the catalyst system is useful. A typical value of the current density used during the experiments was approximately 0.5 mA/cm^2 (or 5 A/m^2). A typical value used in industry would be closer to a few kA/m^2 , which is a factor that is a thousand times higher than the values used in this thesis. To conclude, this is a parameter that should be further examined to prove the usefulness of the method in industry. Higher current density values may be obtained, for example, by applying better mass transfer towards the electrodes, higher potentials or higher concentrations.

Higher concentrations of the different components may improve another important parameter, the process mass intensity (PMI). In this parameter, the total mass of material used is compared to the mass of the product obtained. This takes into account the amount of solvent and electrolyte that would be used. The more concentrated the level at which the work can be done (the more product relative to solvent), the better this value would be. A typical value of 0.05 M for alcohol concentration was used in the research for this thesis and this should be increased to evaluate whether the methods are suitable for industrial application. This is another important factor that can be investigated in the future.

This PMI parameter is also dependent on whether the recycling of components is possible. This provides an interesting direction for further research, which could examine how an efficient recycling of all the different components can be achieved. If we ultimately want to obtain a sustainable synthesis reaction, it is very important that efficient and straightforward recycling of different components is possible. A way to recycle the solvent with electrolyte, might be by using ionic liquids instead. Ionic liquids are conductive by nature and non-volatile, which are interesting properties when recycling is important. Another strategy might be to functionalize the electrode in an efficient way with benzoquinone molecules. In this way this will improve work up and it is an interesting step to improve recyclability.

When looking at industrial applications, cell design is important, and one of the parameters which was not examined during this research was the membrane used. The experiments with 2,6-dimethoxybenzoquinone as the mediator were all performed in a divided cell. This means that the anode and cathode within the cell were separated from each other by a membrane, which, in this work, was a ceramic frit. An efficient membrane should allow efficient charge transfers and have good conductivity, while at the same time, it should be impermeable to

the different components used or formed during electrolysis. In this work, no special attention was given to the membrane and a traditional ceramic membrane was used. Therefore, an interesting parameter that could be further optimized is the membrane used. For example, the use of a proton exchange membrane may be useful in alcohol oxidation electrolysis. In this way, the excess of protons that builds up in the anodic part of the cell can transfer to the cathodic part to be efficiently reduced to hydrogen gas.

Also, electrolysis can be combined with flow cells, which has advantages to simplify the electrochemical cell and might improve the efficiency of the electrochemical cell.

Not only the oxidation of alcohols can be considered but also other oxidation reactions or synthesis reactions. It can be interesting to find out in which way they can be incorporated into an efficient electrochemical synthesis procedure. The use of electricity as a reagent will remain an interesting research area in the coming future.

Publications

J. Lybaert, B.U.W. Maes, K. Abbaspour Tehrani and K. De Wael

The electrochemistry of tetrapropylammonium perruthenate, its role in the oxidation of primary alcohols and its potential for electrochemical recycling, *Electrochimica Acta*, **2015**, 182, 693-698.

J. Lybaert, S. Trashin, B.U.W. Maes, K. De Wael and K. Abbaspour Tehrani

Cooperative electrocatalytic and chemoselective alcohol oxidation by Shvo's catalyst, *Advanced Synthesis & Catalysis*, **2017**, 359, 919-925.

Conference and workshop contributions

- Participation congress, annual symposium Electrocatalysis, KNCV/ISE, Leiden University, Leiden, Nederland 29/11/2013
- Presentation at congress ChemCYS 2014
Electrochemical recycling of a ruthenium catalyst for the oxidation of alcohols
ChemCYS 2014, Blankenberge, België 28/02/2014
- Participation congress, annual symposium Electrochemistry in non-traditional media, KNCV/ISE, Antwerp University, Antwerpen, België 07/11/2014
- Participation congress, Symposium “Chemistry as an enabler for a sustainable society”, Antwerp University, Antwerpen, België 13/05/2015
- Presentation at congress ChemCYS 2016
Towards a sustainable oxidation reaction: a joint action of electrochemistry and Shvo catalyst
ChemCYS 2016, Blankenberge, België 17/03/2016