The winding road from Oppenauer to sustainable catalytic oxidations of alcohols

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PROEFSCHRIFT

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Chapter 1

Catalytic oxidations of alcohols into aldehydes and ketones

Abstract

An introduction is given concerning catalytic oxidation technologies and methodologies affording various environmentally benign processes for the production of fine chemicals, intermediates for various applications such as pharmaceuticals, agrochemicals and fragrances, etc. These catalytic methods avoid the stoichiometric use of inorganic reagents, offer techniques for conducting synthetic organic chemistry safely, cleanly, economically and often have a broad applicability. These considerations served to formulate the aim and scope of this thesis.

1.1 Introduction

The highest priorities of the fine chemical industry with respect to process and product safety and the protection of the environment are reflected in decreased usage of organic solvents, the phasing out of halogenated solvents and research for suitable alternatives. Nowadays, the manufacture of fine chemicals and pharmaceuticals generates in the order of 25-100 times more waste than product and is approximately 1000 times more profligate than bulk chemicals production and oil refining. Sheldon *et al.* have attributed this to the use of traditional synthetic practices and purification procedures for making fine chemicals and pharmaceuticals.[2] Furthermore, fine chemicals are often complex, multifunctional molecules with low volatility and limited thermal stability. For the last twenty years the demand for fine chemical intermediates has increased dramatically due to the development of new products in various major industrial sectors, like the pharmaceutical, agro and food and flavor industry. Unfortunately, synthesis of these high added-value chemicals mainly consists of laborious multistep processes that often lead to unfavorable product/by-product ratios. Multi-purpose equipment is used for the batch-wise production of fine chemicals, unlike bulk chemicals where continuous processes are run in dedicated plants. Furthermore, fine chemicals generally cannot bear the costs of the extensive research program characteristic of the development of a proprietary catalyst for large volume chemicals.[2-4]

Although cleaner and more efficient preparations are essential, novel methods, e.g. for ibuprofen and paracetamol, are often product specific.[1] In recent years, the effort to develop more efficient means of oxidizing alcohols has focussed on the area of catalysis. Much effort has been expended in the development of new transition metal complexes to catalyze the oxidation of alcohols by a variety of inexpensive and environmentally compatible oxidants such as hydrogen peroxide, molecular oxygen and to a lesser extent sodium hypochloride.[5] Catalytic methods avoid the use of stoichiometric inorganic reagents and as a consequence offer environmental benefits. Moreover, selective catalytic processes can reduce operating costs. An illuminating example is the industrial synthesis of hydroquinone, depicted in Figure 1.1.

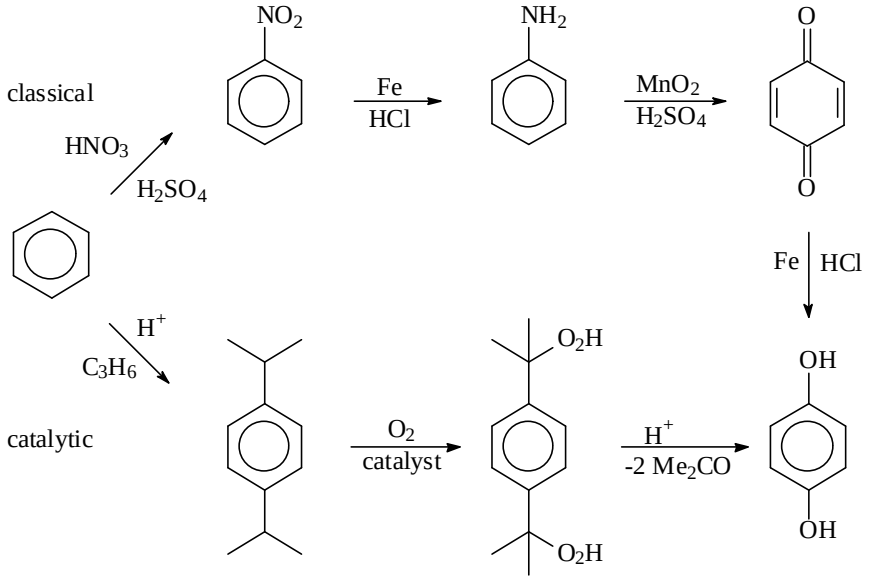


Figure 1.1. *Traditional and catalytic routes to hydroquinone.*

Traditionally hydroquinone was manufactured by oxidation of aniline with a stoichiometric amount of MnO_2 followed by reduction with iron and hydrochloric acid. Aniline derived from benzene via nitration and reduction. In this way, the process generates more than 10 kg of inorganic salts per kg of hydroquinone. In contrast, the modern route involves a catalytic oxidation of *p*-diisopropylbenzene followed by acid-catalyzed rearrangement of the bis-hydroperoxide. *p*-Diisopropylbenzene is derived from benzene by Friedel-Crafts alkylation in the presence of an acid catalyst. The catalytic route produces less than 1 kg of inorganic salts per kg product and gives acetone as a useful organic by-product.[5]

In order to minimize the amounts of waste and the costs of disposal, related catalysis can contribute tremendously to develop cleaner processes for the fine chemical industry. Challenges that have to be tackled are:

- Achieving high chemo-, regio- and stereoselectivity, zero emissions and no by- product formation. This waste-prevention implies that atom efficiencies[6] and the environmental- or EQ-factor (kg waste per kg product times unfriendlyness category of the waste)[7] have to be optimized.
- Valorization of by-products, i.e. extensive use of starting materials.
- Reducing the number of reaction steps to avoid loss of starting material in each step and to save capital investment. The challenging target is a 'one-pot'-reaction.[8]

1.2 Catalytic oxidations

In the production of fine chemicals stoichiometric quantities of classical inorganic oxidants like chromium oxide, potassium dichromate and potassium permanganate are still widely used.[9] In contrast, catalytic oxidation processes are common in the production of bulk chemicals (table 1.1).

Table 1.1. *Selected catalytic oxidations of industrial importance.*[8]

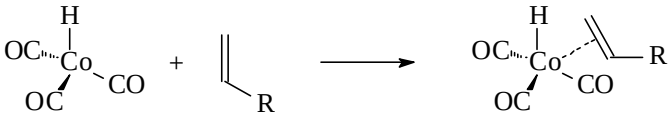
From	To	Catalyst	Conv (%)	Sel (%)
ethylene	acetaldehyde	$PdCl_2/CuCl_2$	35-45	94
ethylene	oxirane	Ag on Al_2O_3	8-10	70-80
anthracene	anthraquinone	CrO_3	99	>90
p-xylene	terephthalic acid	V_2O_5 on Al_2O_3	50	90
propene	*n*-butyraldehyde	$HCo(CO)_4$	80	80

Nowadays, in most industrial oxidation processes heterogeneous catalytic systems prevail over homogeneous ones.[11] However, homogeneous catalysis is often more convenient with respect to mechanistic studies because well-defined metal complexes with a single catalytic site are involved. Catalyst recovery, ligand degradation with concomitant loss of activity and extensive optimization are some of the challenges posed by homogeneous catalysis. Since this

thesis will deal with homogeneous catalysis, the elemental steps (a-c) involved in a homogeneous catalytic cycle will be explained.

(a) Ligand coordination and dissociation

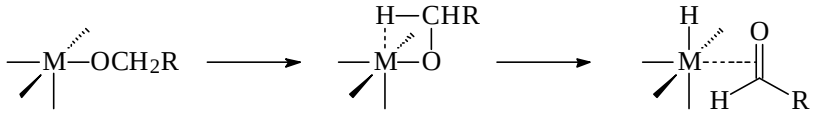
Catalysis of molecular transformations generally requires facile coordination of reactants to metal ions and equally facile loss of products from the coordination sphere. Transition metal complexes with less than 18 valence electrons are called coordinatively unsaturated. An example of ligand coordination is the coordination of an alkene to a cobalt catalyst. This step is the first step in the hydroformylation process in which alkenes react with CO and H_2 to form an aldehyde:



16 electron complex 18 electron complex

(b) Insertion and elimination

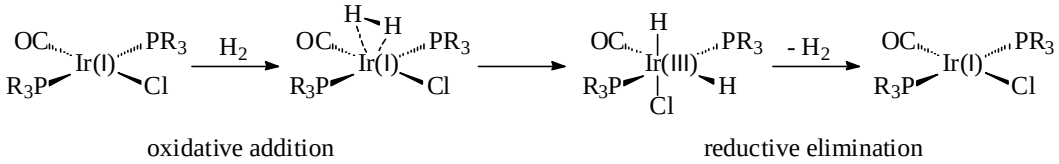
The migration of ligands to unsaturated ligands coordinated to the same metal are insertion reactions. The reverse of insertion is elimination. Elimination reactions include the important β-hydrogen elimination:



(c) Oxidative addition and reductive elimination

Dissociation of a molecule and simultaneous coordination of the fragments to a metal center is called oxidative addition. In this step the oxidation state of the metal increases. The mechanisms of oxidative addition reactions can vary from simple concerted reactions to heterolytic and radical additions. Reductive elimination is the reverse of oxidative addition and often is the subsequent step in a catalytic cycle. An example is the oxidative addition of

hydrogen to an iridium complex. In this example iridium(I) is oxidized into iridium(III) and the reductive elimination regenerates the active catalyst.



1.3 Catalytic oxidations to aldehydes and ketones

Hydroformylation processes[12] are most frequently applied in industry for the production of aldehydes from olefins, carbon monoxide and hydrogen. However, since operational conditions are quite extreme (50-250 bar and 150-200°C), the hydroformylation is not suitable for the production of fine chemical aldehydes.

Important hydrogen transfer reactions avoiding the use of molecular hydrogen are the classical Meerwein-Ponndorf-Verley reduction and the Oppenauer oxidation (MPVO).[13-15] In these reversible reactions hydrogen is transferred from one organic molecule to another. In particular, reactions in which one equivalent of hydrogen is transferred from an alcohol to a ketone or *vice versa* are proposed to proceed through a six-membered transition state in which both reductant and oxidant are coordinated to the metal center of a metal alkoxide catalyst (Figure 1.2).

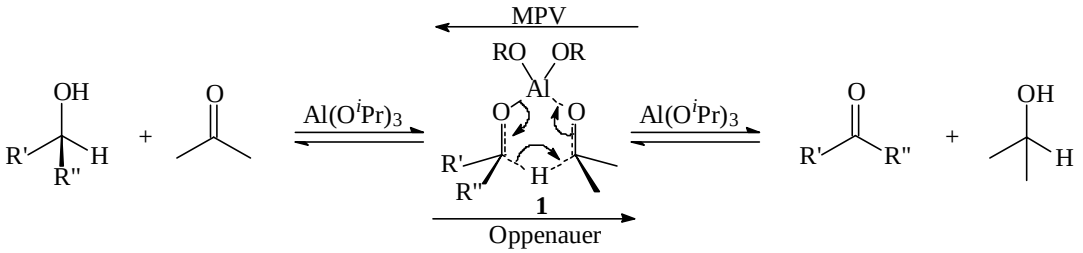


Figure 1.2. *Classical MPVO equilibrium reactions.*

Some important limitations of these reactions are the unfavorable equilibrium when primary alcohols are used as donors, the stoichiometric use of metal oxides and the use of strong acids to reduce the formed metal alkoxide intermediates of type **1**. Although these reactions are successful in the oxidation of secondary alcohols into ketones, the oxidation of primary

alcohols gives rise to side reactions such as aldol condensation, ester formation and over-oxidation to the acid.

To overcome the problem of the unfavorable equilibrium in recent years two types of Oppenauer-like systems have been developed, one by Sheldon and one by Bäckvall *et al*. in recent years. The first type uses molecular oxygen[16-19] or peroxides[16,17-22] as oxidants.

An illustrative example is the system developed by Sheldon *et al*. depicted in Figure 1.3.[19c]

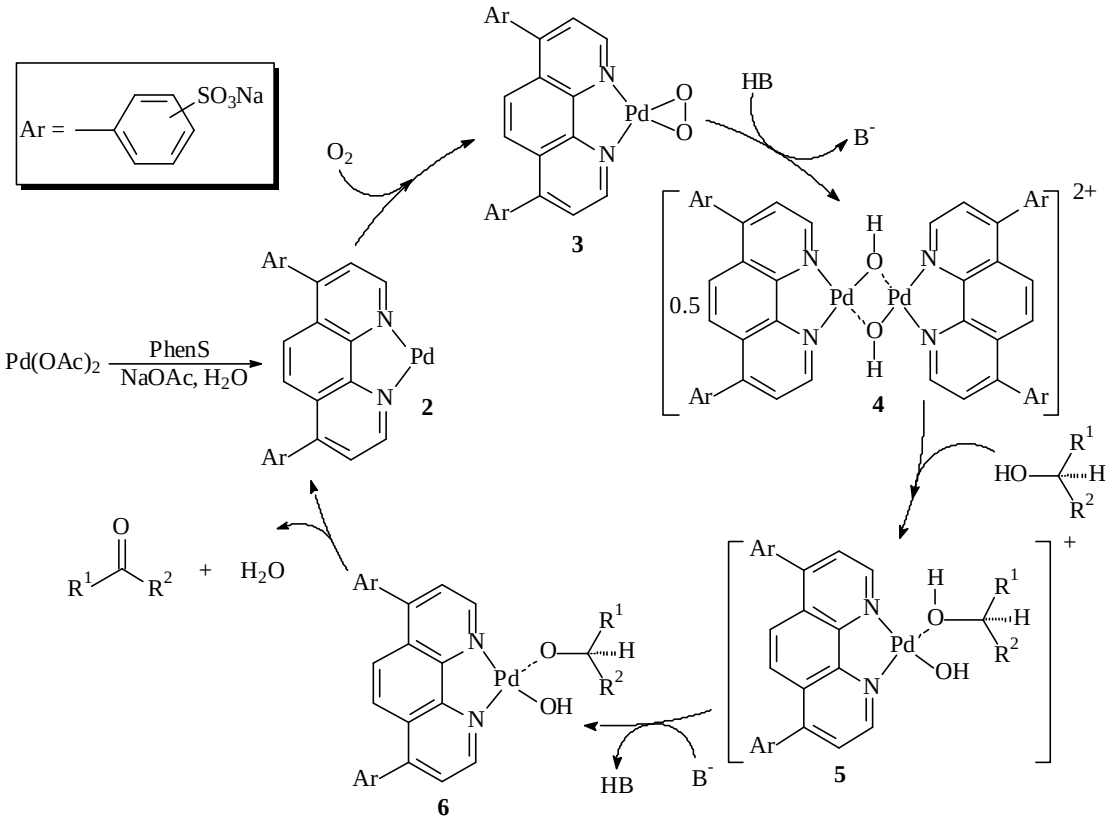


Figure 1.3. *Proposed catalytic cycle for alcohol oxidation with the water-soluble PhenS*Pd(II) catalyst. Ar: aryl, B: base*

In the catalytic cycle the oxidative addition of molecular oxygen to the water-soluble palladium complex of bathophenanthroline disulfonate (**2**) gives a palladium peroxide (**3**). In the next step a bridged Pd complex (**4**) is formed under influence of a base. Subsequent coordination of an alcohol to the metal center (**5**) splits the dimeric structure. Next, a base

abstracts a proton from the coordinated alcohol to form a palladium alkoxide species (**6**). Finally, β-hydrogen elimination leads to the ketone, water and the zerovalent palladium species (**2**). Whereas molecular oxygen as an oxidant enhances the atom efficiency of the reaction, it also implies working under high pressure: 30 bar. Analogously, secondary, primary benzylic and primary allylic alcohols can be selectively oxidized into the corresponding ketones or aldehydes. However, oxidation of primary aliphatic alcohols gives rise to ester formation and over-oxidation to the acid. Catalytic peroxide oxidations of secondary alcohols generally proceed under mild conditions to give the corresponding carbonyl compounds with high efficiency. However, acids[20-22] and esters[20] are major by-products in the catalytic oxidation processes of primary alcohols.

In the second type of Oppenauer-like methods late transition metal alkoxides and hydrides are intermediates in the hydrogen transfer from an alcohol to unsaturated compounds. An example of these reactions is the $RuCl_2(PPh_3)_3$ catalyzed hydrogen transfer proposed by Bäckvall *et al*. (Figure 1.4).[23]

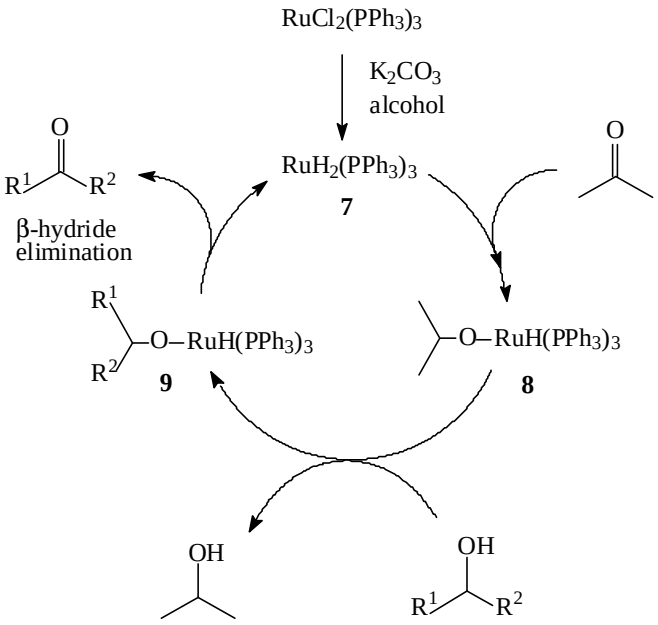
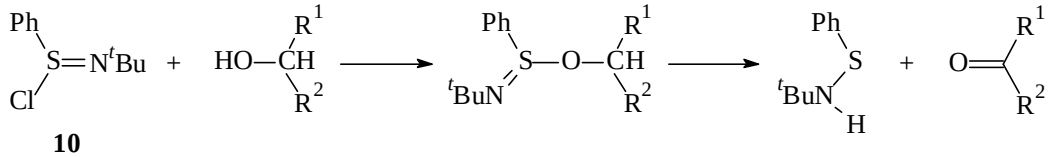


Figure 1.4. *Proposed mechanism of $RuCl_2(PPh_3)_3$ catalyzed hydrogen transfer.*

In this reaction sequence acetone is used as a hydrogen acceptor. The active dihydridoruthenium species (**7**) is formed in a precatalytic step from the dichlororuthenium

catalyst precursor and an alcohol in the presence of a base. In the catalytic cycle acetone coordinates to the metal center with subsequent insertion of a hydride to give the ruthenium alkoxide species (**8**). Next, concomitant dissociation of isopropanol and association of an alcohol molecule occur to afford a second ruthenium alkoxide species (**9**). Finally, this is followed by β-hydrogen elimination to regenerate the active dihydridoruthenium species (**7**).

Apart from these Oppenauer-like systems several other systems have been described recently.[24-28] Mukaiyama *et al*. reported on the oxidation of a variety of secondary as well as primary alcohols into the corresponding ketones and aldehydes using a non-catalytic system with *N*-*tert*-butyl phenylsulfinimidoyl chloride (**10**) as hydrogen acceptor.[24]



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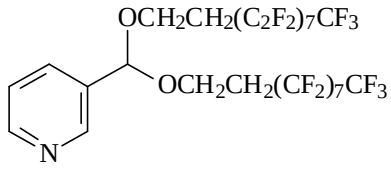
Baiker *et al*. reported on selective oxidations of secondary and primary allylic alcohols in supercritical carbon dioxide over a Pd-Pt-Bi/C catalyst in a continuously operated fixed bed reactor.[25] However, high pressures (90-120 bar) are necessary and relatively fast catalyst deactivation was observed. Uemura *et al*. successfully oxidized various primary and secondary alcohols using molecular oxygen, catalyzed by palladium acetate in the presence of a novel perfluoroalkylated pyridine (**11**) as a ligand in a fluorous biphase system.[26]



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However, in the oxidation of allylic alcohols such as cinnamyl alcohol and geraniol catalyst deactivation occurred. Various primary alcohols could be oxidized selectively into the corresponding aldehyde with stoichiometric amounts of sodium nitrite/acetic anhydride under mild and solvent-free conditions.[27] A promising microbial oxidation was recently reported by Molinari *et al*.[28] In a biphasic system they were able to selectively oxidize various alcohols using acetic acid bacteria.

A recent method still inferior to the catalytic oxidation of secondary alcohols to ketones which again attracted attention, is the ruthenium catalyzed oxidation of alkanes with *tert*-butyl hydroperoxide under mild conditions.[29,30]

1.4 Aim and outline of this thesis

In 1985 the department of economic affairs of the Dutch government started an innovation oriented research program (IOP for Catalysis) in which co-operation between researchers from industry and universities active in catalytic research was stimulated. In these programs, challenging research projects have been defined which aim at the introduction of catalytic methods in organic synthesis directed to industrially relevant fine-chemicals. As pointed out before the fine chemical industry is poorly provided with efficient catalytic tools for large scale production. The research described in this thesis was financed by the Dutch Ministry of Economic Affairs via its innovation oriented research programmes (IOP).

Effective catalytic oxidation of various organic compounds into aldehydes and ketones is important for environmental and economical reasons. In particular, the catalytic oxidation of primary aliphatic alcohols into aldehydes is still challenging due to over-oxidation into esters or acids. Another challenging problem is the unequivocal oxidation of sterols with a double bond at the Δ5 positions (Δ5-(3-hydroxy)-steroids). Due to the energetic benefit of conjugation, double bond migration from the Δ5 positions to the Δ4 position concomitantly occurs. The enone functionality in the A-ring in Δ4-(3-oxo)-steroids is a typical feature of major steroidal hormones such as testosterone, progestosterone, cortisol, and aldosterone. However, retaining the double bond position would be of considerable synthetic and commercial interest.

Within the framework of IOP-Catalysis the objective of the project described in this thesis as defined in 1998 was to investigate catalytic Oppenauer oxidation methodologies to afford various environmentally benign processes for laboratory-scale organic synthesis of aldehydes / ketones including steroid oxidation in the absence of double bond migration.

Chapter 2 describes an attempt to overcome the hurdles of the traditional Oppenauer oxidation method. In order to break through the equilibrium problem usually encountered in

the Oppenauer oxidation the potential of catalytic amounts of metal containing silsesquioxanes in combination with strong H-acceptors is investigated. The results of several H-acceptors in combination with $Zr(O^tBu)_4$ as active catalyst to push the equilibrium to completion are described.

In *chapter 3* alternatives for the classical Oppenauer oxidation are investigated, aimed at shifting the equilibrium to completion. Several catalysts have been tested in the Oppenauer-like oxidation of alcohols into aldehydes and ketones. A systematic study of various combinations of $Ru_3(CO)_{12}$, mono- and bidentate ligands and hydride acceptor is performed to stop the oxidation of primary alcohols at the aldehyde stage. Among many H-acceptors screened, diphenylacetylene (tolane) was the most suitable judged from its smooth reduction. Electron rich and deficient analogues of tolane have been synthesized. Based on competition experiments between these H-acceptors a tentative catalytic cycle for the $Ru_3(CO)_{12}$ - catalyzed oxidations has been proposed. Furthermore, the applicability of triruthenium dodecacarbonyl complex in the selective synthesis of Δ5-(3-oxo)-steroids has been investigated also.

C*hapter 4* deals with a second catalyst / H-acceptor system capable of shifting the equilibrium to completion. $RuCl_2$[*S*-BINAP] demonstrated to catalyze irreversible hydrogen transfer from alcohols to unsaturated compounds like diphenylacetylene. Various combinations of $RuCl_2$[*S*-BINAP] and H-acceptors have been studied for optimal aldehyde and/or ketone formation. In addition, also in this case competition experiments between electron rich and deficient hydride acceptors were investigated. A rationalizing catalytic cycle for $RuCl_2$[BINAP] mediated oxidations has been proposed. In addition, the potential of the chiral $RuCl_2$[S-BINAP] catalyst was investigated in the enantioselective dehydrogenation of several racemic alcohols to perform a kinetic resolution. The applicability of the $RuCl_2$[*S*-BINAP] catalyst for selective oxidation of cholesterol and analogues, as described in chapter 3, has been investigated also.

Finally, in *chapter 5* the catalytic dehydrogenation of alcohols into aldehydes and ketones in the absence of H-acceptor was studied. In the previous chapters a successful breakthrough in shifting the equilibrium was described, according to the Oppenauer-like approach. Herein,

ligands or H-acceptors appeared to be necessary to allow a catalytic pathway. A further improvement from a total atom utilization point of view would be to achieve a favourable shift in the equilibrium in the absence of H-acceptors and solvents. Several acid and base catalyzed dehydrogenation catalysts — prepared *in situ* from commercially available chemicals — have been investigated. The evolving hydrogen gas shifts the equilibrium favorably.

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Chapter 2

Oppenauer oxidations catalyzed by metal containing silsesquioxanes

Abstract

Metal silsesquioxane catalyzed oxidation of alcohols to aldehydes and ketones has been studied. In contrast to the rate accelerating effect of acids, the highly electron deficient silsesquioxane ligands do not tend to accelerate the H-transfer. This might be due to either steric effects of the silsesquioxane framework or a too strong coordination of substrate or product to the electron deficient metal center created by the silsesquioxane framework. Furthermore, several H-acceptors have been screened in the presence of catalytically active $Zr(O^tBu)_4$. Only chloral and tert-butylhydroperoxide (TBHP) have been found to oxidize primary as well as secondary alcohols. Nevertheless, even with these active H-acceptors metal silsesquioxane complexes show little catalytic activity. A spin-off of this study was the observation that with methyl benzoylformate as H-acceptor, trans-esterification prevails over oxidation. Although, several substrates could be converted into their tert-butyl esters, all attempts to realize a catalytic formation of tert-butyl esters failed.

2.1 Introduction

As a result of increasingly stringent environmental constraints it has become forbidden to perform industrial scale oxidations with traditionally stoichiometric oxidants, such as dichromate. Consequently, there is a marked trend towards the use of catalytic alternatives that do not generate aqueous effluents containing large quantities of inorganic salts.[1-3] Furthermore, fine chemicals are often complex, multifunctional molecules with low volatility and limited thermal stability. This necessitates reactions in the liquid phase at moderate temperatures. In addition, many of the desired transformations involve chemo-, regio-, or stereoselectivity. Processing tends to be multipurpose and batch-wise, rather than dedicated and continuous as in bulk chemicals production. This implies that not only raw materials costs but also ease of operation and generic character of the multipurpose installation are important economic and technical considerations. Furthermore, fine chemicals cannot generally bear the

amount of time and costs of an extensive research program to develop a proprietary catalyst for large scale manufacture. Consequently, one may have to be content with a catalyst that perhaps is not optimal but readily available.[4]

Meerwein-Ponndorf-Verley reductions of aldehydes and ketones and Oppenauer oxidations of alcohols (MPVO) are examples of chemoselective reactions that can be performed under mild conditions. The reductants or oxidants are simple, cheap organic molecules and the MPVO reactions are mediated by easily accessible and regenerable metal alkoxides. Furthermore, advantages of the Oppenauer oxidation include chemoselectivity (no over-oxidation towards carboxylic acids), operational simplicity, safe handling and ready adaptation both on laboratory and on a large scale.[5]

The reversible nature of the reduction of aldehydes and ketones was demonstrated by Verley in 1925[6] and shortly thereafter by Ponndorf [7] but it was not until 1937 that Oppenauer first demonstrated applicability in the direct oxidation of Δ5(6)-3-hydroxy steroids to the Δ4-3-ketones by means of aluminum *t*-butoxide and acetone in a benzene solution.[8] This type of oxidation has been used extensively and migration of the double bond from the β,γ to the α,β position was invariably observed (figure 2.1).

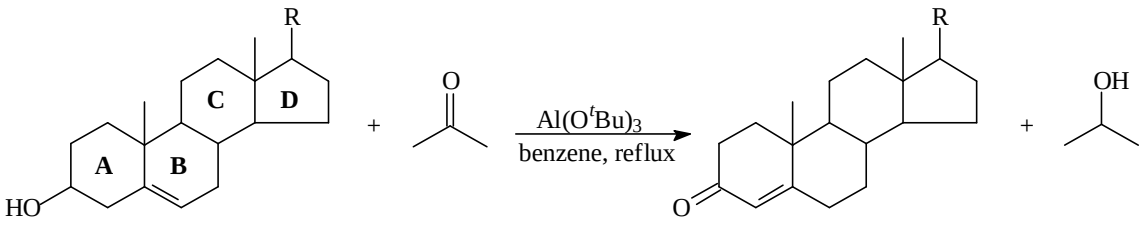


Figure 2.1: *The first direct conversion of Δ5(6)-3-hydroxy steroids to the Δ4-3-ketones by means of aluminum t-butoxide and acetone.*

The Oppenauer oxidation appeared to be superior to other oxidation methods owing to its high yield and mild reaction conditions and was shown to be particularly useful in the synthesis of natural products.[9] While it is common practice to use aluminum alkoxides as catalyst in hydrogen transfer reactions such as the Oppenauer or the Meerwein-Ponndorf-Verley reduction, there are a number of cases e.g. the Cannizzaro reaction and the reduction

of nitro compounds by sodium methoxide, in which the ease of hydrogen transfer by various types of alkali hydroxides or alkoxides is demonstrated. The oxidation of quinine using benzophenone and KO^{t}Bu gave the corresponding ketone in excellent yield while other oxidants such as dichromate and permanganate were less effective (figure 2.2).[10,11]

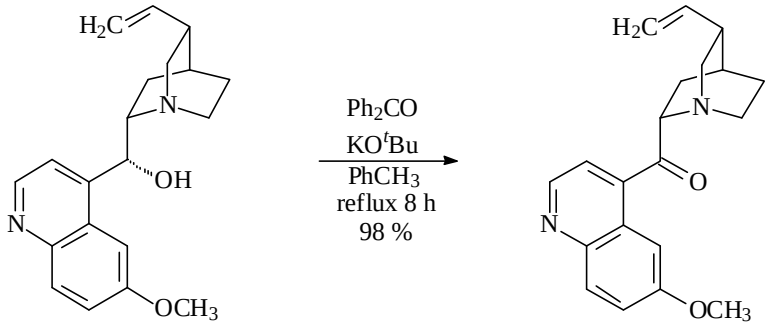


Figure 2.2: *Oxidation of quinine under Oppenauer conditions.*

The first experiments were concerned with attempts to affect the oxidation by the Oppenauer method. Using aluminum *t*-butoxide or aluminum phenoxide as catalyst and a large variety of ketones as oxidant under a wide range of reaction conditions it was not possible to obtain any quininone from quinine.[10,12] It seems probable that the failure of the reaction is due to the acidic nature of the catalyst, that contains an aluminum atom with a sextet of valence electrons. In the presence of base, complexes of the type R_3N—AlR_3 can be formed, that may remove the catalyst from the sphere of action. Such a sequence of events is supported by experiments showing that, in the majority of cases, insoluble precipitates appeared at once on admixture of the reactants.[10]

Furthermore, the reversible nature of the Oppenauer oxidation was used on large scale early in the war between the United States and Japan (1941-1945). It became apparent that a shortage of the supply of quinidine for cardiac therapy would result from the Japanese seizure of the main source of the world's supply on the island of Java. Some, but at that time insufficient amounts could still be obtained from the original but neglected stands of cinchona trees in South America. Hence, it became important to determine whether hitherto commonly employed commercial quinidine could be replaced effectively either by quinine salts, the supply of which was more ample, or by pure quinidine or dihydroquinidine made therefrom.[13] Rabe and Knox were the first to investigate a practical method for converting quinine into

quinidine by double inversion (figure 2.3).[14,15] The first step is the oxidation of quinine into quininone. Via enolization, quinidinone forms that upon reduction of the carbonyl group leads to quinidine.

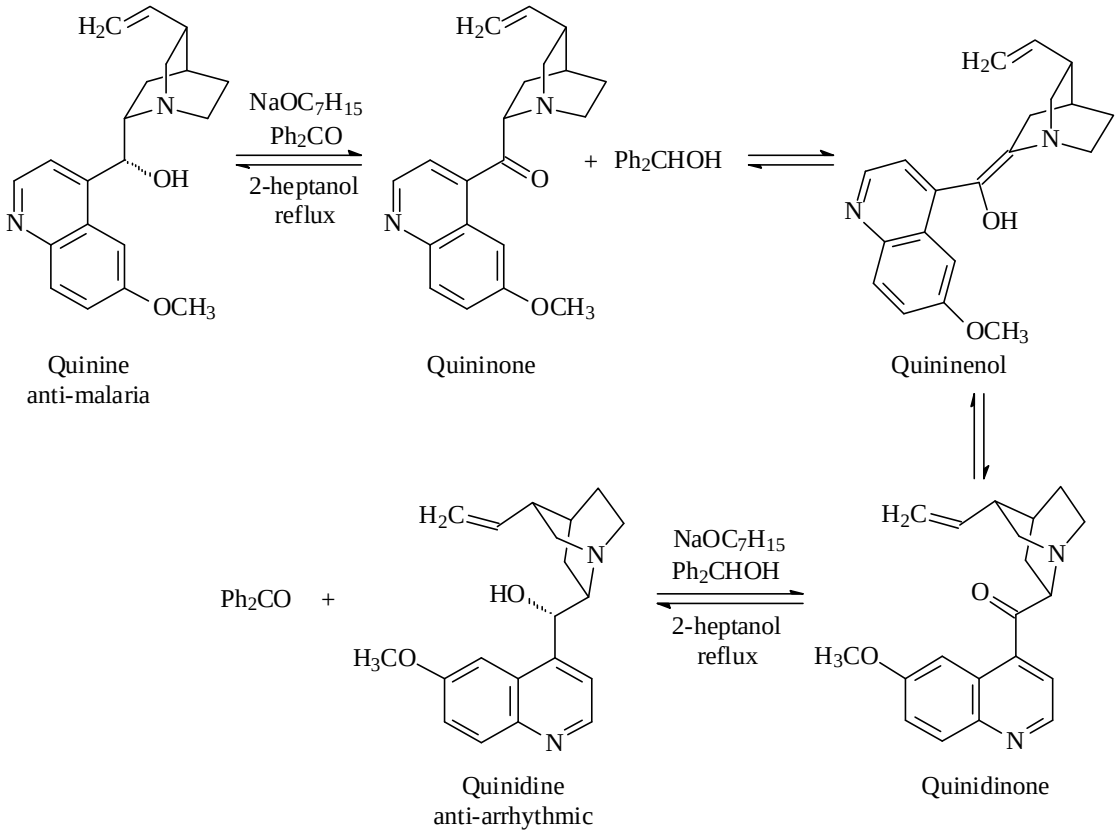


Figure 2.3: *Oppenauer oxidation used in the epimerization of quinine into quinidine.*

For the oxidation of quinine to quininone only a catalytic amount of H-acceptor is required. During the subsequent reduction of quininone or quinidinone the H-acceptor is regenerated, although in practice some H-acceptor is lost through condensation.[15]

2.1.1 Mechanism of the Oppenauer oxidation

In view of the reversible nature of the reaction, many statements concerning the mechanism of the Meerwein-Ponndorf-Verley reduction are equally applicable to the Oppenauer oxidation. The earlier workers postulated the formation of an acetal of type **1**, without giving an adequate explanation for the hydrogen transfer that must occur to account for the course of the reaction.

Meerwein's original hemiacetal structure **1** was revised in favor of the noncommittal molecular addition compound **2** in order to rationalize the function of the aluminum alkoxide (figure 2.4).[16-19]

1 **2**

Figure 2.4: *Postulated intermediates in Meerwein-Ponndorf-Verley-Oppenauer (MPVO) reactions.*

A mechanism involving a cyclic intermediate in which both reductant and oxidant are coordinated to the metal center of a metal alkoxide catalyst, has been suggested by Woodward and Oppenauer (figure 2.5).[10,17] This mechanism is also applicable to oxidations in which alkali alkoxides are employed instead of the aluminum compounds. To favorably shift the equilibrium H-acceptors that are more easily reduced than the pursued product have to be selected in view of thermodynamic product control.

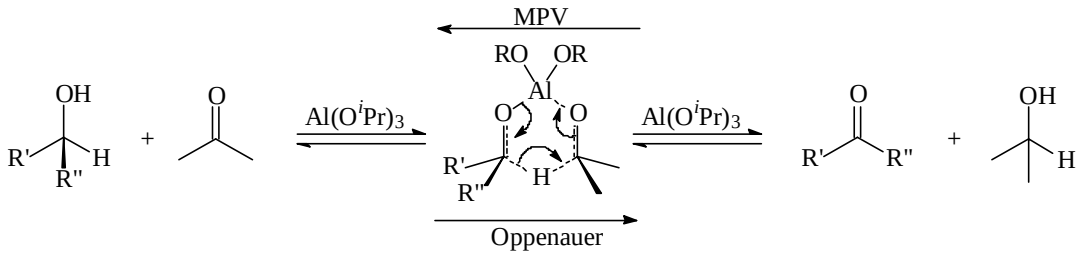


Figure 2.5: *MPVO reactions proceeding via a six-membered transition state.*

Although theoretically only catalytic amounts of metal compound are required in the Oppenauer oxidation, only a few examples have been described employing aluminum alkoxides in the presence of catalytic amounts.[9] Oppenauer oxidations are typically conducted using a stoichiometric amount of aluminum triisopropoxide and excess acetone, which plays the role of oxidizing agent and solvent. However, such conditions can produce substantial amounts of by-products and generate environmentally undesired salts during workup.[20] Furthermore, it has been found that the addition of small amounts of protic acids dramatically

improves the performance of the catalyst in the MPVO reactions, albeit that selectivity decreases, due to enhanced aldol condensation and the Tishchenko reaction.[21-23]

2.1.2 Side reactions commonly encountered in MPVO reactions

The most important side reaction is the aldol condensation, particularly when aldehydes are formed during the Oppenauer oxidation of primary alcohols. The accompanying formation of water leads to deactivation of the alkoxide catalyst (figure 2.6).[9]

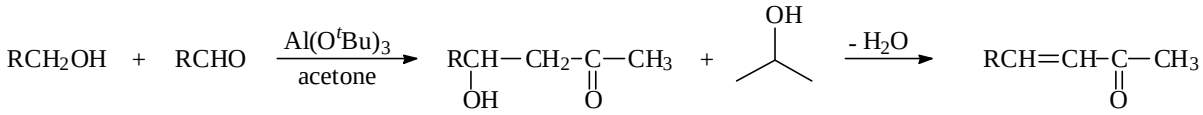


Figure 2.6: *Aldol condensation occurring during the oxidation of primary alcohols.*

A second side reaction may occur with aldehydes lacking α-hydrogen atoms. These compounds may undergo the Tishchenko reaction, yielding esters (figure 2.7).[9]

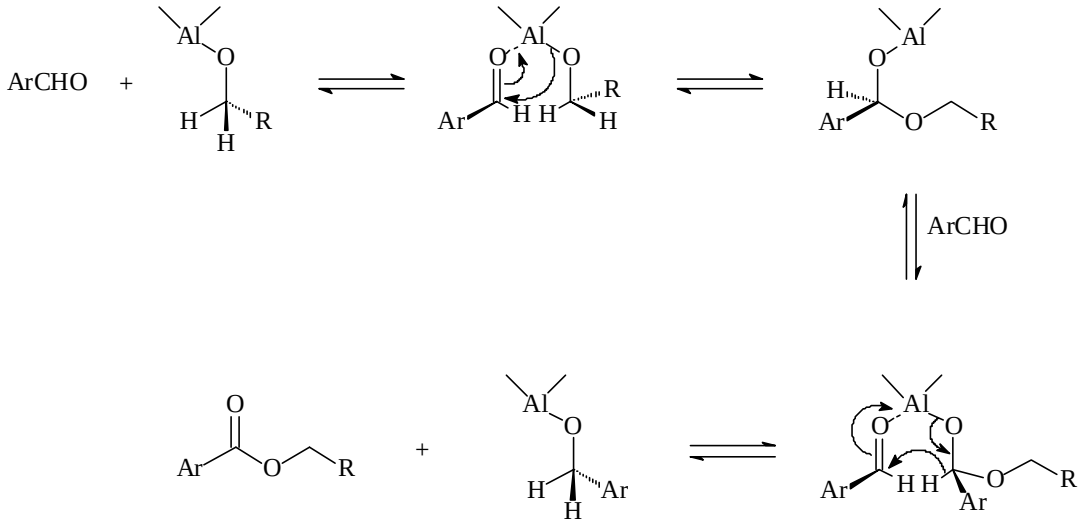


Figure 2.7: *Aldehydes lacking α-hydrogen atoms may undergo the Tishchenko reaction.*

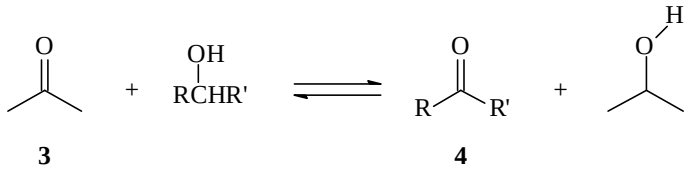
Both side reactions can be suppressed to a large extent by using mild reaction conditions like low reaction temperatures and strong H-acceptors. The more rapid the oxidation by the oxidant (H-acceptor), the less chance there is for significant consecutive reactions.

2.1.3 Influence of solvent

The initial step in the cyclic mechanism of the MPVO reactions involves complexation of the carbonyl and alcohol with the metal atom of the catalyst.[24-26] Polar solvents such as tetrahydrofuran function as donor ligands and thus decrease the electronegativity of the metal and accordingly the reaction rate of the hydride transfer. No reaction could be observed in solvents such as acetonitrile or dimethylformamide. For rapid conversions at low temperatures the least polar solvents such as cyclohexane are most suitable. When problems of solubility arise, toluene or carbon tetrachloride are alternatives.[27] In addition, the choice of solvent and temperature is at times critical, e.g. steroidal diazoketones are stable in boiling benzene solution but are decomposing slowly on reflux in toluene. The conversion of primary alcohols to aldehydes in which higher boiling aldehydes were used as H-acceptors and in which the products is removed by continuous distillation have been performed successfully without solvent.[17]

2.1.4 Influence of H-acceptor

Insight into the thermodynamics of the MPVO equilibria may be helpful in selecting either the reductant or the oxidant properly and in determining the quantity of oxidant. The equilibrium of the Oppenauer oxidation can be estimated from the redox potentials of the two carbonyls **3** and **4** (figure 2.8).[9,28]



3 **4**

Figure 2.8: *The equilibrium can be calculated from the redox potentials **3** and **4**.*

Adkins and Cox have determined redox potentials for a wide range of carbonyl compounds.[29] Carbonyl compounds with high redox potentials like aromatic and aliphatic aldehydes are particularly suitable as oxidants in Oppenauer oxidations. An increase in conversion can be realized by applying: (i) a hydride acceptor with a higher redox potential than the product; (ii) a larger amount of oxidant, which is often achieved by using the oxidant as solvent; (iii) the selective removal of converted oxidant or product by evaporation.[9]

Acetone in combination with benzene as solvent was used exclusively by Oppenauer in his original studies and this ketone has remained one of the most widely used H-acceptors.[8] In spite of its undesirable low oxidation potential (0.129 V) acetone is often selected since it is cheap and can be used in large excess. Even its condensation product mesityl oxide can be removed fairly readily. Cyclohexanone not only has a higher oxidation potential (0.162 volt) than acetone but the higher boiling point permits a shorter reaction time. Cyclohexanone is also readily available and is particularly useful with steroid oxidation since it can be separated from the reaction products by steam distillation.

An unusual reaction observed when diethyl ketone was used as the H-acceptor in the oxidation of vitamin A was the apparent introduction of a double bond into the ionone ring (figure 2.9).[30]

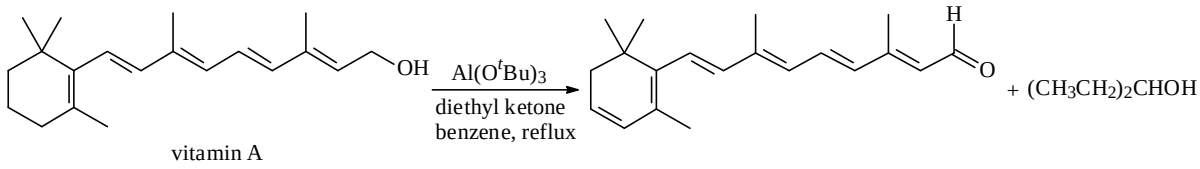


Figure 2.9: *Introduction of a double bond into the ionone ring of vitamin A.*

Another unexpected extension of the Oppenauer oxidation was discovered by Wettstein who noted that replacement of acetone or cyclohexanone by quinone in the oxidation of Δ5(6)-3-hydroxysteroids resulted in the formation of the corresponding Δ4,6-3- ketosteroids (figure 2.10). The yields were not specified but subsequent work has revealed that approximately 40% of the pure doubly unsaturated ketone could be obtained.[31]

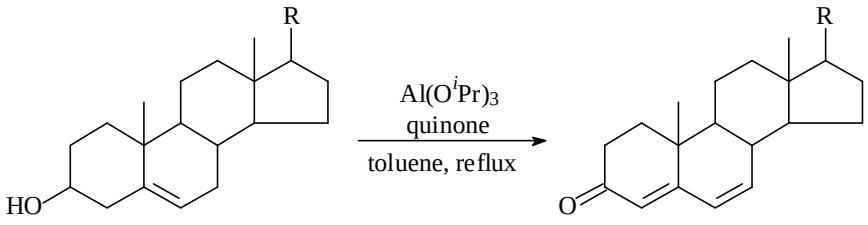


Figure 2.10: *Formation of D4,6-3- ketosteroids from D5(6)-3- hydroxysteroids.*

Aldehydes have only rarely been used as H-acceptors. The use of benzaldehyde, cinnamaldehyde, anisaldehyde has been cited. The Tishchenko condensation of the latter and the tendency for condensation of the products complicate the processes.

With keto alcohols simultaneous oxidation and reduction may be achieved in the absence of additional H-acceptor.

2.1.5 Oxidation of primary alcohols

In 1926, Ponndorf showed that 1-menthol could be oxidized to menthone with aluminum isopropoxide in the presence of cinnamaldehyde as H-acceptor by continuous removal of menthone. This procedure was subsequently extended to primary alcohols such as benzyl alcohol and 1-butanol but has not found general applicability because of the large excess of alcohol necessary. Furthermore, the aldehydes formed often react further with the H-acceptor. When acetone or cyclohexanone were used as H-acceptor, it has been possible to oxidize unsaturated or aromatic primary alcohols to the corresponding aldehydes. Benzyl and anisyl alcohol gave 50-60% of the corresponding aldehyde, while furfuryl alcohol gave 20% of furfural and geraniol 38% of citral. Saturated alcohols, such as 1-heptanol or 3-phenyl-1-propanol gave only very poor yields (5-8%) of aldehyde.

Schinz and Lauchenauer have developed a preparative method for the Oppenauer oxidation of low-molecular-weight primary alcohols to aldehydes.[32] The procedure is essentially a reversal of the Meerwein-Ponndorf-Verley reduction but does not require an excess of alcohol. The alcohol to be oxidized is completely converted into its aluminate and an aldehyde (e.g. cinnamaldehyde or anisaldehyde) with a boiling point some 50°C higher than the expected product is added to serve as the H-acceptor. As a result, the product is slowly distilled under reduced pressure.[17]

2.1.6 Amount and nature of the catalyst

The nature of the catalyst is of great relevance for MPVO reactions. In MPVO reactions, ligand exchange, hydride transfer or both dominate the rate of reaction. Traditional aluminum-based catalysts usually show too slow ligand exchange to enable the use of catalytic amounts. Alkali, alkaline earth metals have very high ligand exchange rates, but low charge density (Na, K) or low coordination number (Li) which mostly prevents catalytic use in this case too. More recently, lanthanides with very high ligand exchange rates as well as

tin, iridium, zirconocene and hafnocene complexes have been applied successfully. Furthermore, heterogeneous systems with activated alumina, hydrous zirconium oxide or zirconium *i*-propoxide on silica gel were also successfully applied. Their advantages are easy catalyst handling, work-up and recycling.[9] Furthermore, the titanium 1- and 2-propoxides, $Zr(acac)_2$ and ZrO_2 showed no catalytic activity. Highly activated alumina introduced in this context by Posner *et al.* and also the silica-supported zirconium catalyst were catalytically active.[33]

The aggregation states of the alkoxides for catalytic activity are also very important. It is known from the work of Shiner and Wittacker that freshly prepared trimeric $Al(^{i}OPr)_3$ is ca. 1000 times more active as the aged tetrameric material.[26,27] Accordingly, the dimeric $Al(O^{t}Bu)_3$ is a superior catalyst, the efficiency of which is, however, largely surpassed by the monomeric $Zr(O^{t}Bu)_4$. In addition $Zr(O^{n}Pr)_4$ showed low activity stressing the particular role of the *t*-butoxide. The advantage of the zirconium catalyst is the ability to act in catalytic amounts. This may — at least in part — be attributed to a much faster exchange rate of the alcohols present in the reaction environment.

Recently, Ajjou *et al.* developed the first water soluble transition-metal catalyst for the Oppenauer oxidation. The catalytic system composed of $[Ir(COD)Cl]_2$, dipotassium-2,2'-biquinoline-4,4'-dicarboxylate and sodium carbonate is highly efficient for the oxidation of benzylic and aliphatic secondary alcohols to the corresponding ketones with catalyst/substrate ratios ranging from 0.4 to 2.5%.[34] Although the system is more reactive than the water-insoluble analogues, it was not successful for primary alcohol oxidation.

2.1.7 Variations of the Oppenauer oxidation

Usually a large excess of acetone or cyclohexanone is used as H-acceptor and in many cases, the product has to be removed by continuous distillation to shift the equilibrium towards the product side. A new variation of the Oppenauer oxidation presented by Krohn *et al.* uses chloral as the H-acceptor and $Zr(O^{t}Bu)_4$ as catalyst.[27,28] The reaction proceeds under mild conditions (20 °C) with a substoichiometric amount of $Zr(O^{t}Bu)_4$ (usually 20 mol %). The commercially available aldehyde chloral was found to be one of the best H-acceptors. Its redox potential of 0.277 volt, is higher than that of most aldehydes that are typically in the range of 0.186 volt for cinnamaldehyde to 0.226 volt for acetaldehyde. An additional practical

advantage is that any excess may be removed by a simple aqueous extraction of the chloral hydrate. High yields can generally be obtained for alcohols with redox potentials up to about 200 mV, particularly when a small excess of chloral is used. However, by-products were detected, even at very low reaction temperatures. Probably, aldol type or Tishchenko reactions occurred in the presence of the basic $Zr(O^tBu)_4$ catalyst. To overcome the unsatisfactory yields less basic but sufficiently active catalysts have to be used. A good solution to the problem was found by using the heterogeneous silica gel supported zirconium catalyst ($SiO_2/Zr(O^nPr)_x$) initially prepared by Inada *et al.* for Meerwein-Ponndorf-Verley reactions.[35]

A second Oppenauer-like mechanism reported by Krohn and Kaneda *et al.* is operational when *tert*-butylhydroperoxide (TBHP) is used as H-acceptor (figure 2.11).[36,37] In this catalytic reaction the hydride is irreversibly transferred to the activated O-O bond of the hydroperoxide leading to the ketone or aldehyde, *tert*-butanol and the di-ligated zirconium species **5**. The catalyst is regenerated by reaction of **5** with substrate and TBHP, releasing water. Water may decompose the catalyst by hydrolysis and for this reason must be trapped very efficiently. Furthermore, the removal of water shifts the equilibrium favorably. However, one major drawback of this method is over-oxidation of the aldehydes to the corresponding acids.

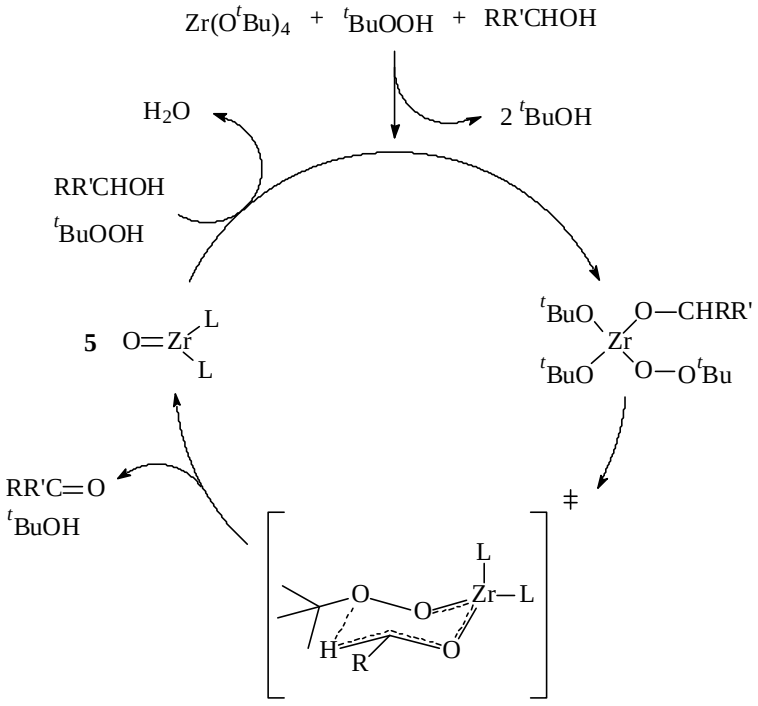


Figure 2.11: *Zirconium-mediated hydride transfer to TBHP.*

Bäckvall *et al.* have recently developed several ruthenium catalyzed Oppenauer-type oxidations of secondary alcohols.[38,39] Ruthenium (II) ensures dehydrogenation of the alcohol and the hydride transfer to a ketone. These reactions will be described extensively in chapters 3 and 4.

Strauss *et al.* developed an environmentally benign method of selective transfer-hydrogenation employing inexpensive, renewable reagents with no inorganic salts introduced or formed.[40] The reaction is performed without metallic catalyst, acids or bases but employs elevated temperatures (220-400°C). However, fine chemicals are often complex, multifunctional molecules with low volatility and limited thermal stability. This necessitates reactions in the liquid phase at moderate temperatures and makes the method of Strauss not applicable in the synthesis of fine chemicals.[4]

2.1.8 Silsesquioxanes

The silicon industry started with commercialization of silicon resins consisting primarily of silsesquioxanes for electrical insulation at high temperatures. Presently, however, polydimethylsiloxane is the predominant material in the industry. Development research was started in the 1930s in Corning Glass Works and General Electrics Company. Even though silsesquioxane chemistry spans more than half a century, interest continues to increase. Silsesquioxanes can be considered as small soluble chunks of silica with the empirical formulas $RSiO_{3/2}$ where R is hydrogen or any organo-functional derivative (figure 2.12). Their chemistry has, however, remained underdeveloped for a long time due to a lack of facile methods for their synthesis in useful quantities. Most precursors to silsesquioxanes find their origin in trichlorosilanes.[41]

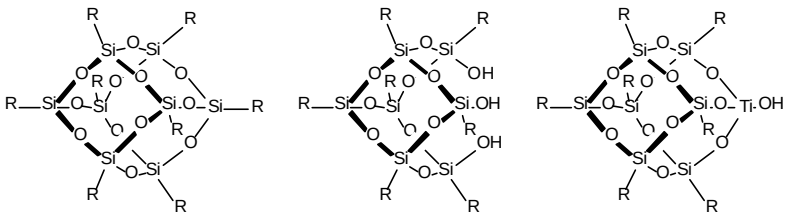


Figure 2.12: *Organosilsesquioxane complexes may be considered as small soluble chunks of silica.*

Incompletely condensed silsesquioxanes — first reported by Brown and Vogt in 1965 — can be prepared in surprisingly good yields by the hydrolytic condensation of $C_6H_{11}SiCl_3$ and have been used as molecular models for hydroxylated silica surfaces, as ligands in homogeneous analogues of silica supported catalysts and as building blocks for the systematic construction of structurally well-defined Si-O-M clusters.[42-44] Over the last decade, many main group and transition metal complexes have been reported that contain silsesquioxane silanolate ligands. In 1986 Feher *et al.* synthesized compounds incorporating ZrCp (Cp = cyclopentadiene) into the cube-like silsesquioxane framework.[45] From the ease with which zirconium, one of the larger transition metals, can be incorporated into the cubane siloxane framework, Feher suggested that it will be possible to synthesize a wide variety of materials containing different metals.[44] The resulting complexes are resistant to leaching and self-oxidation and can be described as self-repairing.[46] Furthermore, it is now evident that these complexes are capable of catalyzing an impressive range of chemical processes such as hydrocarbon oxidation, olefin and alkyne polymerization and metathesis.[47]

Replacement of alkoxy groups on aluminum by more electronegative ligands should increase the rate of MPVO reactions by facilitating coordination of aluminum to the carbonyl compound. This replacement should be achieved most simply by addition of a suitable protic acid to a solution of the aluminum alkoxide.[21] However, synthetic applications of the method are limited by the fact that protic acid and aluminum alkoxide mixtures are potent aldol condensation catalysts, particularly for simple aliphatic aldehydes. However, the electron withdrawing properties of the Si/O skeletons make them highly suitable for accelerating Lewis acid catalyzed reactions in which electron deficient metal centers are required such as Oppenauer oxidations. Aluminum alkoxide moieties grafted onto siliceous mesoporous MCM-41 via siloxide linkages revealed enhanced activity in MPVO reactions.[48] Over the past several years, silsesquioxane complexes have been used to mimic silica surfaces and silica supported metal catalysts. Furthermore, coordination of transition metals to a silsesquioxane framework tends to generate electrophilic metal centers. The silsesquioxane framework is approximately as electron-withdrawing as a CF_3 group. This property is likely to increase the catalytic activity of silsesquioxane complexes when compared to that of related compounds bearing conventional alkoxide or siloxide ligands. This concept has been exploited in newly developed catalysts for alkene metathesis, polymerization, epoxidation and Diels-Alder reactions of enones.[49]

2.2 Objectives

In this chapter the metal containing silsesquioxanes are investigated as catalysts in Oppenauer oxidations. A major aim is the selective oxidation of primary alcohols into aldehydes with catalytic amounts of metal containing silsesquioxanes and without using a large excess of H-acceptor. Due to the unfavorable equilibrium which exists in the oxidation of primary alcohols, primary alcohols can only be oxidized when very strong H-acceptors are applied. In this chapter various easily reducible H-acceptors have been investigated in combination with $Zr(O^tBu)_4$ as catalyst to overcome the unfavourable equilibrium.

2.3 Results and discussion

In the field of aldehyde and ketone synthesis, a problem of continuing interest is the development of a general, highly efficient method for the conversion of alcohols into aldehydes or ketones under mild reaction conditions without producing waste and with good atom economy. Krohn *et al.* demonstrated that $Zr(O^tBu)_4$ in combination with chloral[28] or TBHP[36] as H-acceptor showed high catalytic activity in the oxidation of primary and secondary alcohols. However, chloral is toxic and not an acceptable H-acceptor on large scale in the fine chemical industry.

2.3.1 Screening for H-acceptors

In view of the high activity of $Zr(O^tBu)_4$ in combination with TBHP or chloral, several easily reducible H-acceptors were tested with 1-decanol as substrate and 10 mol% $Zr(O^tBu)_4$ as catalyst. All experiments were conducted in CH_2Cl_2 at reflux except those of entries 1, 2 and 13 that were performed at room temperature (table 2.1). From the results it can be concluded that 1-decanol can be oxidized at ambient temperature when TBHP (t = 20 h, y = 68%) or chloral (t = 1 h, y = 44%) are used as H-acceptor. When TBHP was used in combination with 10 mol% $C_5T_7O_3ZrO^tBu$ as catalyst in refluxing CH_2Cl_2, a conversion of only 13 % was reached after 100 hours. All other H-acceptors tested were not suitable to oxidize 1-decanol to the pursued aldehyde. Of both suitable H-acceptors, the most attractive and environmentally friendly one would be TBHP which produces water and *t*-butanol as by-product.

Table 2.1: *Easily reducible H-acceptors tested with $Zr(O^tBu)_4$ as catalyst.*

Entry	H-acceptor	E_0 (mV)	Time (h)	Yield (%)
1	chloral	277	1	44
2	methyl benzoylformate	282*	24	60**
3	*tert*-butyl benzoylformate	282*	21	16
4	pivaldehyde	211	19	6
5	dimethoxyacetone	350	1	0
6	2,6-dimethoxy-1,4-benzoquinone	-	2	0
7	diethyl ketomalonate	-	2.5	4
8	2,2'-pyridil	-	4	0
9	benzil	-	4	19
10	dimethyl 1,3-acetonedicarboxylate	-	24	0
11	1,3-dihydroxyacetone	-	4	0
12	dimethyl carbonate	-	19	0
13	TBHP / toluene	-	1	40
14	H_2O_2 / ^{t}BuOH	-	1	0

* isopropyl benzoylformate

** decyl ester

With methyl benzoylformate as H-acceptor, the decyl ester was formed in high yield showing that trans-esterification prevails over oxidation. *Tert*-butyl benzoylformate could be obtained quantitatively within 1.5 h when $Zr(O^tBu)_4$ (0.25 eq) was used in combination with *tert*-butanol as solvent. Furthermore, $Zr(O^tBu)_4$ has also been used successfully in the quantitative trans-esterification of methyl alaninate to the corresponding *tert*-butyl ester. However, all attempts to make the trans-esterification work in a catalytic fashion failed.[50]

2.3.2 Screening of metal silsesquioxane complexes

Several available metal containing silsesquioxane complexes were screened in the Lewis acid catalyzed Oppenauer oxidation (figure 2.13). As model substrates 1-octanol and 2-decanol

were selected in view of the applications of the corresponding aldehydes and ketones in the food and flavour industry. Furthermore, for screening experiments the easily oxidizable benzyl alcohol was selected. All exploratory experiments were performed with 1 to 10 mol % of catalyst at reflux (98°C) with chloral as H-acceptor and in the absence of solvent. To reach higher reaction temperatures experiments were performed with benzophenone as H-acceptor in refluxing *p*-xylene (138°C) or at 150°C in the absence of solvent. Acetone as in the classical Oppenauer oxidation can not be used as a H-acceptor because all silsesquioxanes precipitate in its presence. As a consequence this property makes catalyst recovery easy.

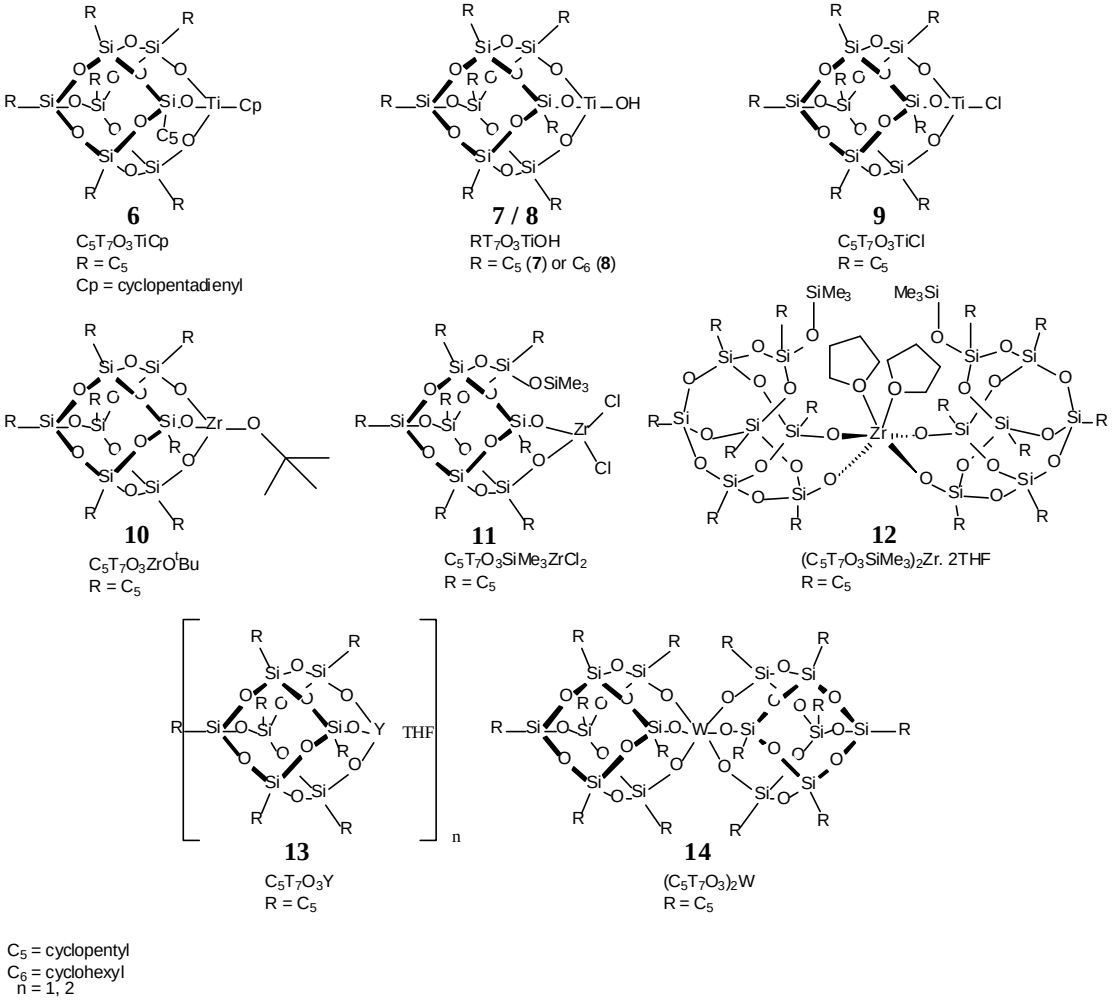


Figure 2.13: *Metal containing silsesquioxane complexes tested in the Oppenauer oxidation.*

All experiments performed with benzophenone as H-acceptor showed inactivity in the oxidation of 1-octanol, benzyl alcohol and 2-decanol. Furthermore, even with the very strong H-accceptor chloral, all catalysts tested showed inactivity in the oxidation of primary aliphatic alcohols. However, the easily oxidizable benzyl alcohol could be oxidized in moderate to good yields in 24 hours (table 2.2).

Table 2.2: *Metal containing silsesquioxane complexes active in the oxidation of benzyl alcohol.*

entry	catalyst	mol % catalyst	yield (%)
1	$C_5T_7O_3TiCp$	1	90
2	$C_5T_7O_3TiOH$	1	81
3	$C_5T_7O_3TiCl$	10	39
4	$C_5T_7O_3SiMe_3)_2Zr.2THF$	1	92

The only catalyst able to oxidize 2-decanol was $C_5T_7O_3TiOH$ (10 mol%, 70%). This catalyst was also tested in the oxidation of cholesterol. Although Oppenauer could oxidize several steroids with acetone or cyclohexanone as H-acceptor, $C_5T_7O_3TiOH$ in combination with chloral or benzophenone were not able to oxidize cholesterol to the pursued Δ4-cholestenone.

Although titanium and zirconium are well-known Oppenauer oxidation catalysts and have good ligand exchange rates, the titanium and zirconium silsesquioxane analogues display little or no activity towards the oxidation of primary and secondary alcohols. The low activity might be attributed to steric effects of the silsesquioxane framework, in combination with a very low exchange rate between substrate, H-acceptor or product, caused by the highly electrophilic metal center in the silsesquioxane framework.

2.4 Conclusions

Replacement of alkoxy groups on aluminum with more electronegative ligands should increase the rate of the classical MPVO reactions by facilitating coordination of aluminum to the carbonyl compound. In this way it should be possible to use catalytic amounts of template and to reduce the amount of by-products and environmentally undesirable salts during work-up. However, in contrast to the rate accelerating effect of acids the very electron deficient

silsesquioxane ligands do not tend to accelerate the H-transfer. The low activity of the silsesquioxane catalysts might be attributed to steric effects and low exchange rates of the silsesquioxane framework. One way to overcome the steric problem of the silsesquioxane framework might be to locate the active center further remote from the silsesquioxane framework. Exploratory work in this direction was started, but not completed.

Furthermore, several H-acceptors were screened with very active $Zr(O^tBu)_4$ as catalyst. Only chloral and tert-butylhydroperoxide (TBHP) were found to oxidize primary as well as secondary alcohols. Nevertheless, even with these strong H-acceptors metal silsesquioxane complexes show little catalytic activity in producing aldehydes from primary aliphatic alcohols and ketones from secondary alcohols. However, most catalysts could oxidize benzyl alcohol in good to moderate yields. 2-Decanol could only be oxidized with $C_5T_7O_3TiOH$ in combination with chloral. In addition, primary alcohols can only be oxidized with H-acceptors featuring themselves a higher tendency to be reduced than the pursued aldehyde. However, by using strong H-acceptors like TBHP primary alcohols are often oxidized to the corresponding acids and it is difficult to stop the oxidation at the aldehyde stage. Acetone often used in the classical Oppenauer oxidation cannot be used as a H-acceptor because all silsesquioxanes precipitate in the presence of acetone. An unusual side reaction was observed when methyl benzoyl formate was used as H-acceptor with $Zr(O^tBu)_4$ as catalyst. For this substrate trans-esterification prevailed over oxidation. However, all attempts to make the trans-esterification work in a catalytic fashion failed.

2.5 Experimental

General. All metal containing silsesquioxane complexes were obtained from the Inorganic Chemistry Department of the Eindhoven University of Technology and were synthesized according to literature procedures.[49,51-52] All other starting materials were obtained from commercial suppliers and used as received. All reactions were performed under an atmosphere of dry argon. ^{1}H-NMR, ^{13}C-NMR were recorded on a 400 MHz NMR (Varian Mercury, 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR), or on a 300 MHz NMR (Varian Gemini, 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR). Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS) whereas the carbon chemical shifts are reported in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. Abbreviations used are s = singlet, d = doublet, dd= double doublet, t = triplet, dt = double triplet, m = multiplet. GC analyses were performed using a Zebron ZB-35 column on a Perkin

Elmer Autosystem. Conversion and yields were determined by using 1,3,5-tri-*tert*-butylbenzene as internal standard. GC/MS measurements were obtained on a Shimadzu GC/MS-QP5000 using a Zebron ZB-35 column.

$C_5T_7O_3TiCp$ (6)

Compound **I** was prepared according to a literature procedure.[49]

$C_5T_7O_3TiOH$ (7)

Compound **II** was prepared according to a literature procedure.[49]

$C_6T_7O_3TiOH$ (8)

Compound **III** was prepared according to a literature procedure.[49]

$C_5T_7O_3TiCl$ (9)

Compound **IV** was prepared according to a literature procedure.[49]

$C_5T_7O_3ZrO^tBu$ (10)

Compound **V** was prepared according to a literature procedure.[51]

$C_5T_7O_3SiMe_3ZrCl_2$. 2THF (11)

Compound **VI** was prepared according to a literature procedure.[51]

$(C_5T_7O_3SiMe_3)_2Zr$. 2THF (12)

Compound **VII** was prepared according to a literature procedure.[51]

$C_5T_7O_3Y$ (13)

Compound **VIII** was prepared according to a literature procedure.[52]

$(C_5T_7O_3)_2W$ (14)

Compound **IX** was prepared according to a literature procedure.[53]

$Zr(O^tBu)_4$ catalyzed oxidations of 1-decanol, general procedure:

In general, the reactions were run in oven-dried 10 ml two-necked flasks, equipped with a magnetic stirring bar and a rubber septum. In a typical procedure a mixture of the alcohol (1.5 mmol), H-acceptor (3.0 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 16 mg, 0.06 mmol) dissolved in

CH_2Cl_2 (2 ml) was stirred at room temperature. A small aliquot was taken from the alcohol solution for GLC analysis beforehand. The reaction was then started at room temperature by addition of catalyst (0.15 mmol in 1 ml CH_2Cl_2) and monitored by GLC analysis. Conversion of the alcohol and yield in the aldehyde were determined by GLC analysis. After conversion of the starting material, the reaction was quenched by the addition of 10 % HCl or H_2O. The mixture was filtered, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($NaSO_4$), filtered and the solvent was removed at reduced pressure, the residue was purified by bulb-to-bulb distillation.

Anhydrous *tert*-butylhydroperoxide (TBHP).

Anhydrous TBHP was prepared and titrated as described in literature.[54]

$Zr(O^tBu)_4$ catalyzed oxidations with TBHP, general procedure:

The oxidation reactions were run in oven-dried 10 ml two-necked flasks, equipped with a magnetic stirring bar and a rubber septum. In a typical procedure a mixture of the alcohol (1.5 mmol), anhydrous TBHP (3.0 mmol), freshly activated molecular sieves (3Å, 600 mg) and internal standard (1,3,5-tri-*tert*-butylbenzene, 16 mg, 0.06 mmol) dissolved in CH_2Cl_2 (2 ml) was stirred at room temperature. A small aliquot was taken from the alcohol solution for GLC analysis beforehand. The reaction was started at room temperature by addition of catalyst (0.15 mmol in 1 ml CH_2Cl_2) and monitored by GLC. Conversion of the alcohol and yield in the aldehyde were determined by GLC analysis. After complete conversion of the starting material, the reaction was quenched by the addition of 10 % $Na_2S_2O_3$. The mixture was filtered, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($NaSO_4$), filtered and the solvent was removed at reduced pressure, the residue was purified by bulb-to-bulb distillation.

Silsesquioxane catalyzed oxidations, general procedure:

An oven-dried 10 ml two-necked flask, equipped with a magnetic stirring bar, was flushed with argon before it was charged with silsesquioxane catalyst (0.01 or 0.10 mmol). The reaction was started by addition of a mixture of the alcohol (1.0 mmol), H-acceptor (12 mmol) and it was monitored by GLC. The reaction mixture was heated to reflux (98°C when chloral was used as H-acceptor). Conversion and yield were determined by GLC analysis. After conversion of the starting material, the reaction mixture was diluted with diethyl ether and quenched by the addition of H_2O. The mixture was filtered, the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried ($NaSO_4$), filtered and the solvent was removed at reduced

pressure and the residue was purified by bulb-to-bulb distillation. NMR-data revealed the presence of benzaldehyde or 2-decanone, respectively.

Decanal:

1-Decanol (237 mg, 1.5 mmol) was oxidized with chloral (44 mg, 3 mmol) and 0.15 mmol $Zr(O^tBu)_4$ catalyst in 1 ml CH_2Cl_2 according to the procedure described above. The product was characterized (GLC) by comparison with authentic samples. The yield (44 %) was determined with GLC. The spectral data was in accordance with literature.[55] ^{1}H-NMR ($CDCl_3$): δ = 9.85 (s, 1H); 2.41 (t, 2H); 1.62 (m, 2H); 1.30 (m, 12H); 0.88 (t, 3H). ^{13}C-NMR ($CDCl_3$): δ = 202.7, 43.8, 31.8, 29.4, 29.3, 29.1, 29.1, 22.6, 22.0, 14.0.

Benzaldehyde:

Benzyl alcohol (108 mg, 1.0 mmol) was oxidized with chloral (177 mg, 12 mmol) and 0.01 to 0.1 mmol silsesquioxane catalyst for 24 hours according to the procedure described above. The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC. The spectral data was in accordance with literature.[55] ^{1}H-NMR ($CDCl_3$): δ = 9.95 (s, 1H), 7.90-7.40 (m, 5H). ^{13}C-NMR ($CDCl_3$): δ = 192.2, 136.4, 134.3, 129.6, 128.9. GC/MS *m/z* M^+: 106.

2-Decanone:

2-Decanol (158 mg, 1.0 mmol) was oxidized with chloral (177 mg, 12 mmol) and 0.1 mmol C_5T_7TiOH (94 mg, 0.1 mmol) according to the procedure described above. The product was characterized (GLC) by comparison with an authentic sample. The yield (70%, t = 4 h) was determined with GLC. The spectral data was in accordance with literature.[55] ^{1}H-NMR ($CDCl_3$): δ = 2.40 (t, 2H); 2.10 (s, 3H); 1.62-1.0 (m, 12H); 0.84 (t, 3H);. ^{13}C-NMR ($CDCl_3$): δ = 209.2, 43.8, 31.7, 29.8, 29.2, 29.1, 23.9, 23.8, 22.6, 14.1. GC/MS *m/z* M^+: 156.

Transesterification of methyl benzoyl formate:

An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with internal standard (1,3,5-tri-*tert*-butylbenzene, 50 mg, 0.20 mmol), methyl benzoyl formate (410 mg, 2.5 mmol), toluene (0.6 ml) and *t*-butanol (2.5 ml, 26 mmol). The reaction tube was placed in 12 Tube Radley Reaction Carousel, stirred and heated to 80ºC. After sampling for GLC analysis, 0.13 M zirconium tetra-*t*-butoxide (0.25 mmol) dissolved in toluene (1.9 ml) was added to the reaction mixture. The reaction was monitored by GLC.

Work-up: To the reaction mixture toluene (14 ml) and saturated $NH_4Cl_{(aq)}$ (6 ml) were added. After filtration, the layers were separated and the water layer was extracted twice with toluene (10 ml). The toluene layers were combined and toluene was evaporated under reduced pressure. The yield (100%, t = 1.5 h) was determined by GLC. ^{1}H NMR ($CDCl_3$) δ = 8.0-7.5 (m, 5H); 1.6 (s, 9H); GC/MS (relative intensity in %): m/z = 51 (49), 57 (100), 77 (20), 105 (45).

Transesterification of methyl alaninate:

An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with internal standard (1,3,5-tri-*tert*-butylbenzene, 5 mg, 0.02 mmol), methyl alaninate.HCl (140 mg, 1.0 mmol), triethylamine (100 mg, 1.0 mmol), powdered freshly activated 4 Å molecular sieves (2.0 g), methylene chloride (4.2 ml) and *t*-butanol (6.0 ml, 63 mmol). The reaction tube was placed in 12 Tube Radley Reaction Carousel and stirred. After sampling for GLC analysis, 0.13 M zirconium tetra-*t*-butoxide (0.10 mmol) dissolved in methylene chloride (0.8 ml) was added to the reaction mixture. The reaction was monitored by GLC.

Work-up: To the reaction mixture diethyl ether (14 ml) and saturated $Na_2CO_{3(aq.)}$ (6 ml) were added. After filtration, the layers were separated and the diethyl ether layer was dried with $MgSO_4$ and filtrated. The diethyl ether was evaporated under reduced pressure. The yield (82%, t = 74 h) was determined by GLC. ^{1}H NMR ($CDCl_3$) δ = 3.9 (q, 1H); 1.7 (d, 3H); 1.5 (s, 9H); GC/MS (relative intensity in %): m/z = 57 (100), 74 (2), 102 (1).

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Chapter 3

Triruthenium dodecacarbonyl catalyzed dehydrogenation of alcohols

Abstract

The $Ru_3(CO)_{12}$ catalyzed oxidation of alcohols to aldehydes and ketones was studied. To stop the oxidation of primary alcohols at the aldehyde stage a systematic study of mono- and bidentate ligands was performed. The screening experiments of ligands demonstrated that the cone angle of the ligand-metal system influences the conversion rate of the alcohol and the selectivity towards the aldehyde considerably. Diphenylacetylene (tolane) was the best among the many H-acceptors screened. Also electron rich and deficient analogues of tolane have been synthesized and used as H-acceptor. Competition experiments between these different H-acceptors demonstrated that cooperativity between the electron rich and deficient analogues exists. Based on the results obtained a tentative catalytic cycle is proposed.

3.1 Introduction

Although ruthenium has already been discovered in 1844 by Karl Karlovitsch Klaus in Tartu Estonia (ruthenia is Latin for Russia), the organometallic chemistry of ruthenium and its potential applicability in homogeneous catalysis has only developed strongly during the last 20-30 years.[1,2] Ruthenium with its $4d^7 5s^1$ electron configuration shows the widest scope of oxidation states (from a valency of – 2 in $Ru(CO)_4^{2-}$ to a valency of + 8 in RuO_4) of all elements in the periodic table. Moreover, various coordination geometries may be present in each oxidation state. For instance, in the lower oxidation states 0, II and III, ruthenium complexes normally prefer trigonal-bypiramidal and octahedral structures.[3] This feature makes the chemistry very diverse. The application of ruthenium in homogeneous catalysis mainly started with the discovery of dichlorotris(triphenylphosphine)ruthenium ($RuCl_2(PPh_3)_3$ in 1965. This ruthenium complex has proven to be an invaluable precursor of many ruthenium (II) complexes. Since coordinatively saturated (18-electrons) metal complexes are normally not very active as catalyst, it is not surprising that the coordinatively unsaturated (16-electrons) $RuCl_2(PPh_3)_3$ complex is a promising homogeneous catalyst, in particular in the

field of hydrogen transfer reactions. Before 1980 the reported useful synthetic methods using ruthenium reagents and catalysts were limited to a few reactions, which include hydrogenation reactions and oxidations with RuO_4.[4,5] Later, in 1987, Ley et al. introduced tetrapropylammonium perruthenate (TPAP) as a very successful catalytic oxidant for the oxidations of alcohols into aldehydes or ketones.[6,7] Since 1980 ruthenium complexes are used as catalyst in a numerous of organic syntheses.[2]

3.1.1 Ligands: bite and cone angles

It has long been recognized that changing substituents on phosphorus ligands can cause marked changes in the behavior of the free ligands and of their transition metal complexes. Before 1970, almost everything was rationalized in terms of electronic effects. Since 1970 a large number of papers have appeared which demonstrate that steric effects are generally at least as important as electronic effects and dominate in many cases. Molecular structures, rate and equilibrium constants and NMR chemical shifts have been correlated with ligand cone and bite angles (figure 3.1).[8-12]

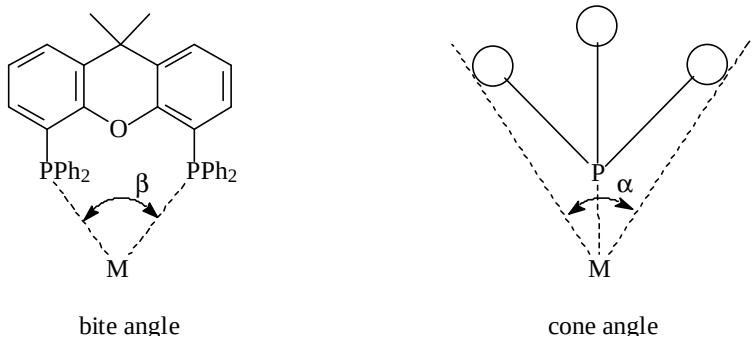
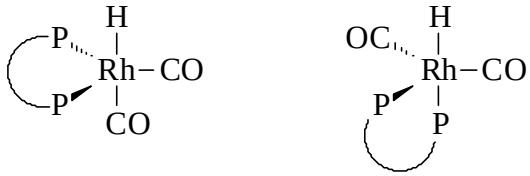


Figure 3.1: *Ligand's bite and cone angles.*

The ligand cone angle α was introduced after it became clear that the ability of phosphorus ligands to compete for coordinative positions on Ni(0) could not be explained in terms of their electronic character.[10] The ligands $P(OMe)_2Me$, PMe_3, $P(OPh_3)$ and $P(t\text{-}Bu_3)_3$ show a decreasing binding ability in that order. CPK molecular models of these ligands clearly show an increase in congestion around the bonding phase of the phosphorus atom in the same order. The steric parameter α for symmetrical ligands is defined as the apex angle of a cylindrical cone, centered 2.28 Å from the center of the phosphorus atom. [8]

The bite angle β is a similar steric parameter defined as the preferred chelating angle determined by the ligand backbone and not by metal valence angles.[9] The major difference between mono- and bidentate ligands and thus the cone and the bite angle is the ligand backbone, a scaffold which keeps two phosphorus atoms at a specific distance. In a catalytic process the choice of a chelating ligand preferring a bite angle of 90° for instance, stabilizes square planar geometries (figure 3.2). Furthermore, ligands that enforce a well-defined bite angle can be used to induce distortions of certain geometries and as a consequence destabilize them. In this way a reaction can be controlled by influencing the initial state, transition state or final state of the metal complex involved during the reaction. This will not only have impact on the activity and selectivity of a catalytic reaction but pathways causing by-product formation can even become inaccessible.[9,10] The impact of designing the proper ligands for homogeneous catalysis can be illustrated by the optimization of the rhodium-catalyzed hydroformylation.[11,12] Van Leeuwen *et al*. reported that the rhodium diphosphine catalyzed hydroformylation very selectively gave linear aldehydes using ligands with bite angles of 120°. This could indicate that a reaction path in which the phosphorus atoms are coordinated in an equatorial-equatorial fashion (**ee**) is favored over a reaction path in which these are coordinated in an equatorial-apical (**ea**) fashion.



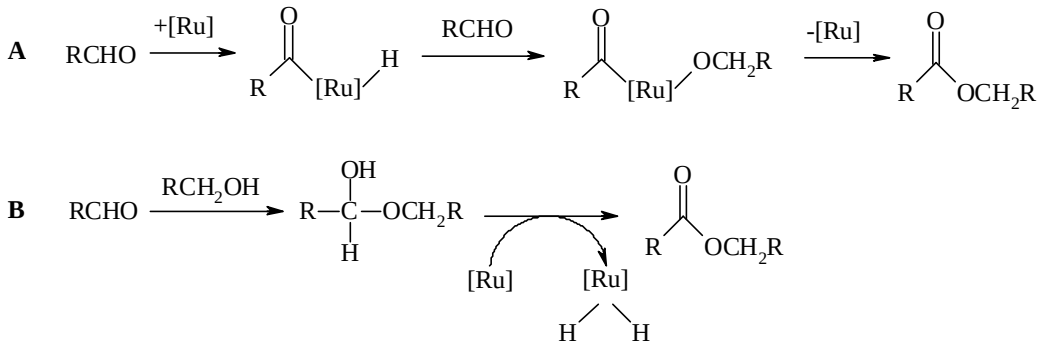
ee **ea**

Figure 3.2: *Equatorial-equatorial (**ee**) and equatorial-apical (**ea**) coordination of ligands.*

Since homogeneous catalysis is becoming increasingly more important in industry, modifying catalysts by changing the electronic and steric properties of the ligands is an appropriate tool in optimizing catalytic processes.

3.1.2 Oxidative transformation of alcohols into esters

The major by-products of the catalytic oxidation of primary alcohols (RCH_2OH) are the corresponding acids (RCO_2H) and the esters (RCO_2CH_2R). When performing the reactions under oxygen-free conditions over-oxidation into the acid is prevented. However, ester formation still occurs. It has been reported that oxidative transformations of primary alcohols into the esters are catalyzed by late transition metal complexes like $Pd(OAc)_2$,[14] $RhH(PPh_3)_3$,[15] $Ru(CO)_3(\eta^4$-tetracyclone)[16] (tetracyclone = 2,3,4,5-tetraphenyl-cyclopentadiene-1-one), $Ru_3(CO)_{12}$ [17,18] and $RuH_2(PPh_3)_4$.[14,19,20] For the ester formation two pathways have been proposed, both starting from the aldehyde (scheme 3.1).[21,22]



Scheme 3.1: *Proposed pathways towards ester formation.*

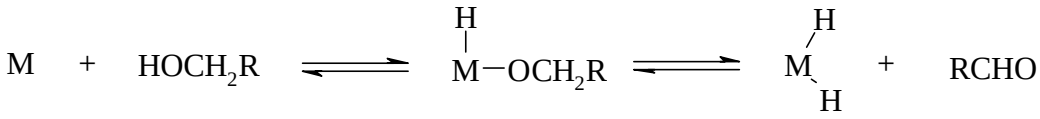
In the first pathway, hydrogen transfer from one aldehyde to another via oxidative addition of the aldehyde has been proposed.[21] The acylruthenium hydride formed via oxidative addition would react with another aldehyde to produce an acylruthenium alkoxide. The latter gives then ester via reductive elimination. In the second pathway, reaction of an aldehyde with an alcohol would give a hemiacetal.[22] The latter can be dehydrogenated by the ruthenium catalyst to give the ester and a ruthenium dihydride, which in turn can be dehydrogenated by a H-acceptor. Although one cannot exclude pathway **A** completely, there are more precedents for the reaction steps involved in pathway **B**.[22] Since the catalyst is involved in both catalytic pathways, introducing more steric phosphine ligands could suppress the ester formation. However, this could also be accompanied in a decrease in reaction rate.

3.1.3 Late transition metals in hydrogen transfer reactions

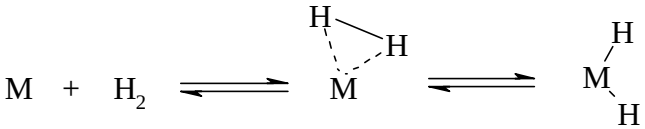
Homogeneous hydrogenation of organic compounds by transition metal complexes is one of the most thoroughly investigated processes of homogeneous catalysis.[23] The most important stage in the mechanism is the activation of the H-H bond in molecular hydrogen.

A similar process is the activation of C-H and O-H bonds by transition metal compounds.[23,24] Since all catalytic oxidation processes are hydrogen transfer reactions, transition metal derivatives are likely to be suitable catalysts in catalytic oxidations. Catalytic hydrogen transfer from organic compounds has much in common with homogeneous hydrogenation by molecular hydrogen. Like homogeneous hydrogenation, the mechanism includes two steps:

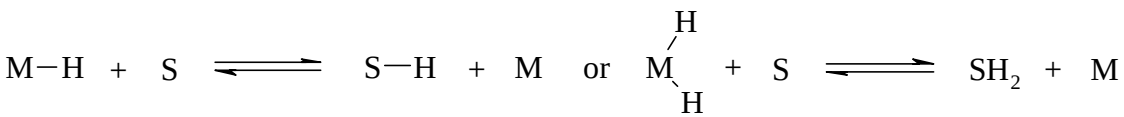
1: Dissociation of the C-H or O-H bond and hydrogen transfer to the metal (M).



The catalytic oxidation of an alcohol can be divided into two parts. The first is the oxidative addition of an alcohol to the metal center. The second is a β-hydrogen elimination from the alkoxide to the metal center. In homogeneous hydrogenation, molecular hydrogen is coordinated and oxidatively added to the metal center.



2: Hydrogen transfer from the metal center to an unsaturated substrate (S).



The second pathway is similar to hydrogenation. Consequently, the specific features of hydrogen transfer processes and, therefore, catalytic oxidation reactions are related to the features of the first pathway. Development of Oppenauer-like catalysts for the oxidation of alcohols requires transition metals characterized by:

1. ability to form metal alkoxide and metal hydride complexes,
2. displaying β-hydrogen elimination to afford unsaturated compounds.

It is known that the late transition metals ruthenium, rhodium, palladium, osmium, iridium and platinum are able to form such complexes.[25,26] Although it is commonly accepted that metal-oxygen bond energies are relatively small, late transition metal alkoxide complexes have been postulated as intermediates in many important transformations. This late transition metal bonding has often been rationalized using the ideas of Pearson, who suggested that the 'soft-soft' interactions characteristic of late transition metal fragments and carbon fragments could be more stabilizing than the 'hard-soft' interactions associated with these metals and less polarizable atoms such as oxygen and nitrogen.[27] Nevertheless, many β-hydrogen elimination processes of late transition metal alkoxide complexes have been reported.[28-32] Apart from choosing a suitable metal catalyst and hydrogen acceptor it is important that the reaction can be performed under mild reaction conditions.

The reaction under discussion can be generalized as depicted in equation 1. The acceptor compound A can be any organic compound whose reduction potential is sufficiently low so that hydrogen transfer from donor to acceptor can occur.

$$DH_2 + A \xrightarrow{\text{catalyst}} AH_2 + D \qquad (1)$$

In catalytic hydrogen transfer reactions organic compounds with various functional groups can be used as H-acceptor molecules. A number of olefins, acetylenes, nitriles, azo, carbonyl, and nitro compounds have been used in hydrogen transfer reactions.[24] For example, Blum *et al*. reported the dichlorotris(triphenylphosphine)ruthenium ($RuCl_2(PPh_3)_3$) catalyzed hydrogen transfer from alcohols into saturated and α,β- unsaturated ketones.[33] An illustrative example of using acetylenes as hydrogen acceptor is the iridium-catalyzed hydrogen transfer described by Tani *et al*. (figure 3.3).[34-36]

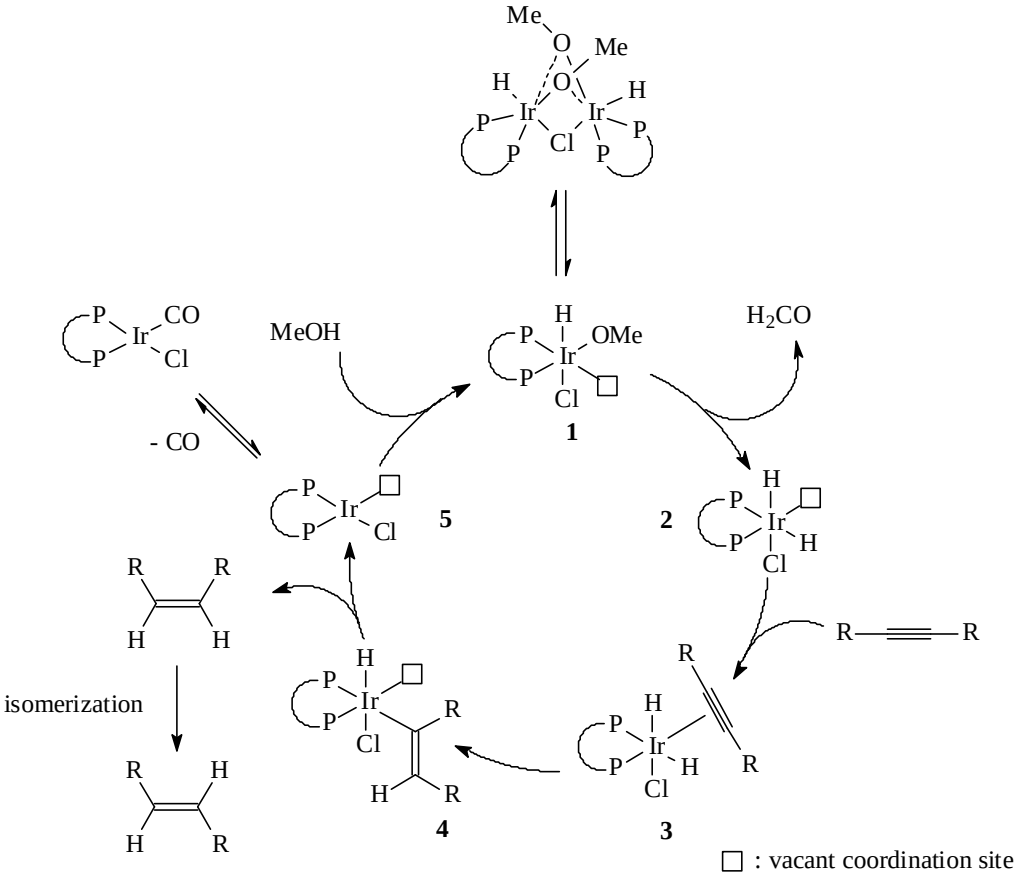


Figure 3.3: *The iridium catalyzed hydrogen transfer to diphenylacetylene.*

In the catalytic cycle depicted in figure 3.3 a dimeric hydrido(methoxo)iridium(III) complex is thought to split into an active monomeric hydrido(methoxo)iridium(III) complex **1**. Then β-hydrogen elimination from the methoxo ligand takes place, followed by dissociation of a formaldehyde molecule, leaving dihydrido iridium species **2**. Coordination of acetylene **3** and insertion of a hydride into the coordinated acetylene gives hydrido(vinyl)iridium species **4**. Subsequent hydride insertion from an unstable 14-electron complex **5** to which methanol adds oxidatively to restore the monomeric hydrido(methoxo)iridium(III) complex **1**. With diphenylacetylene or 1-phenylpropyne conversions of 100% were reported.

Another Oppenauer-type oxidation in which late transition metal alkoxides and hydrides are intermediates in the hydrogen transfer from an alcohol to unsaturated compounds is the $RuCl_2(PPh_3)_3$ catalyzed hydrogen transfer proposed by Bäckvall *et al.* (figure 3.4).[37,38]

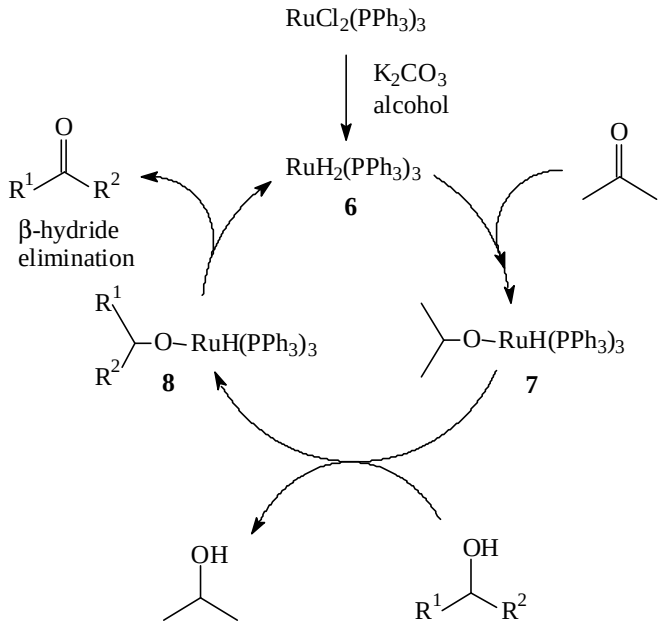


Figure 3.4: *$RuCl_2(PPh_3)_3$ catalyzed hydrogen transfer to acetone.*

Bäckvall used acetone as hydride acceptor. The active dihydridoruthenium species **6** is formed in a precatalytic step from the dichlororuthenium catalyst precursor and an alcohol in the presence of a base. In the catalytic cycle acetone coordinates to the metal center with subsequent insertion of a hydride, forming a ruthenium alkoxide species **7**. Concomitant dissociation of isopropanol and association of an alcohol molecule gives a second ruthenium alkoxide species **8**. This is followed by β-hydrogen elimination to restore the active dihydridoruthenium species **6**. Unfortunately, this Oppenauer-type oxidation is only reported to be successful for the oxidation of secondary alcohols. The presence of base strongly accelerates the hydrogen transfer from alcohol to H-acceptor. Although the role of base remains unclear, it is generally believed that base increases the nucleophilicity of the alcohol, so a ruthenium alkoxide species is formed more easily.[37]

3.1.4 Triruthenium dodecacarbonyl metal clusters

A few compounds containing metal-metal bonds and metal atom clusters have first been isolated in the middle of the nineteenth century. However, it was only with the application of X-ray crystallographic techniques during the late 1930s and 1940s that the existence of metal-metal bonds (e.g. in $W_2Cl_9^{3-}$) and metal atom clusters (of the type $Mo_6Cl_8^{4+}$) were recognized. Even so, it was not until the early 1960s that some sense of the possible aspects of such

chemistry started to develop. A key step was the discovery of the $[Re_3Cl_{12}]^{3-}$ ion, since this led to the first general discussion of the existence of an entire class of "metal atom cluster" compounds. A metal atom cluster may be defined as two or more metal atoms in which there are substantial and direct bonds between the metal atoms.[3] The triatomic $Ru_3(CO)_{12}$ cluster was synthesized for the first time in 1910 by Mond *et al*. but not recognized as such (figure 3.5).[39]

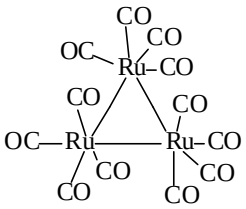
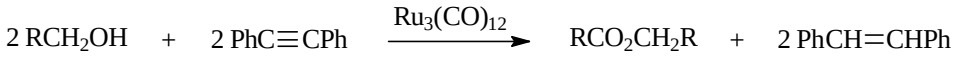


Figure 3.5: *The triatomic $Ru_3(CO)_{12}$ cluster often used in catalysis.*

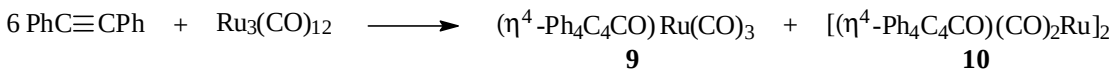
The $Ru_3(CO)_{12}$ cluster is electronically saturated, namely, it has a sufficient number of electrons to provide each metal atom with an 18-electron, closed shell configuration. While the $Ru_3(CO)_{12}$ cluster is rather unreactive, it can be converted into more reactive species, allowing the development of valuable chemistry in many directions.[3] Several substituted derivatives of $Ru_3(CO)_{12}$ have been synthesized. Bruce *et al*. found that heating mixtures containing $Ru_3(CO)_{12}$ with a four- to seven-fold excess of ligand for short times in *n*-octane afforded moderate to good yields of the tetra-substituted complexes.[40,41] The non-carbonyl ligands occupy equatorial positions in the ruthenium triangle, one on each of the two metal atoms and two on the third. Furthermore, there is a lot of interest in the relationship between heterogeneous and homogeneous catalysis. This gave rise to a special effort to determine the general usefulness of clusters as catalysts and to produce particularly reactive clusters. Despite profound interest in these compounds, less effort has been devoted to basic mechanistic studies of their reactions. It is not at all clear in many cases whether the clusters themselves are the catalysts rather than active mononuclear fragments derived from them.[42] It has been established that even the apparently simple formation of $Ru_3(CO)_9(PBu_3)_3$ from $Ru_3(CO)_{12}$ occurs via mononuclear fragments. It has also been shown that $Ru_3(CO)_9(PPh_3)_3$ undergoes various reactions including readily reversible fission at 50 ºC into two fragments probably corresponding to $Ru_2(CO)_6(PPh_3)_2$ and $Ru(CO)_3PPh_3$.[43-45] Despite the easy fragmentation of $Ru_3(CO)_{12}$, it has been frequently applied in catalysis.[46-49]

For instance, Shvo *et al.* reported the $Ru_3(CO)_{12}$ catalyzed formation of esters from alcohols in which diphenylacetylene (tolane) was used as H-acceptor.[17,18]



$$2\,RCH_2OH + 2\,PhC{\equiv}CPh \xrightarrow{Ru_3(CO)_{12}} RCO_2CH_2R + 2\,PhCH{=}CHPh$$

A search for the catalytically active species operative in this reaction led to the discovery that two mononuclear, tetrahaptotetracyclonetricarbonylruthenium **9** and a related dimer bis(tetrahaptotetracyclonetricarbonylruthenium) **10** were present.

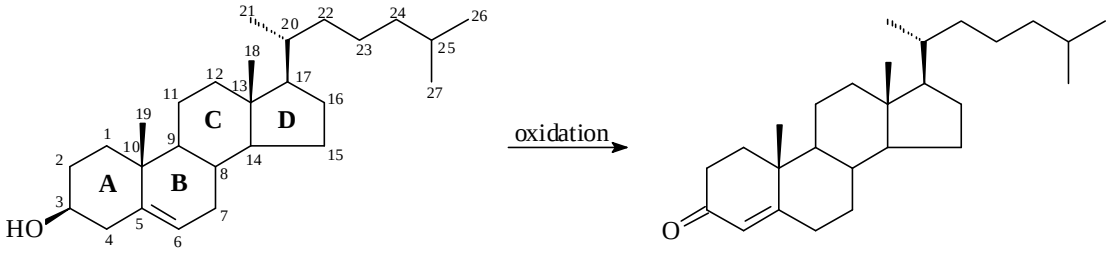


$$6\,PhC{\equiv}CPh + Ru_3(CO)_{12} \longrightarrow \underset{\mathbf{9}}{(\eta^4\text{-}Ph_4C_4CO)Ru(CO)_3} + \underset{\mathbf{10}}{[(\eta^4\text{-}Ph_4C_4CO)(CO)_2Ru]_2}$$

These two complexes could be independently prepared and were found to be of higher reactivity than $Ru_3(CO)_{12}$. So during catalysis $Ru_3(CO)_{12}$ is degraded by tolane into a mononuclear catalytically active species. Tolane is not only acting here as a H-acceptor but also as a catalyst precursor.[50,51]

3.1.5 Steroid oxidation

The lipid fractions isolated from plants and animals contain an important group of compounds known as steroids. Steroids are vital regulators of the lives of mammals as they control a variety of body functions such as reproduction (as male and female sex hormones), carbohydrate metabolism (glucocorticoids), ion transport (mineralocorticoids, etc.[52] Since applications of steroids in human and veterinary drugs are numerous, there is a continuing need for efficient processes of natural hormones and their analogues. Formally steroids are derivatives of the perhydrocyclopentanophenanthrene ring system. The carbon atoms of this ring system are numbered as shown in figure 3.6 for 5-cholestene-3β-ol, also known as cholesterol. The four rings are designated as **A-D**. Cholesterol, one of the most widely occurring steroids, was first isolated in 1770. In the 1920s, Windaus and Wieland outlined the absolute structure for cholesterol, which occurs widely in the human body and is known to serve as an intermediate in the biosynthesis of all the steroids in the body (figure 3.6).



5-cholestene-3-ol 4-cholestene-3-one

Figure 3.6: *The structure of cholesterol as outlined by Windaus and Wieland.*

When steroids like cholesterol with a double bond at the Δ5(6) position (Δ5(6)-(3-hydroxy)-steroids) are oxidized using agents such as Cr(VI) reagents, $Al(O^iPr)_3$,[53] or catalysts like $RuCl_2(PPh_3)_3$,[54] double bond migration takes place from the Δ5(6) position to the Δ4 position due to conjugation. The enone functionality in the A-ring in Δ4-(3-oxo)-steroids is a typical feature of major steroidal hormones such as testosterone, progestosterone, cortisol, and aldosterone. However, retaining the double bond would be of considerable synthetic and commercial interest since the industrial synthesis of Δ5(6)-(3-oxo)-steroids from Δ5(6)-(3-hydroxy)-steroids proceeds via bromination of the double bond forming a *vic*-dibromide. The hydroxyl group of the dibromide is subsequently oxidized into the ketone which is debrominated with zinc to give the Δ5(6)-(3-oxo)-steroid (figure 3.7).[55]

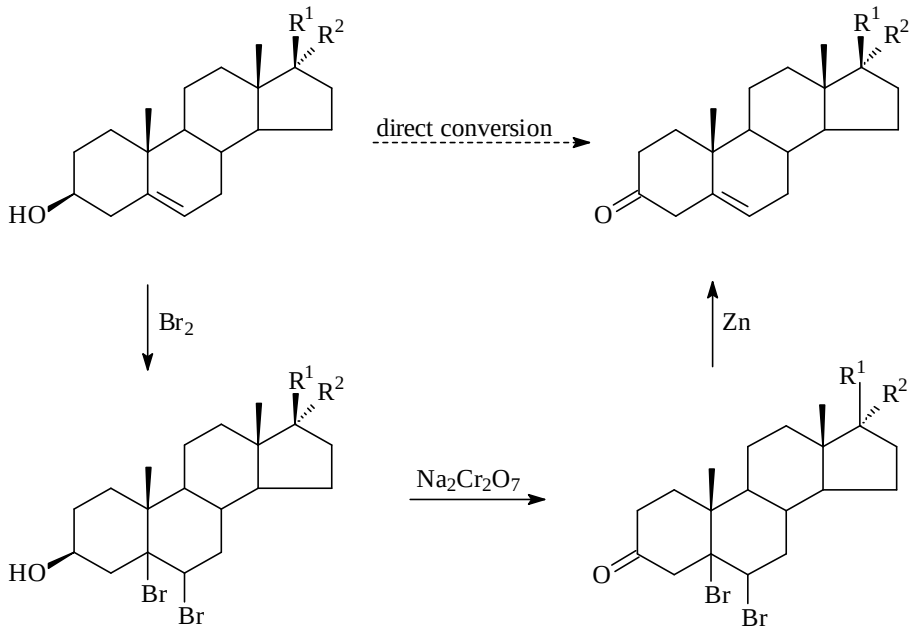


Figure 3.7: *Direct and indirect routes to Δ5(6)-(3-oxo)-steroids.*

In spite of considerable efforts aimed at developing more efficient alternatives,[56] this method still appears the best choice. The major problem of synthesizing β,γ-unsaturated ketones is rapid isomerization to the α,β-unsaturated ketones under mildly acidic or basic conditions.[57] Therefore, developing selective processes for the synthesis of Δ5(6)-(3-oxo)-steroid is a major challenge in steroid oxidation.

3.2 Objectives

Oxidation of primary alcohols usually gives rise to ester formation or over-oxidation to the acid. In this chapter the "triruthenium dodecacarbonyl" -catalyzed, irreversible hydrogen transfer from alcohols to unsaturated compounds like diphenylacetylene, will be discussed. The challenge is to stop the oxidation of primary alcohols at the aldehyde stage, as, literature indicates that primary alcohols are oxidized into esters (RCO_2CH_2R). Various combinations of triruthenium dodecacarbonyl, ligand and hydride acceptor have been screened for optimal aldehyde and ketone formation. Furthermore, the effect of base on the rate of hydrogen transfer from alcohol to the H-acceptor was investigated. As a model compound for aliphatic primary alcohols 1-octanol was selected in view of the application of the corresponding aldehyde in the food and flavor industry. As hydrogen acceptor diphenylacetylene was applied because of its ease of reduction. Effort is expended to isolate catalytic intermediates and a plausible catalytic cycle describing the mechanism is proposed.

Chemoselective oxidation of β,γ-unsaturated steroids is still a major challenge. The major problem in synthesizing β,γ-unsaturated ketones is fast isomerization to the α,β-unsaturated ketones. In this chapter the applicability of triruthenium dodecacarbonyl complex in the selective oxidation of cholesterol will be discussed.

3.3 Results and discussion

There is an increasing demand for efficient, highly selective oxidations and reductions allowing recycling of unreacted reactants and catalysts. The classical Oppenauer oxidation in principle fulfills these requirements. However, this reaction is only effective in the oxidation of secondary alcohols. Also the Oppenauer-type oxidation presented by Bäckvall is only successful for the oxidation of secondary alcohols. Due to the unfavorable equilibrium which exists in the oxidation of primary alcohols, primary alcohols can only be oxidized when very strong H-acceptors like chloral or peroxides are applied. However, by using strong H-

acceptors primary alcohols are often oxidized into the corresponding acids or the esters and it is difficult to stop the oxidation at the aldehyde stage.

Compared to the classical Oppenauer oxidation and the Oppenauer-type oxidation presented by Bäckvall, hydrogen transfer via late transition metal alkoxide intermediates with small organic molecules like tolane as oxidant are more efficient. The catalytic system can be generalized as depicted in figure 3.8.

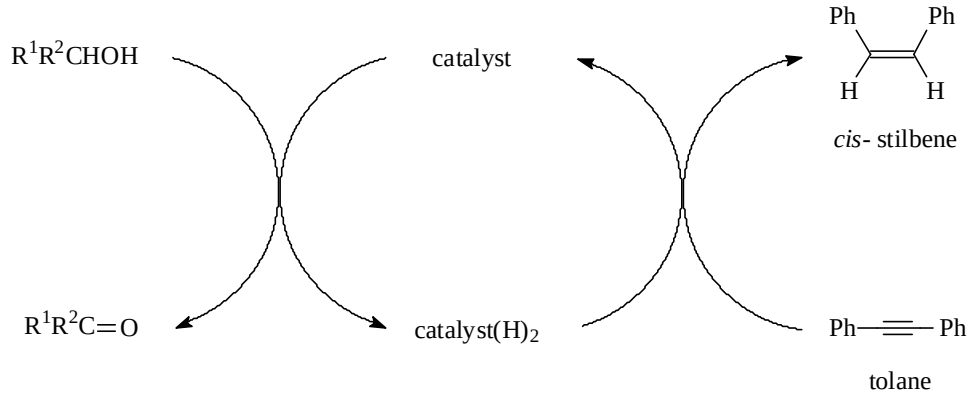
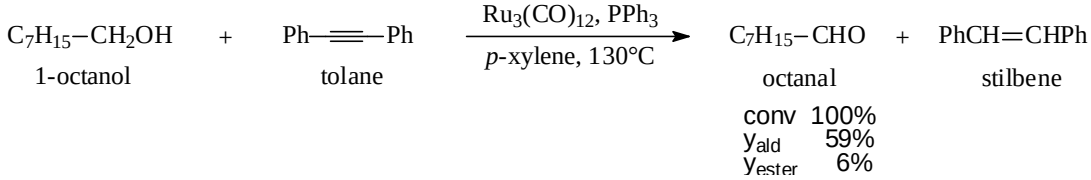


Figure 3.8: *Irreversible hydrogen transfer from alcohols to unsaturated compounds.*

3.3.1 Late transition metals screened for irreversible hydrogen transfer

Various commercially available late transition metal complexes were screened in the catalytic oxidation. Although platinum and palladium are well-known dehydrogenation and hydrogenation catalysts respectively and platinum has good β-hydrogen elimination properties, they display little or no activity towards the oxidation of 1-octanol or 1-decanol. In exploratory experiments $(PPh_3)_2Pd(OAc)_2$ was used as catalyst with tolane as H-acceptor in toluene. Both 1- and 2-decanol could be oxidized at 150°C in an autoclave (t = 5 h, conv = 60%). However, small amounts of decyl decanoate were formed by over-oxidation of the aldehyde (up to 15%). Other catalysts like $(PPh_3)_4Pd$, $(PPh_3)_3IrH(CO)$ and $(PPh_3)_3RhH(CO)$ in combination with tolane gave similar results. All screened platinum catalysts like $Pt(PPh)_4$ and $PtCl_2(PPh_3)_2$ were completely inactive. The $RuCl_2(PPh_3)_3$ catalyst, which is very active in the hydrogen transfer to acetone as proposed by Bäckvall *et al.*, showed no catalytic activity. However, when $Ru_3(CO)_{12}$ was employed as catalyst in combination with triphenylphosphine as ligand (M/L molar ratio = 1/1) and tolane as H-acceptor, aldehydes could be obtained in 60 to 80% yield together with small amounts of ester. $Ru_3(CO)_{12}$ catalyzed oxidations without

additional ligand solely yielded the ester. The maximum yield in ester (RCO_2CH_2R) which can be obtained is 50% since 1 mol ester consumes two moles of alcohol.



3.3.2 Influencing side reactions by variation of the catalysts ligands

The ester formation might be influenced by variation of the catalysts ligand's cone or bite angle. For this reason several ligands with different cone and bite angles were tested with $Ru_3(CO)_{12}$. The results for ligands with different cone angles are depicted in table 3.1. All experiments were performed at 100°C with 1-octanol as substrate in the presence of 5 mol% catalyst, 17 mol% of ligand (M/L molar ratio = 1/1.1) and with 2 equivalents of tolane. Toluene was used as solvent and the reactions were stopped after 4 hours.

Table 3.1: *Screening of ligands differing in cone angle.*

Entry	Ligand	Cone angle	Conv (%)	$Y_{aldehyde}$ (%)	Y_{ester} (%)
1	$P(OEt)_3$	109	73	0	31
2	$P(OPh)_3$	130	68	0	22
3	PPh_3	145	100	80	0
4	$(p\text{-}CH_3C_6H_4)_3P$	145	100	64	8
5	$(p\text{-}CH_3OC_6H_4)_3P$	145	100	60	9
6	$(p\text{-}CF_3C_6H_4)_3P$	145	82	60	3
7	$(o\text{-}CH_3C_6H_4)_3P$	194	93	46	0
8	$(n\text{-}Bu)_3P$	132	42	12	0
9	$(C_6H_{11})_3P$	170	100	11	0
10	tri-2-furylphosphine	-	75	9	21
11	diphenyl-2-pyridylphosphine	-	80	0	30
12	2,2'-dipyridyl	-	100	0	50

With PPh_3, $(p\text{-}CH_3OC_6H_4)_3P$ or $(o\text{-}CH_3C_6H_4)_3P$ as ligand only a very small amount of ester was formed. The other ligands tested gave lower conversions or too much ester.

Ligands with different bite angles were also tested in combination with $Ru_3(CO)_{12}$. The results of these experiments are depicted in table 3.2. All experiments were performed at 130°C with 1-octanol as substrate in the presence of 5 mol% catalyst, 5 mol% of ligand (M/L ratio = 1/0.3) and with 2 equivalents of tolane. Furthermore, all experiments were performed in *p*-xylene and were stopped after 5 hours.

Table 3.2: *Screening of ligands differing in bite angles.*

Entry	Ligand	Bite angle	Conv (%)	Y_{ester}*	$Y_{aldehyde}$
1	$Ph_2PCH_2PPh_2$	72	100	50	0
2	$Ph_2P(CH_2)_2PPh_2$	83	100	47	0
3	$Ph_2P(CH_2)_3PPh_2$	92	100	47	0
4	$Ph_2P(CH_2)_4PPh_2$	97	72	12	0
5	$Ph_2P(CH_2)_5PPh_2$	-	85	22	0
6	$Ph_2P(CH_2)_6PPh_2$	-	88	26	0

* 50% yield corresponds to 100% conversion of the alcohol (RCH_2OH) in ester (RCO_2CH_2R).

A clear trend becomes apparent when the bite angle is changed from small angles to larger angles. The yield of ester formation is strongly dependent on the bite angle as is depicted in figure 3.9. Increasing flexibility of a ligand backbone raises the chance of an arm-off η^1 co-ordination. The latter may explain the drastically different efficiency of $Ph_2P(CH_2)_3PPh_2$ compared to that of $Ph_2P(CH_2)_4PPh_2$ as shown in entries 3 and 4 respectively. However, the bidentate ligands tested did not suppress the ester formation and did not yield aldehyde.

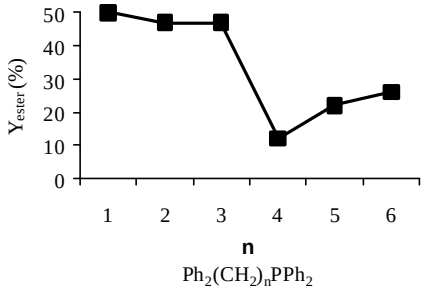


Figure 3.9: *Effect of bite angle on ester formation in the ligand series $Ph_2P(CH_2)_nPPh_2$.*

All other bidentate ligands screened like: DPEphos, Xantphos, Thixantphos, BINAP, DIOP, dpp-benzene and dppf did not give the desired results and no clear trends in the conversion rate or yield of the aldehyde could be observed. The structures of these ligands including their bite angles are depicted in figure 3.10.

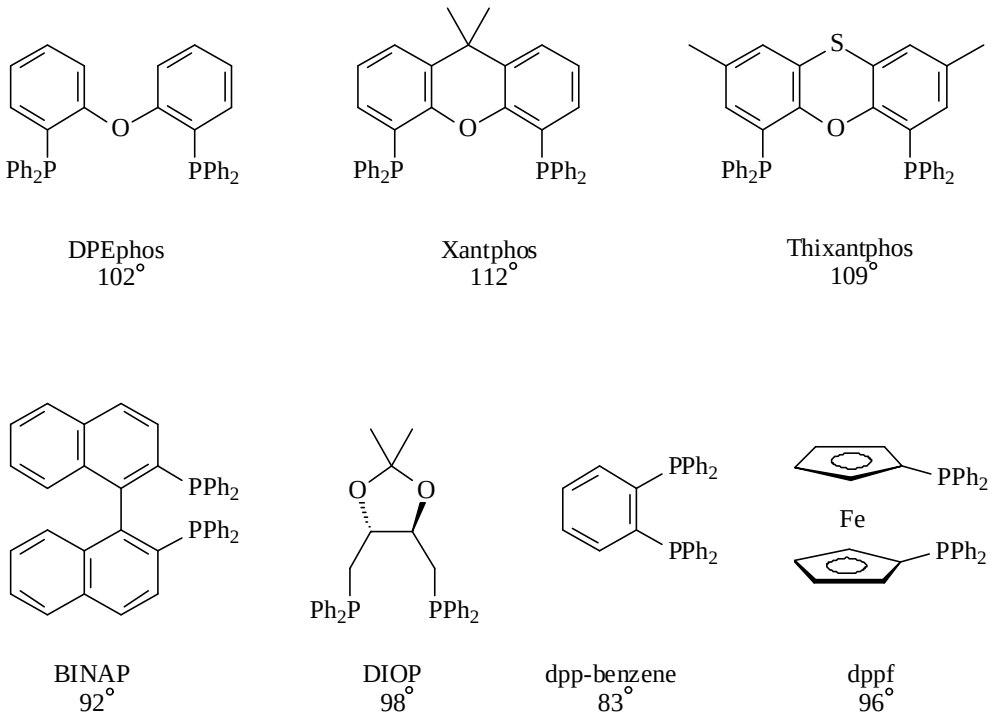


Figure 3.10: *Bidentate ligands screened for suppressing ester formation.*

From the results depicted in tables 3.1 and 3.2 it can be concluded that ester formation is almost completely suppressed when $Ru_3(CO)_{12}$ is used as catalyst in combination with PPh_3 as ligand (cone angle 145°).

3.3.3 Preventing ester formation

One ester molecule is produced from one molecule of aldehyde and one molecule of alcohol. By keeping the alcohol concentration as low as possible, there is a chance that ester formation could be suppressed. This was accomplished by adding 1 equivalent of alcohol over a period of 1 h to a mixture of 5 mol% $Ru_3(CO)_{12}$, 17 mol% PPh_3 and 2 equivalents of tolane. Furthermore, the reaction was performed in *p*-xylene as solvent and at 130°C. And indeed after the slow addition of all the alcohol and stirring the reaction mixture for another 5 hours, ester formation could be suppressed substantially (figure 3.11).

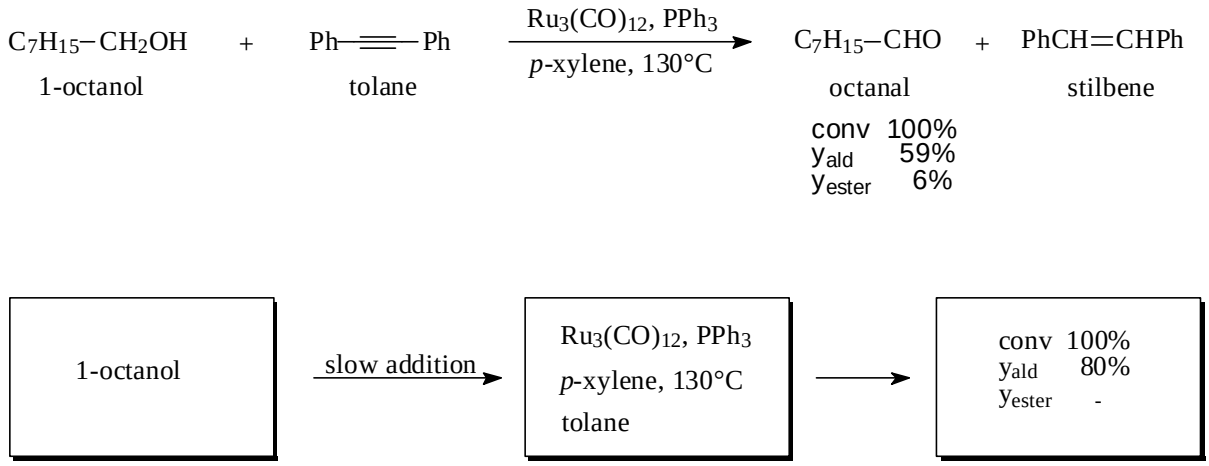


Figure 3.11: *Suppressing ester formation by slow addition of substrate.*

However, when a mixture of the alcohol and 2 equivalents of tolane were both slowly added to 5 mol% $Ru_3(CO)_{12}$ and 17 mol% PPh_3, the reaction became slower (t = 5 h, conv = 70 %, y = 23 %) and a larger amount of ester was produced (up to 12 %). An explanation for this behavior might be that tolane is not only acting as a H-acceptor but is also needed to form the active catalyst.

To suppress ester formation completely and still perform the oxidation in a short reaction time, the effect of the amount of PPh_3 was studied (table 3.3). All experiments were conducted at 130°C with 1-octanol as substrate in the presence of 5 mol% catalyst and with 2 equivalents of tolane. The metal to ligand (M/L) ratio was changed in every experiment. Furthermore, all experiments were performed in *p*-xylene and were stopped after 5 hours.

Table 3.3: *Search for the optimal amount of PPh_3.*

M / L ratio	Conv (%)	Y_{ald} (%)	Y_{ester} (%)	S_{ald} (%)
1.1	100	59	6	59
2	100	62	0	62
4	88	41	0	47

The conversion and selectivity to the aldehyde were nearly the same when a metal to ligand ratio of 1/1.1 or 1/2 was choosen. By using higher M/L ratios the reaction became slower and the selectivity lower. Probably excess of ligand is blocking free co-ordination sites on the catalyst and consequently the reaction rate is poor. The optimal amount of PPh_3 would be in between a M/L ratio of 1/1.1 to 1/2. Due to the small difference in selectivity between the two ratios all other experiments where performed with a M/L ratio of 1/1.1. Furthermore, the optimum amount of tolane was found to be 2 equivalents. Less than 2 equivalents (1.1 eq) led to lower reaction rates and more ester formation. Larger amounts (4 eq) deminished reaction rates but did not affect the selectivity. The observation that lower concentrations of the H-acceptor in an experiment where a mixture of 1-octanol and tolane was added to a mixture of $Ru_3(CO)_{12}$ and PPh_3, indicates that tolane is not only acting as a H-acceptor but is also playing the role of a ligand in suppressing ester formation.

3.3.4 Investigated substrates

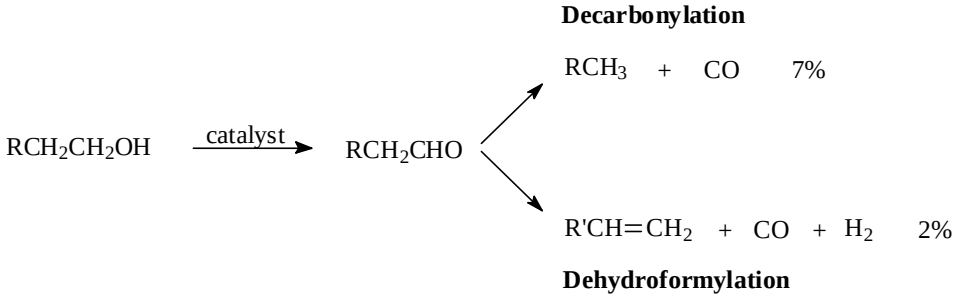
Several primary and secondary alcohols have been subjected to oxidation. For the oxidation of primary alcohols, 17 mol% PPh_3 (M/L = 1/1.1) was always used to suppress ester formation. Oxidation of primary alcohols without addition of Ph_3P yields solely the ester. In contrast, from secondary alcohols ketones can be produced with relatively high rates and selectivities. No additional ligand is needed to suppress side-reactions and lower concentrations of the catalyst can be used. A special challenge is the direct conversion from Δ5(6)-(3-hydroxy)-steroids into Δ5(6)-(3-oxo)-steroids without protection of the double bond. During oxidation of Δ5(6)-(3-hydroxy)-steroids the double bond often migrates, resulting in Δ4-(3-oxo)-steroids. The best results obtained are collected in table 3.4.

Table 3.4: *Oxidation of primary and secondary alcohols with $Ru_3(CO)_{12}$*

Entry	Substrate	Catalyst (mol%)	Temp (°C)	Time (h)	Conv (%)	Y (%)
1[a]	1-octanol	5	130	5	100	80
2	1-octanol	5	130	5	100	59
3	1-decanol	5	130	5	100	54
4	geraniol	5	100	4	100	82
5	(*S*)-citronellol	5	130	5	100	77
6	benzyl alcohol	5	100	4	100	71
7	*p*-methoxybenzyl alcohol	5	100	4	100	99
8	cinnamyl alcohol	5	100	2	100	90
9	2-decanol	0.5	100	4	94	92
10	cholesterol	5	150	12	100	94
11	4-t-butylcyclo-hexanol	0.5	130	12	100	88

a) Slow addition experiment.

The yield of oxidizing 1-octanal could be enhanced from 59 to 80% when the alcohol was slowly added to the catalyst (entries 1 and 2). Alcohols containing functional groups like double bonds can be oxidized, leaving the double bond intact (entries 4, 5, 8 and 10). When primary alcohols are oxidized around 20% of the material balance is missing except in the case of *p*-methoxybenzyl or cinnamyl alcohol. Part of the product loss can be rationalized by dehydroformylation and decarbonylation of the aldehyde as a consequence of the high temperature. When 1-dodecanol was oxidized, these side reactions accounted for ~10% loss. When lower boiling alcohols depicted in table 3.4 were oxidized, the decarbonylated and dehydroformylated products were evaporated from the reaction mixture. Also high boiling aldol condensation products might have been formed though no experimental evidence has been found for this reaction. However, both side-reactions can only occur when the primary alcohols are first oxidized into the aldehydes. In case of entries 7 and 8 decarbonylation and dehydroformylation is prevented due to conjugation between carbonyl and the carbon double bond or aromatic ring. (scheme 3.2).



Scheme 3.2: *Consecutive reactions observed during the oxidation of primary alcohols.*[59, 60]

There is also some evidence that ester molecules formed during the reaction coordinate to the metal center of the catalyst. When half the amount of catalyst was used nearly half the amount was missing in the material balance. Attemps to release material from the catalyst by adding strongly co-ordinating ligands, like cyanide or by phosphine ligands failed, however. So it remains unclear what the fate of the missing material is.

Studying the oxidation of cholesterol (Δ5(6)-(3-hydroxy)-steroid, entry 10) with ^{13}C-NMR unfortunately revealed that the double bond had migrated resulting in 4-cholestene-3-one (Δ4-(3-oxo)-steroid). The migration is probably due to the high temperature at which this reaction is performed. Milder reaction conditions have to be found to overcome the hurdle of spontaneous migration. Also as steroids with the double bond in the Δ5(10) position, the industrially important steroid **11** depicted in figure 3.12 was chosen as substrate. It is of interest to oxidize steroid **11** in one step into steroid **12**. However, due to the presence of a hydroxyl group next to an acetylene group, which can also act as a H-acceptor, a very low selectivity was obtained. ^{1}H and ^{13}C NMR as well as IR showed no hydroxyl and no acetylene groups in the reaction products.

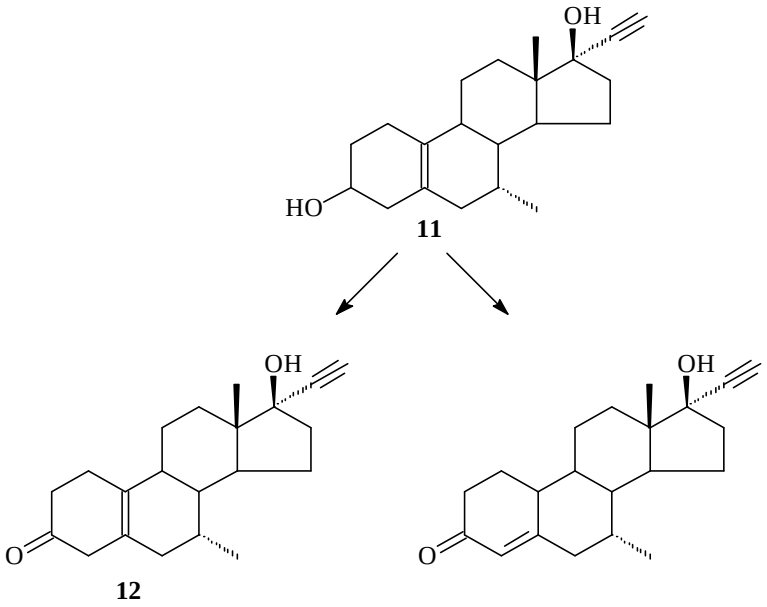
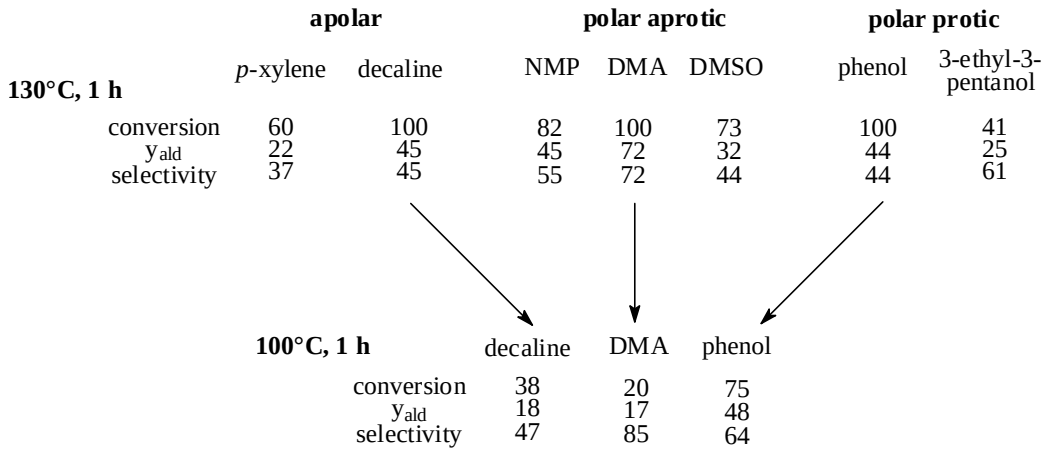


Figure 3.12: *Attempted oxidation of steroids with the double bond in the D5(10) position.*

All alcohols studied, containing unsubstituted ethylene or acetylene groups, always yielded a substantial number of by-products and were not further investigated. Even alcohols with substituted acetylenes like 6-phenyl-5-hexyn-3-ol yielded mixtures of products. Herein, the hydride can be transferred intra- or intermolecularly to the acetylene of 6-phenyl-5-hexyn-3-ol or to the actual H-acceptor tolane.

3.3.5 Solvent effects

The first oxidation experiments with $Ru_3(CO)_{12}$ have been performed in toluene as solvent in an autoclave at 150 °C. Later experiments demonstrated that the same results could be obtained when the reactions were performed in *p*-xylene at 130°C in standard glassware equipment. To determine the influence of solvents, the catalytic oxidation of 1-octanol was also performed in a various solvents. The results are collected in scheme 3.3.

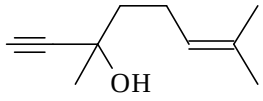


Scheme 3.3: *Solvents studied in the catalytic oxidation of 1-octanol.*

The experiments were performed at 130ºC and stopped after 1 hour. The results demonstrate that the oxidation was complete within 1 hour when decaline, DMA or phenol were used as solvents and that the highest selectivity towards the aldehyde is obtained in DMA. However, due to the high reaction temperature the aldehyde can give rise to either aldol condensation or ester formation and so the selectivity decreases. To reach a higher selectivity and to find the best solvent in terms of reaction rate, oxidation of 1-octanol was also performed in decaline, DMA and phenol at 100ºC. Again the highest selectivity is reached in DMA but the reaction appeared to be fastest in the polar protic solvent phenol. Both solvents have high boiling points which are often close to the boiling points of important substrates and products, which makes separation difficult. In addition when phenol is used as solvent phenyl esters (RCO_2Ph) are produced in relatively high quantities. In aprotic solvents the reaction can be accelerated by addition of K_2CO_3 as is also described in the Oppenauer-type oxidation presented by Bäckvall.[37]

3.3.6 Screening of cheap and easily removable H-acceptors

Another aspect investigated is the replacement of tolane as H-acceptor. It is transformed into cis-stilbene which is difficult to remove from the product. For this reason other cheap H-acceptors like nitrobenzene, *m*-dinitrobenzene, azobenzene, phenazine, diisopropyl azodicarboxylate, *tert*-butylperoxide, dehydrolinalol, nicotinamides and analogues were screened.



dehydrolinalol

The results with these alternative H-acceptors are, however, disappointing. Surprisingly, when tolane was replaced by phenylpropyne, high conversions to the ester and only small amounts of the aldehyde could be obtained, indicating that small changes in H-acceptor can have a dramatic effect on the selectivity. Furthermore, it also indicates that tolane is not only acting as H-acceptor but is also playing a role as an efficient ligand helping to suppress ester formation. Other substituted analogues of tolane with electron withdrawing or electron releasing substituents have been synthesized. These analogues may provide information about the catalytic mechanism. In the catalytic cycle the H-acceptor has to coordinate to the metal center first. After coordination a hydride is transferred from the metal center to the H-acceptor. Electron rich H-acceptors coordinate well to the metal center but are poor hydride acceptors. The opposite is true for electron poor H-acceptors. These compounds would take up the hydride easily but would not coordinate very well. The coordinating- and the hydride accepting strength of these ligands are schematically represented in figure 3.13.

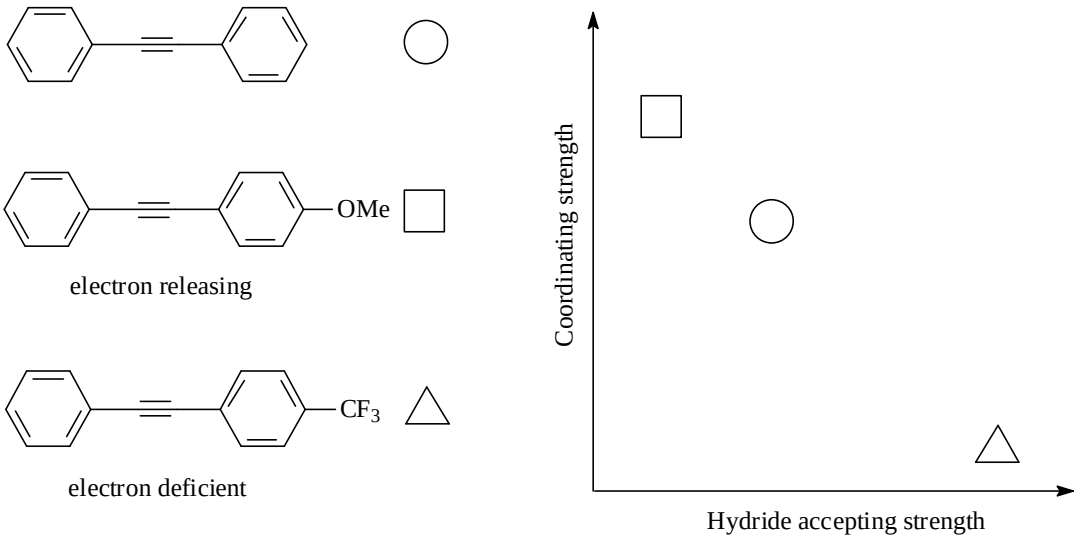
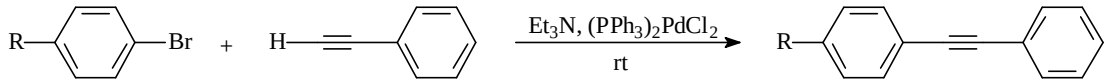


Figure 3.13: *Schematic representation of the coordinating and hydride accepting properties of tolane and its substituted analogues.*

For this reason, the MeO (electron rich) and CF_3 (electron deficient) substituted analogues of tolane have been synthesized.[60] Both substituted analogues could be isolated in 80% yield and were studied in the oxidation of 1-octanol (figure 3.14).



R = MeO (**13**), CF_3 (**14**)
y = 80%

Figure 3.14: *Substituted analogues of tolane with electron donating or electron withdrawing substituents.*

1-Octanol was oxidized at 130°C in *p*-xylene as solvent. The reaction in which $Ru_3(CO)_{12}/PPh_3$ (M/L ratio = 0.9) was used as catalyst was stopped after 5 hours. The results of the experiments with different H-acceptors are depicted in table 3.5.

Table 3.5: *Oxidation of 1-octanol with tolane and substituted analogues.*

	$Ru_3(CO)_{12}$	
	Conv (%)	Y (%)
tolane	100	72
4-MeO-tolane	93	61
4-CF_3-tolane	50	22

The results show that in the catalytic systems tolane is the best H-acceptor followed by the electron rich 4-MeO-tolane. Both tolane and 4-MeO-tolane coordinate better to the metal center than 4-CF_3-tolane does. Due to the slower complexation of 4-CF_3-tolane, the rate of hydride insertion is lower compared to the other two H-acceptors. The difference between tolane and the electron rich 4-MeO-tolane can be explained by the fact that the electron rich H-acceptor will take up the hydride with some more difficulty than tolane does despite faster complexation. In addition, experiments with equimolar mixtures of two H-acceptors were performed. The results after 5 hours are depicted in table 3.6.

Table 3.6: *Conversion of 1-octanol with equimolar mixtures of H-acceptors.*

	$Ru_3(CO)_{12}$	
	Conv (%)	Y (%)
tolane/ 4-MeO-tolane	93	58
tolane/ 4-CF_3-tolane	56	22
4-MeO-tolane/ 4-CF_3-tolane	100	70

Compared to the oxidations with tolane, 4-MeO-tolane or the mixture of tolane and 4-MeO-tolane, the reaction with a mixture of 4-MeO-tolane and 4-CF_3-tolane is surprisingly fast. The conversion of 4-CF_3-tolane to 4-CF_3-stilbene is even higher than those of tolane or 4-MeO-tolane into the corresponding stilbene compounds (table 3.7).

Table 3.7: *Conversion of the H-acceptor in mixed experiments.*

	$Ru_3(CO)_{12}$
	Conv (%)
tolane/4-MeO-tolane	46/51
4-MeO-tolane/ 4-CF_3-tolane	35/64

The conversion of tolane and 4-MeO-tolane is nearly the same indicating that both compounds are comparable in coordinating and accepting the hydride. From the mixture of 4-MeO-tolane/ 4-CF_3-tolane it would be expected that the overall conversion would be much lower compared to the mixture of tolane/ 4-MeO-tolane (table 3) and that the conversion of 4-MeO-tolane would be higher than the conversion of 4-CF_3-tolane. That the conversion of 4-CF_3-tolane is higher indicates that both H-acceptors play an important role in the oxidation process. First the electron rich 4-MeO-tolane will co-ordinate to the metal center and induce a higher electron density on the metal center. As a result the electron deficient 4-CF_3-tolane can co-ordinate and will be reduced very fast. The asymmetry introduced by the substituents on the hydride acceptor may also play an important role in the coordinating and hydride accepting properties of the H-acceptor. The effect of a symmetrically di-substituted tolane was not studied further and leaves room for speculation.

3.3.7 Effect of a radical scavenger on the catalytic reaction

Furthermore, experiments were performed with a radical scavenger to determine whether the oxidation of alcohols is a one or a two electron process. Standard reaction conditions were used with the exception that in these experiments 2,6-di-tert-butyl-4-methylphenol was added as a radical scavenger. The results are comparable to the experiments which were performed under standard reaction conditions without radical scavenger. Hence, it can be concluded that the oxidation is not of radical nature (figure 3.15).

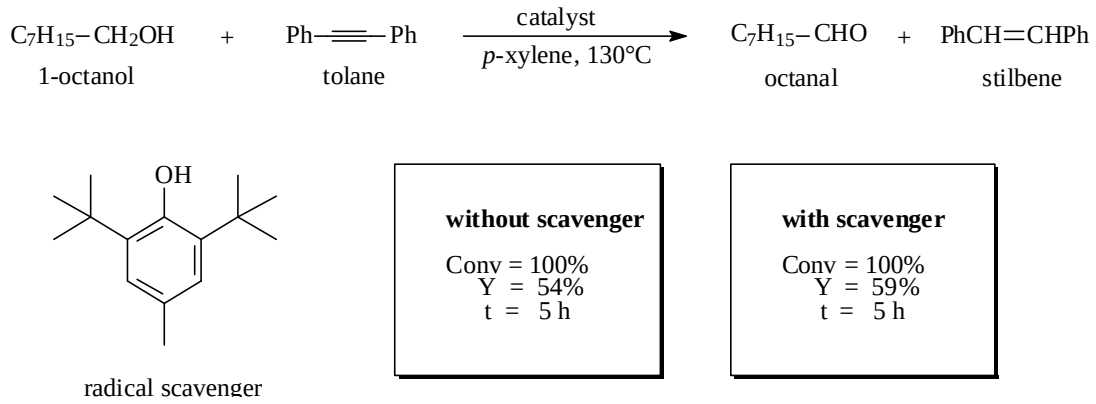


Figure 3.15: *Addition of a radical scavenger revealed that the oxidation is a concerted process.*

3.3.8 Elucidation of the catalytic cycle

Attemps to unravel the mechanistic pathway of the catalytic reaction were also initiated. Ruthenium complexes formed during the $Ru_3(CO)_{12}$ catalyzed oxidation of 1-octanol in combination with tolane as H-acceptor and PPh_3 as ligand, precipitated. The MALDI-TOF spectrum of this solid showed 4 different molar masses (figure 3.16).

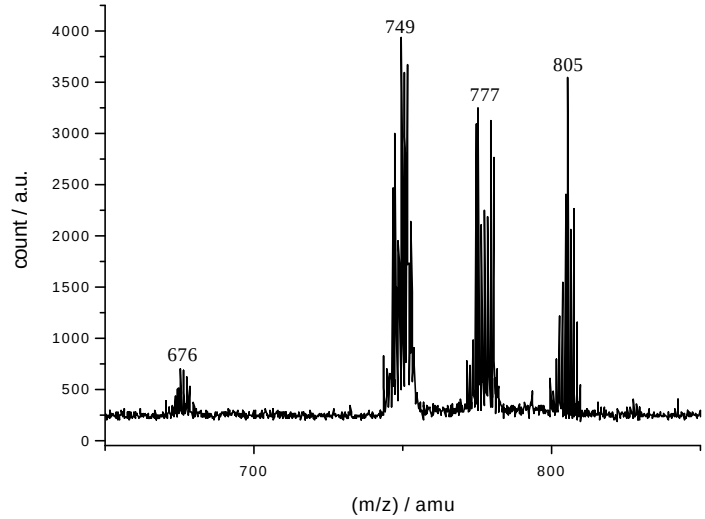


Figure 3.16: *MALDI-TOF spectrum obtained from a ruthenium complex isolated from a reaction mixture.*

The masses obtained from the MALDI-TOF measurement were assigned to the structures shown in figure 3.17.

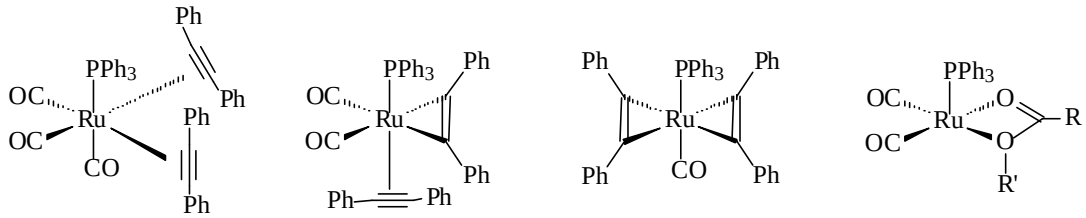


Figure 3.17: *Structures assigned to the molar masses obtained from MALDI-TOF***.**

The mass of 805 corresponds to a ruthenium complex in which both tolane molecules are coordinated as a monodentate ligand to the metal center. However, it is known that tolane can act as a monodentate, bidentate, tridentate or quadridentate ligand (figure 3.18).[61] The complexes with masses (m/z) of 777 and 749 correspond to molecules in which one or both tolane molecules are coordinated as bidentate ligand to the ruthenium center. When tolane is going from a monodentate ligand into a bidentate ligand one CO molecule is released. Both fragments are formed during the MALDI-TOF measurement. In addition a molecular mass with m/z of 676 was also observed: presumably originating from a ruthenium complex in which one ester molecule coordinates to the metal center.

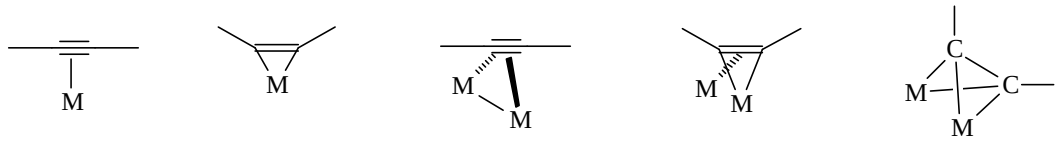


Figure 3.18: *Alkynes as monodentate- up to quadridentate ligand.*

Moreover in this particular case, crystals were obtained from one ruthenium complex. The X-ray structure of these crystals revealed a mass of 805 corresponding to the structure depicted in figure 3.19.

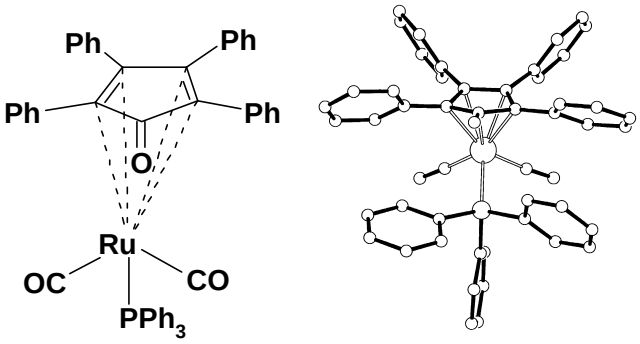


Figure 3.19: *X-ray structure of the isolated ruthenium complex.*

In this complex tetracyclone, formally composed of two tolane molecules and one carbon monoxide molecule, acts as a ligand. An envelope structure is adopted by the tetracyclone ring. The distances between the diene carbons are similar in length (C-C 1.44-1.45 Å), indicating delocalization of the double bonds over the four atoms. The ruthenium complex has been tested for its catalytic activity. Unfortunately, it turned out that this complex is not the active species in the catalytic cycle.

Since little mechanistic information about the $Ru_3(CO)_{12}$ catalyzed reactions is available, it proved to be difficult to obtain information about the catalytic cycle. Nevertheless, based on the results obtained sofar, particularly those from the competition experiments with the electron rich and electron deficient tolane analogues, a tentative catalytic cycle can be proposed (figure 3.20).

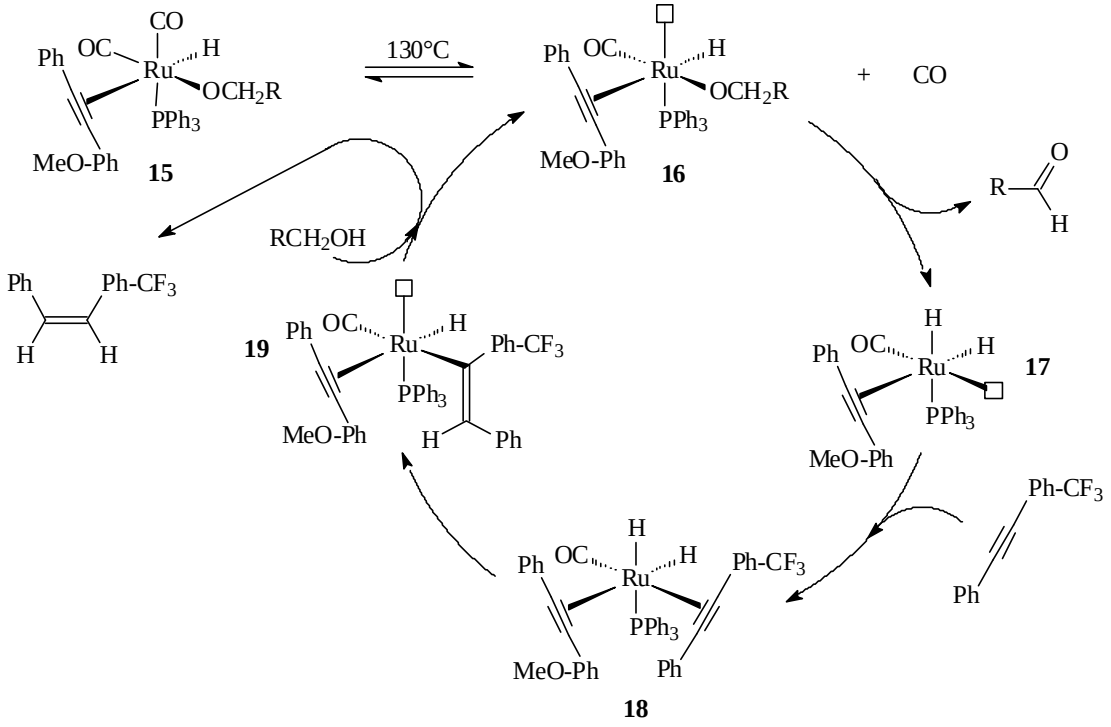


Figure 3.20: *Proposed catalytic cycle for the $Ru_3(CO)_{12}$ catalyzed dehydrogenations.*

In this catalytic cycle the $Ru_3(CO)_{12}$ metal cluster is proposed to be defragmented by PPh_3, the electron rich 4-MeO-tolane and the alcohol leading to the monometallic ruthenium complex **15**. Due to the high temperature a CO molecule is released generating a free coordination site **16**. β-Hydride elimination from the alkoxide gives rise to a ruthenium hydride species **17** and one aldehyde or ketone molecule is released. Subsequently, the electron deficient 4-CF_3-tolane can coordinate to the metal center **18** due to the higher electron density on the metal induced by the electron rich 4-MeO-tolane. One hydride is inserted in the 4-CF_3-tolane ligand and a free coordination site is generated **19**. Concomitant reductive elimination from the 4-CF_3-tolane followed by an oxidative addition of an alcohol molecule gives ruthenium complex **16** again and in this way the catalytic cycle is closed.

3.4 Conclusions

In contrast to the classical Oppenauer and the Oppenauer-like oxidation presented by Bäckvall, it was found that the thermodynamic uphill reaction of oxidizing primary as well as secondary alcohols is catalyzed by $Ru_3(CO)_{12}$, in combination with tolane as H-acceptor. The screening experiments with several ligands demonstrated that the cone angle of the ligand-metal system has a considerable influence on the conversion rate of the alcohol and the

selectivity towards the aldehyde but selectivities never exceeded 80%. Consecutive ester formation is almost completely suppressed when triphenylphosphine is used as a ligand. For the oxidation of primary alcohols additional ligand (PPh_3) is needed to suppress ester formation. Bidentate ligands of the type $Ph_2P(CH_2)_nPPh_2$ never led to aldehydes. Alcohols oxidized into non-conjucated aldehydes, often give decarbonylation and dehydroformylation as side reaction. Probably, some complexation of products with the metal occurs. A significant solvent effect has been observed for these reactions in which phenol would be the best solvent. No PPh_3 and less $Ru_3(CO)_{12}$ is needed for the oxidation of secondary alcohols and still high conversions and selectivities are obtained.

Oxidation studies of steroids revealed that the double bond always migrate from the Δ5(6)- or Δ5(10) position to the Δ4 position.

Addition of a radical scavenger to the reaction revealed that the oxidation reaction is not a radical process.

From one reaction mixture, a ruthenium complex could be isolated and a crystal structure of this compound could be obtained. Herein two tolane molecules and a CO molecule are arranged in the couple to resemble tetracyclone which acts as a ligand. Unfortunately, the isolated complex was not active in oxidizing alcohols, suggesting that its formation reduces the catalytic activity.

From the competition experiments with the electron rich 4-MeO-tolane and the electron deficient 4-CF_3-tolane an unexpected cooperativity between these two H-acceptors was observed. Taking into account all the experimental results a catalytic cycle is proposed.

3.5 Experimental

General. All starting materials were obtained from commercial suppliers and used as received. All reactions were performed under an atmosphere of dry argon. Analytical thin layer chromatography was performed on Kieselgel 60 F-254 precoated silica gel plates. Visualization was accomplished with UV light or iodine vapour. Column chromatography was performed on Merck silica gel 60 or on Merck aluminum oxide 90. ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR-spectra were recorded on a 400 MHz NMR (Varian Mercury, 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR), or on a 300 MHz NMR

(Varian Gemini, 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR). Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS) whereas the carbon chemical shifts are reported in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. The phosphorus shifts were referenced to 85% H_3PO_4. Abbreviations used are s = singlet, d = doublet, dd= double doublet, t = triplet, dt = double triplet, m = multiplet. IR-spectra were recorded on a Perkin Elmer ATR-IR Spectrum One. MALDI-TOF-spectra were obtained on a PerSeptive Biosystems Voyager DE PRO spectrometer using α-cyano-4-hydroxycinnamic acid as a matrix. GC analyses were performed using a Zebron ZB-35 or a Chirasil-Dex-CB column on a Perkin Elmer Autosystem in combination with a Flame Ionisation Detector. Conversion and yields were determined by using 1,3,5-tri-*tert*-butylbenzene as internal standard. GC/MS measurements were obtained with a Shimadzu GC/MS-QP5000 using a Zebron ZB-35 column.

Screening of mono- and bidentate ligands, general procedure:

All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment consisted of the following. An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with $Ru_3(CO)_{12}$ (61.2 mg, 0.096 mmol), tolane (684 mg, 3.84 mmol) and 0.326 mmol monodentate ligand or 0.096 mmol bidentate ligand. 1-Octanol (250 mg, 1.92 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 ml) were added to the mixture. A small aliquot was taken from the alcohol/internal standard solution for GC analysis. The reaction tube was placed in a 12 Tube Radley Reaction Carousel and the mixture was brought to reflux and stirred for several hours. Small aliquots of reaction mixture were taken for GC analysis after 4 hours in the case of monodentate ligands and after 5 hours for bidentate ligands. The product was characterized by GLC by comparison with an authentic sample. The conversion and yield were determined with GLC (tables 3.1 and 3.2).

$Ru_3(CO)_{12}$ catalyzed oxidations, general procedure:

All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment consisted of the following. An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with $Ru_3(CO)_{12}$ (61.2 mg, 0.096 mmol), tolane (684 mg, 3.84 mmol) and triphenylphosphine (85.59 mg, 0.326 mmol). Alcohol (1.92 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 ml) were added to the mixture. A small aliquot was taken from the alcohol/internal standard solution for GC analysis. The reaction tube was placed in a 12 Tube Radley Reaction Carousel and the mixture was heated and stirred with a magnetic stirrer for several hours. Small aliquots of reaction mixture could be taken for

GC analysis. The products were characterized GLC and GC/MS by comparison with an authentic samples. The conversions and yields were determined with GLC (table 3.4).

Octanal:

1-Octanol was oxidized according to the procedure described above. The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC. The reaction mixture was purified by bulb-to-bulb distillation yielding 80 % of octanal. ^{1}H-NMR ($CDCl_3$): δ = 9.85 (s, 1H); 2.41 (t, 2H); 1.62 (m, 2H); 1.30 (m, 8H); 0.88 (t, 3H). ^{13}C-NMR ($CDCl_3$): δ = 203.1; 44.3; 31.9; 29.5; 29.3; 23.0; 22.4; 14.5; GC/MS *m/z* M^+: 128.

Benzaldehyde:

Benzyl alcohol was oxidized according to the procedure described above. The product was characterized (GLC) by comparison with authentic samples. The yield were determined with GLC (71 %). For spectral data see chapter 2.

2-Decanone:

2-Decanol was oxidized according to the procedure described above. The product was characterized (GLC) by comparison with an authentic sample. The yield was determined with GLC (92 %). For spectral data see chapter 2.

4-Cholestene-3-one:

Cholesterol was oxidized according to the procedure described above. The product was characterized (GLC) by comparison with an authentic sample. The yield was determined with GLC. Purification of the reaction mixture by flash column chromatography (silica gel, with dichloromethane/diethyl ether (20:1)) yielded 4-cholestene-3-one as a light brown/white powder (94 %). The spectral data was in accordance with literature.[54] ^{1}H-NMR ($CDCl_3$): δ = 5.75 (s, 1H); 2.48-2.22 (m, 2H); 2.05-1.95 (m, 2H); 1.88-1.75 (m, 2H), 1.74-1.22 (m, 12H), 1.20 (s, 3H), 1.19-0.94 (m, 8H), 0.91 (d, 3H), 0.86 (dd, 6H), 0.71 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ = 199.7, 171.7, 123.7, 56.1, 55.8, 53.9, 42.4, 39.6, 39.5, 38.6, 36.1, 35.7, 35.7, 35.6, 34.0, 32.9, 32.0, 28.16, 28.0 24.2, 23.8, 22.8, 22.6, 21.0, 18.6, 17.4, 11.9.

Solvent effects:

Analogous to the general procedure, the oxidation of 1-octanol was performed with 2.50 ml of the solvent at 130 °C and all reactions were stopped after 1 h. The conversion was monitered by GC analysis. All reactions that reached 100 % conversion after 1 hour were also performed at 100 °C and again stopped after 1 h. The results are depicted in scheme 3.3.

Screening of H-acceptors:

Analogous to the general procedure, the oxidation of 1-octanol was performed with 2 equivalents of the alternative H-acceptor. All reactions were stopped after 5 h. The conversion was monitered by GC analysis.

1-Phenylethynyl-4-trifluoromethyl-benzene (14):

A mixture of phenylacetylene (2.50 g, 24.48 mmol), 4-iodobenzotrifluoride (5.50 g, 20.22 mmol), CuI (0.5 g, 2.63 mmol), dichlorobis(triphenylphosphine)palladium (II) (0.70 g, 0.10 mmol) and triethylamine (30 ml, 220 mmol) was stirred at RT. After stirring overnight, the mixture was poured into H_2O (100 ml) and extracted with diethyl ether (100 ml). The organic layer was washed successively with H_2O (50 ml) and brine (50 ml) before drying ($MgSO_4$). Evaporation of the solvent followed by bulb-to-bulb distillation under reduced pressure (150 °C/0.03 Torr), gave phenyl-(4-trifluoromethyl-phenyl)-acetylene (3.9 g, 78 %) as an off-white solid. The spectral data was in accordance with literature.[62] Mp 97 °C.^{1}H-NMR ($CDCl_3$): δ = 7.68-7.35 (m, 9H); ^{13}C-NMR ($CDCl_3$): δ = 132.7, 132.1, 132.0, 129.5, 129.1, 128.7, 127.4, 125.5, 125.4, 122.8, 92.0, 88.2; IR (ATR): υ = 3036, 2221, 1609, 1487, 1442, 1405, 1322, 1165, 1154, 1128, 1104, 1065, 1018, 919, 842, 757, 689 cm^{-1}. GC/MS *m/z* M^+ 246

1-Methoxy-4-phenylethynyl-benzene (13):

A mixture of phenylacetylene (6.0 g, 58.74 mmol), 4-iodobenzotrifluoride (11.7 g, 53.42 mmol), CuI (1.0 g, 5.25 mmol), dichlorobis(triphenylphosphine)palladium (II) (1.5 g, 2.14 mmol) and triethylamine (65 ml, 466 mmol) was stirred at RT. After stirring overnight, the mixture was poured into H_2O (200 ml) and extracted with diethyl ether (200 ml). The organic layer was washed successively with H_2O (100 ml) and brine (100 ml) before drying ($MgSO_4$). Evaporation of the solvent followed by bulb-to-bulb distillation under reduced pressure (150 °C/0.03 Torr), gave phenyl-(4-trifluoromethyl-phenyl)-acetylene (8.4 g, 81 %) as a light yellow solid. The spectral data was in accordance with literature.[63] Mp 58 °C.^{1}H-NMR ($CDCl_3$): δ = 7.4–7.29 (m, 3H); 7.25–7.10 (m, 3H); 6.75-6.65 (m, 3H); 3.64 (s, 3H);. ^{13}C-NMR ($CDCl_3$): δ = 160.0, 133.3, 131.7, 128.6, 128.2, 123.9, 115.6, 114.3, 89.7, 88.4, 55.5; IR (ATR): υ = 3053, 3010, 2838, 2213, 16.4, 1593, 1567, 1507, 1457, 1439, 1287, 1246, 1173, 1137, 1106, 1069, 1025, 835, 820, 710, 688 cm^{-1}. GC/MS *m/z* M^+ 208.

Oxidation with equimolar mixtures of H-acceptor:

Analoqous to the general procedure, the oxidation of 1-octanol was performed with a 1 to 1 mixture of H-acceptor (total 2 equivalents of H-acceptor). All reactions were stopped after 5 h. The conversion was monitered by GC analysis (tables 3.5-3.7).

Oxidation with radical scavenger:

The oxidation of 1-octanol was performed according to the general procedure including 2,6-di-tert-butyl-4-methylphenol (427 mg, 1.94 mmol). The conversion was monitered by GC analysis (figure 3.15).

Isolation of $(Ph_4C_4\text{-}CO)Ru(CO)_2PPh_3$ formed during the oxidation of 1-octanol:

After the oxidation of 1-octanol according to the standard procedure the reaction mixture was allowed to cool to room temperature overnight. A yellow solid had precipitated. Removal of the mother liquor by filtration yielded a yellow solid that was purified by colloum chromatography (silica gel, CH_2Cl_2) and crystallized from CH_2Cl_2 : hexane, the product was obtained as yellow crystals. ^{1}H-NMR ($CDCl_3$): δ = 7.44–6.94 (m, 35H); ^{13}C-NMR ($CDCl_3$): δ = 202.2, 202.1, 133.5, 133.1, 133.0, 132.6, 132.6, 132.1, 131.2, 130.3, 130.1, 130.0, 128.2, 128.1, 127.6, 126.7, 125.9, 105.6, 105.5, 81.8; ^{31}P-NMR ($CDCl_3$): δ = 39.0; IR (ATR): υ = 3051, 2006, 1951, 1605, 1575, 1498, 1486, 1445, 1435, 1401, 1312, 1091, 1072, 1029, 1001, 838, 805, 757, 740, 727, 708, 690 cm^{-1}. MALDI-TOF *m/z* 777, 749, 805; R_f = 0.22; mp = 205 °C decomposes.

X-ray structure determination of $(Ph_4C_4\text{-}CO)Ru(CO)_2PPh_3$:

A yellow colored crystal of having approximate dimensions of 0.27 x 0.42 x 0.54 mm mounted on top of a glass capillary was used for X-ray study. The data were collected on a Nonius KAPPA-CCD diffractometer. Accurate unit-cell parameters and orientation matrix were determined by least-squares fitting of the setting angles of a limited set of reflections. Reduced-cell calculations did not indicate higher lattice symmetry. All data were collected at 150 K in ù scan mode using graphite-monochromated MoK*a* radiation (γ = 071073 Å). All structures were solved by automatic direct methods SHELXS-86.[64] The structures were refined on F^2, using full-matrix least squares techiques. Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[65] Geometrical calculations and illustrations were performed with PLATON.[66]

Crystal data:

$C_{49}H_{35}O_3PRu$, CH_2Cl_2, M = 888.74, tetragonal, space group I41/a (No. 88), a = 22.1040(1), b = 22.1040(1), c = 33.2826(2) Å, α = 90° β = 90° γ = 90°, V = 16261.44(14) Å^3, Z = 16, D_{calc} = 1.452 g cm^{-3}, m(MoK$\acute{a}$) = 0.600 mm^{-1}, F(000) = 7264, T =150 K, Crystal size 0.27 x 0.42 x 0.54, crystal color: yellow.

Data Collection:

θ_{min}, θ_{max} = 1.8, 27.5º, Cell determination (no. refl, θ range) = 9325, 1.8-27.5, Data set = -28:28, -28:28, -43:42, Total data = 123055, Total unique data = 9325 (R_{int} = 0.050), No. of refined params = 514, Final R = 0.0312, Final wR2 = 0.0803, Goodness of fit = 1.03, Min. and max. residual density = –0.86, 0.68 e $Å^{-3}$.

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Chapter 4

$RuCl_2$[BINAP] catalyzed dehydrogenation of alcohols

Abstract

The $RuCl_2$[BINAP] catalyzed oxidation of alcohols to aldehydes or ketones was studied. In contrast to the $Ru_3(CO)_{12}$ catalyzed oxidations described in chapter 3, no additional ligand is needed to suppress side-reactions. For this reason no systematic study of a variety of mono- and bidentate ligands had to be performed. Screening experiments of H-acceptors showed that also in this case diphenylacetylene (tolane) was the best choice. Electron rich and deficient analogues of tolane have been synthesized and used as hydride acceptor. Competition experiments between these hydride acceptors revealed that cooperativity between the electron rich and deficient analogues exists. From the results obtained a tentative catalytic cycle for $RuCl_2$[BINAP] catalyzed oxidations is proposed. In addition, the chiral $RuCl_2$[(S)-BINAP] catalyst was tested in the oxidation of racemic 1-phenylethanol, to investigate the possibility of kinetic resolution upon oxidation.

4.1 Introduction

In general, it can be stated that low valent ruthenium species are excellent catalysts for hydrogen transfer reactions because of their low redox potentials and high affinity towards heteroatoms.[1] As stated in the previous chapter in hydrogen transfer reactions hydrogen is transferred from a donor molecule to an acceptor molecule. Although ruthenium complexes can promote hydrogen transfer from hydrocarbons,[2] aldehydes,[3] amines[4] and cyclic ethers,[5] donors are frequently alcohols.[6-19]

The $RuCl_2(PPh_3)_3$ catalyzed system, proposed by Bäckvall *et al.* utilizes acetone as hydrogen acceptor.[7] The system is reported to be only successful for the oxidation of secondary alcohols. To get insight into aspects that can increase the reaction rate of ruthenium catalyzed hydrogen transfer reactions in which ruthenium alkoxides are intermediates, kinetic and mechanistic studies have been performed to determine the rate determining step.[8-13] Markó *et al.* reported that the rate determining step of the $RuCl_2(PPh_3)_3$ hydrogen transfer from benzyl alcohol to benzylideneacetone (an α,β-unsaturated ketone) is the dehydrogenation of the

alcohol.[8] This is consistent with the observations of Cole-Hamilton *et al.*[9] and Bäckvall *et al.*[10] that the presence of base has a dramatic effect on the rate of hydrogen transfer. The addition of base induced a dramatic rate-acceleration of the $RuCl_2(PPh_3)_3$ or [(tetracyclone)$_2$(μ-H)(CO)$_4$Ru$_2$] catalyzed oxidation in acetone as solvent and H-acceptor. Indeed, this led to initial turnover frequencies (TOF) of up to 1500 h^{-1}, in contrast to 0.1 to 2 h^{-1} in the absence of base, implying an acceleration in the order of 10^3 to 10^4. No primary kinetic isotope effect was observed for the catalytic oxidation of α-deuterated 1-phenylethanol (k_H/k_D = 1.1).[11] This shows that β-hydrogen elimination from a ruthenium alkoxide intermediate is not the rate-limiting step. Although the exact role of base remains unclear, it is generally thought that it increases the nucleophilicity of the alcohol.[13]

Novel, more active ruthenium catalysts have been developed for the oxidation of alcohols which dramatically increased TOF. The highest TOF reported sofar, 118.000 h^{-1}, has been observed with complexes of the type $RuCl_2(PPh_3)$(PON) (PON = 1-(diphenylphosphino)-2-ethoxy-1-(2-pyridyl)ethane) acting on 2-propanol as a substrate.[14] The reaction can be applied to alkyl ketones as well as to aryl ketones as H-acceptors. These hydrogen transfer reactions can be extended to the aerobic oxidation of alcohols reported by Bäckvall *et al.* (figure 4.1).[15,16] However, in this way, a catalytic amount instead of an excess of H-acceptor is needed in the oxidation of secondary alcohols in an O_2 atmosphere to run a multi electron-transfer process.

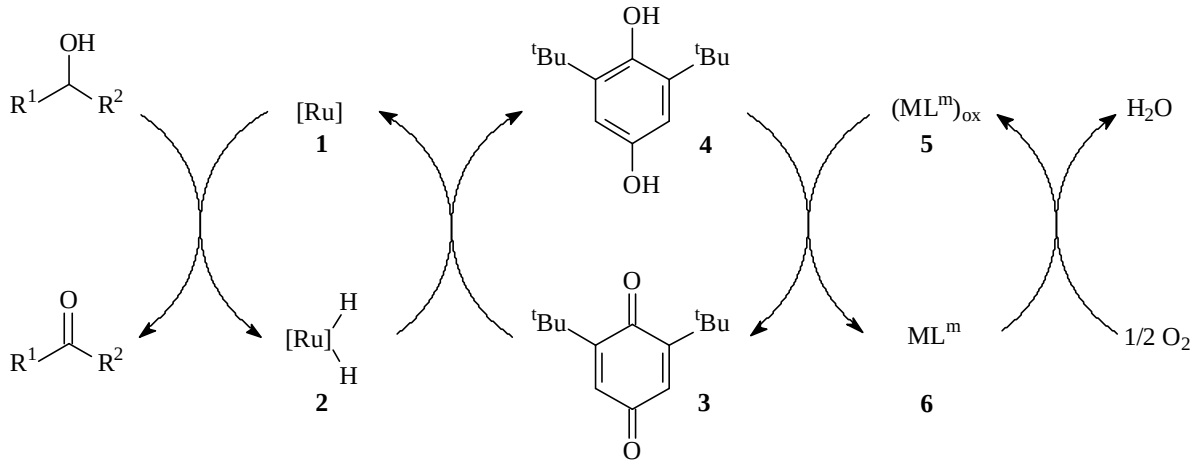
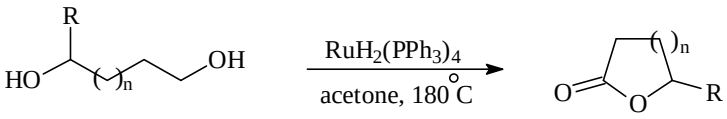


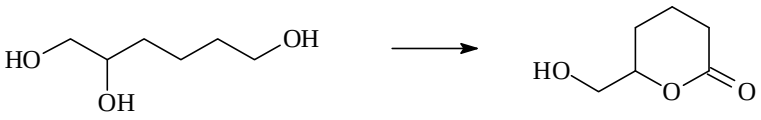
Figure 4.1. *Aerobic oxidation of alcohols by a triple catalytic system (ML^m = cobalt macrocycle).*

As shown in figure 4.1 hydrogen is transferred from an alcohol to the ruthenium complex **1** leading to ruthenium dihydride species **2**, from which hydrogen transfer occurs to the quinone **3** to give the hydroquinone **4** and **1**. The reaction of hydroquinone with the second catalyst $(ML^m)_{ox}$ **5** affords the quinone and ML^m **6** which is regenerated to **5** with molecular oxygen to close the catalytic cycle. Typically, a secondary alcohol is selectively oxidized into the corresponding ketone at 20°C with a catalytic system consisting of $RuCl(OAc)(PPh_3)_3$, $Co(salophen)(PPh_3)_3$ and 2,6-di-*tert*-butylhydroquinone. A similar type of multistep electron-transfer process is offered by the combination of $[RuCl_2(p\text{-cymene})]_2$ catalyst, MnO_2 and 2,6-di-*tert*-butylquinone in the presence of a base.[17] A drawback of this type of reactions is the need for a triple catalytic system.

An interesting application of the oxidative transformation of alcohols is the synthesis of lactones from diols.[18,19] Such a reaction is particularly interesting in comparison with enzyme-catalyzed oxidation reactions. For example, 1,4- and 1,5-diols are easily lactonized into γ- and δ-lactones in excellent yields when reactions are performed in the presence of 3 equivalents of acetone (eq. 1). Compared to the conventional oxidations with stoichiometric oxidants, involving initial abstraction of an α-hydrogen atom from alcohols in a radical fashion, ruthenium catalyzed hydrogen transfer processes are considerably affected by the steric bulkiness around the catalytic sites. So, very remarkable chemoselectivities can be observed. Indeed primary alcohols are oxidized with a stoichiometric amount of $RuCl_2(PPh_3)_3$ into the corresponding aldehyde under mild conditions 50 times faster than secondary alcohols.[20] This higher reactivity of primary hydroxyl groups compared to secondary ones can be ascribed to the difference in spatial congestion between primary and secondary hydroxyl groups. The abovementioned chemoselectivity has also been observed in the lactonization of diols.[19,21] Unsymmetrical primary diols with bulky substituents are oxidized at the sterically less hindered side. The formation of the γ-lactone in eq. 2 exemplifies this type of reactivity.[21]



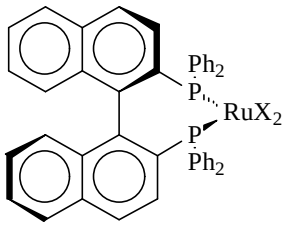
(83 - 100%) (1)



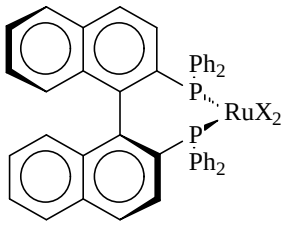
(71%) (2)

4.1.1 The $RuCl_2$[BINAP] system

Not only chemoselectivity but even enantioselectivity has been pursued in the last decades. Since 1980, much progress has been made in the field of asymmetric hydrogenations with homogeneous ruthenium complexes bearing chiral phosphine ligands.[22] BINAP catalysts are very effective in the enantioselective hydrogenation processes. The best known examples of such catalysts are rhodium(I)- and ruthenium(II)-BINAP complexes developed by Noyori *et al*.[20]



[*R*-BINAP]-RuX_2
(X = OAc, halogen)



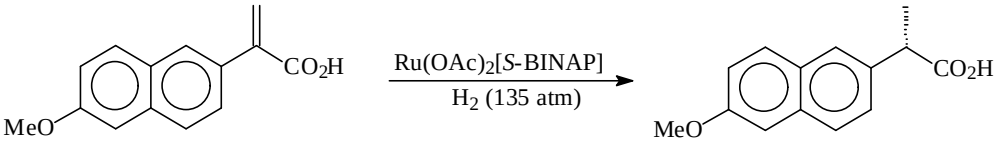
[*S*-BINAP]-RuX_2

2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl abbreviated as BINAP is a rigid, axially chiral diphosphine first synthesized by Noyori *et al*. from 2,2'-dihydroxy-1,1'-binaphthyl (bisnaphthol).[23] They were able to achieve optical resolution with the aid of a chiral palladium(II) complex and reported that (*S*)- and (*R*)-BINAP-incorporated rhodium(I) complexes served as excellent catalysts for the asymmetric hydrogenation of α-(acylamino)-acrylic acids.

BINAP has numerous unique features.[20] The large diphosphine ligand exerts steric influence, provides polarizability, and enhances the Lewis acidity of the metal complex. Another feature is that in metal-BINAP complexes the chirality which is originally issued by the binaphthyl

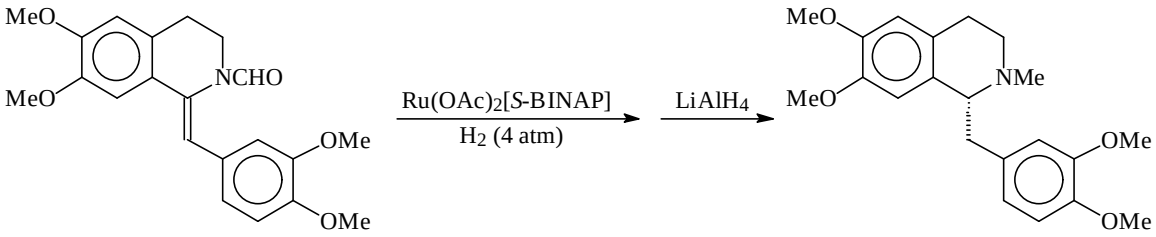
skeleton is transmitted to the other metal coordination sites through phosphorus-metal interactions, where the phenyl rings attached to the phosphorus atom exert a significant role.

In the presence of ruthenium-BINAP complexes asymmetric hydrogenations have been performed with a variety of prochiral olefinic substrates such as α,β-unsaturated carboxylic acids (eq. 3),[24] carbonates,[25] enamides (eq. 4),[26,27] and allylic alcohols.[28] The reaction provides a practical method for the enantioselective synthesis of the biological antiinflammatory compounds, naproxen (eq.3) and isoquinoline alkaloids such as (*R*)-laudanosine (eq. 4).



(3)

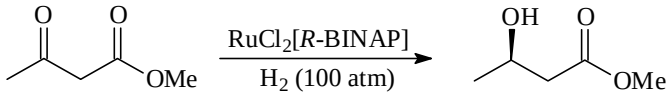
(*S*)-naproxen, 97% ee



(4)

(*R*)-laudanosine, 99% ee

The RuX_2[BINAP] complexes, for which X = dicarboxylate proved to be the best catalyst for enantioselective hydrogenation of olefins, were totally ineffective to the asymmetric hydrogenation of β-keto esters. In 1987, Noyori *et al*. reported the synthesis of dichloro[*R*- or *S*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium, $RuCl_2$[*R*- or *S*-BINAP], by treatment of $Ru(OAc)_2$[*R*- or *S*-BINAP] with HCl.[29] The enantioselective hydrogenation of various β-keto esters in methanol under a hydrogen pressure of 80-100 atmospheres proceeded smoothly using less than 0.1 mol% of catalyst (eq. 5).[29,30]



(5)

R 99% ee

These high enantioselectivities are rationalized by assuming the transition states depicted in figure 4.2 wherein a β-keto ester acts as a bidentate σ-donor ligand. The characteristic chiral conformation of the BINAP ligand will make the difference in energetically favorable conformation between the more and less stable transition state.

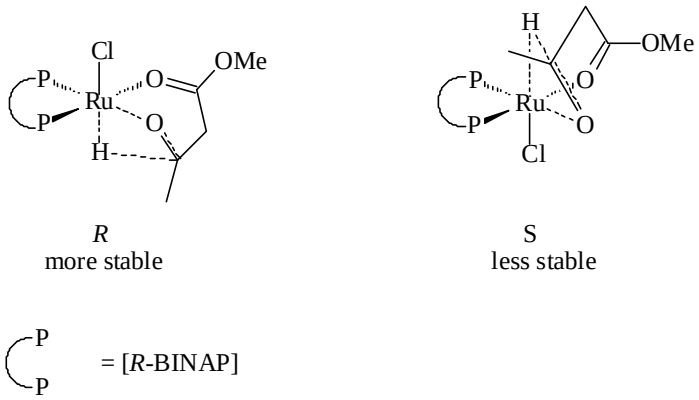


Figure 4.2. *Proposed transition states in the asymmetric hydrogenation of b-keto esters.*

It is not surprising that $RuCl_2$[*S*-BINAP], formally a 14-electron complex shows a high activity in homogeneous catalysis and particularly in H-transfer from alcohols to unsaturated compounds like tolane.

4.2 Objectives

In this chapter the $RuCl_2$[*S*-BINAP] catalyzed irreversible hydrogen transfer from alcohols to unsaturated compounds like diphenylacetylene, is described. Various combinations of $RuCl_2$[*S*-BINAP] and H-acceptors have been screened for optimal aldehyde and/or ketone formation. Furthermore, the effect of base on the rate of hydrogen transfer from alcohol to the H-acceptor was investigated.

A major aim was the selective oxidation of primary alcohols into aldehydes. As a model compound of aliphatic primary alcohols 1-octanol was selected in view of the application of the corresponding aldehyde in the food and flavor industry.

Chemoselective oxidation of β,γ-unsaturated steroids is still a major challenge. The problem in synthesizing β,γ-unsaturated ketones is fast isomerization to the α,β-unsaturated ketones under mildly acidic or basic conditions.[31-33] Therefore, developing selective processes for the

synthesis of Δ5(6)-(3-oxo)-steroid is a challenge in steroid oxidation.[34] In this chapter the applicability of the $RuCl_2$[*S*-BINAP] catalyst for selective oxidation of cholesterol and analogues, as described in chapter 3, will be discussed.

Taking advantage of the optical activity of $RuCl_2$[BINAP] complexes also a study of kinetic resolution during oxidation of racemic 1-phenylethanol is investigated. Ruthenium-BINAP complexes allow the performance of asymmetric hydrogenations with a variety of prochiral olefinic substrates. Furthermore, effort has been invested to isolate catalytic intermediates and a possible mechanism of the catalytic cycle is proposed.

4.3 Results and discussion

In the field of aldehyde and ketone synthesis, a problem of continuing interest is the development of a general, highly efficient method for the conversion of alcohols into aldehydes or ketones under mild reaction conditions without producing waste and with good atom economy. During exploration of these reactions a novel $RuCl_2$[*S*-BINAP] catalyzed oxidation of alcohols was discovered. $RuCl_2$[*S*-BINAP] is a highly active catalyst, and the oxidation of primary and secondary alcohols into aldehydes and ketones can be performed upon treatment with only 2 equivalents of tolane in *p*-xylene as solvent at 130°C, giving aldehydes or ketones in excellent yield. As an example, the oxidation of 1-octanol is depicted in figure 4.3.

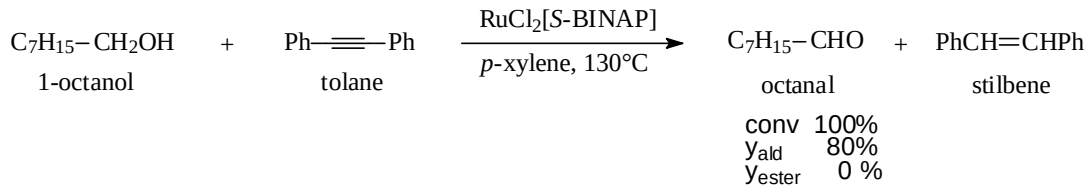


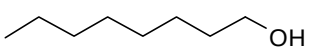
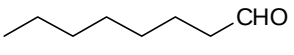
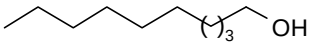
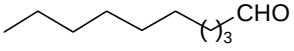
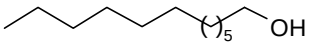
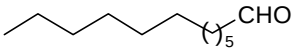
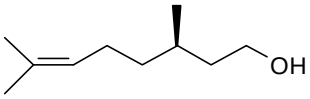
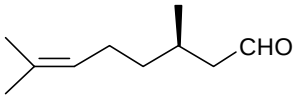
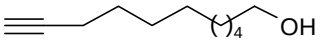
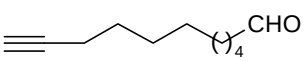
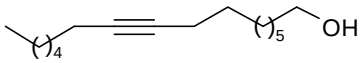
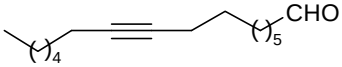
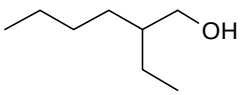
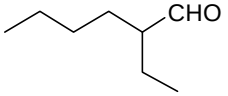
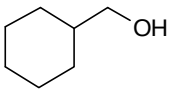
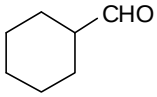
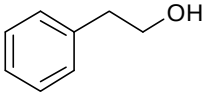
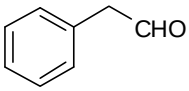
Figure 4.3: *Irreversible hydrogen transfer from alcohols to tolane, exemplified for 1-octanol.*

It is noteworthy that in contrast to the $Ru_3(CO)_{12}$ catalyzed oxidations of primary alcohols, described in chapter 3, the $RuCl_2$[*S*-BINAP] catalyzed oxidations do not need additional ligand to suppress consecutive reactions such as ester formation. For this reason no systematic study of a series of mono- and bidentate ligands was performed. The mechanism of the $RuCl_2$[*S*-BINAP] catalyzed oxidations will resemble that depicted in chapter 3, figure 3.20.

4.3.1 Applicability of the $RuCl_2$[*S*-BINAP] complex in oxidation reactions

The $RuCl_2$[*S*-BINAP] complex was tested with various primary alcohols as substrates. The results collected in table 4.1 reveal a high activity towards the oxidation of different functionalized primary alcohols into the corresponding aldehydes. All experiments were performed in *p*-xylene as a solvent at 130°C in the presence of 2.0 molar equivalents of tolane as H-acceptor and 5.0 mol% $RuCl_2$[*S*-BINAP] as catalyst.

Table 4.1. *Catalytic oxidation of a series of primary alcohols.*

entry	substrate	product	time (h)	Conv. (%)	$Y_{ald.}$ (%)	$S_{ald.}$ (%)
1			2	100	81	81
2			4	92	74	80
3			5	85	68	80
4			2	94	68	73
5			4	100	40	40
6			2	100	97	97 [a)]
7			5	85	71	84
8			2	79	69	87
9			2	60	32	53

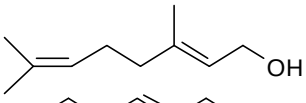
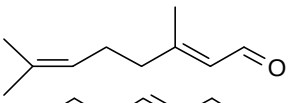
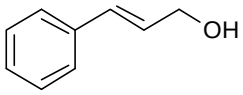
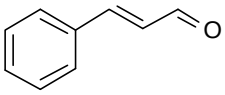
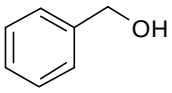
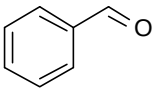
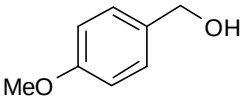
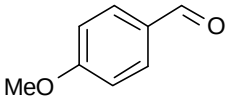
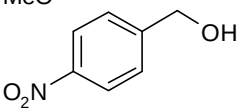
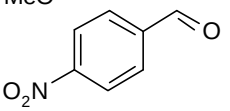
[a] After 5 hours the selectivity in the aldehyde had decreased to 82% and 9-hexadecenal (16%) had also been formed.

The reaction rate decreases when longer primary aliphatic alcohols like 1-decanol (entry 2) and 1-dodecanol (entry 3) were oxidized. Selectivity, however, remains constant at about 80%. In the oxidation of L-citronellol (entry 4), the double bond is not reduced.

All alcohols containing unsubstituted ethylene or acetylene groups, like in entry 5, yielded a lot of by-products and were for this reason not further investigated. Alcohols containing non-terminal acetylenes like 9-hexadecyn-1-ol (entry 6) always yielded a mixture of products due to the partial hydrogenation of the triple bond. Moreover in this case the hydride can be transferred in an intra- or intermolecular fashion to the triple bond of 9-hexadecyn-1-ol or to the actual H-acceptor tolane. Oxidizing more sterically hindered primary aliphatic 2-ethyl-1-hexanol (entry 7), cyclohexylmethanol (entry 8) and 2-phenylethanol (entry 9) was very sluggish presumably due to difficulties to expose the primary hydroxyl group to the catalytically active center.

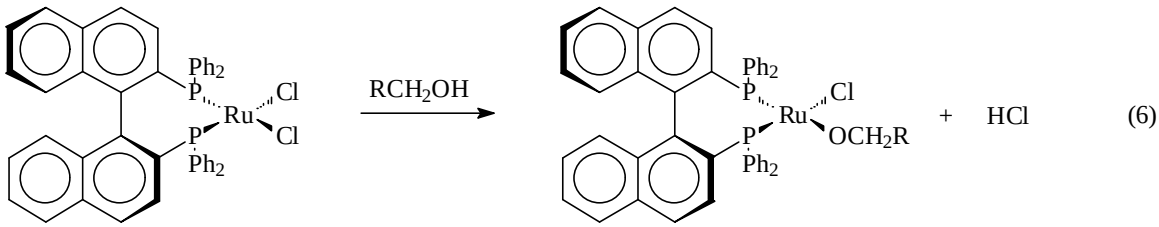
Catalytic oxidation of various primary allylic and benzylic alcohols, collected in table 4.2, indicate that the formation of conjugated systems during oxidation increased selectivity. All experiments were performed in *p*-xylene as solvent at 130°C in the presence of 2.0 molar of equivalents tolane as H-acceptor and 5.0 mol% $RuCl_2$[*S*-BINAP].

Table 4.2. *Catalytic oxidation of primary allylic and benzylic alcohols*

entry	substrate	product	time (h)	Conv (%)	Y_{ald} (%)	$S_{ald.}$ (%)
1			2	100	81	81
2			2	100	100	100
3			4	100	92	92
4			4	100	99	99
5			4	98	56	58

(E,Z)-3,7-Dimethyl-2,6-octadien-1-ol (geraniol) could be oxidized into the corresponding aldehyde without reduction of the double bonds with a selectivity of 81% (entry 1), similar to L-citronellol. However, when 3-phenyl-2-propen-1-ol (cinnamyl alcohol) was used, selectivity increased to 100% (entry 2). Selectivities higher than 90% were observed for

benzyl alcohol (entry 3) and *p*-methoxybenzyl alcohol (entry 4). Apparently, the oxidation of primary aliphatic alcohols is accompanied by loss of about 20% in contrast to that of benzylic- and allylic alcohols were no product loss was observed. To clarify this problem of incomplete mass balance, the oxidation of 1-octanol was studied in more detail. First it was observed that the reaction is disturbed by opening the reaction tube for sampling. The disturbance is either due to loss of hydrogen chloride which is present as a gas in the reaction tube or to the sensitivity of the catalyst towards oxygen. The formation of hydrogen chloride is expected as a result of the reaction of the alcohol with the ruthenium catalyst to form a ruthenium alkoxide species equation (6).[14]



[*S*-BINAP]-RuX_2

To circumvent the problem of sampling, six separate experiments were performed to monitor the oxidation of 1-octanol as a function of time (figure 4.4).

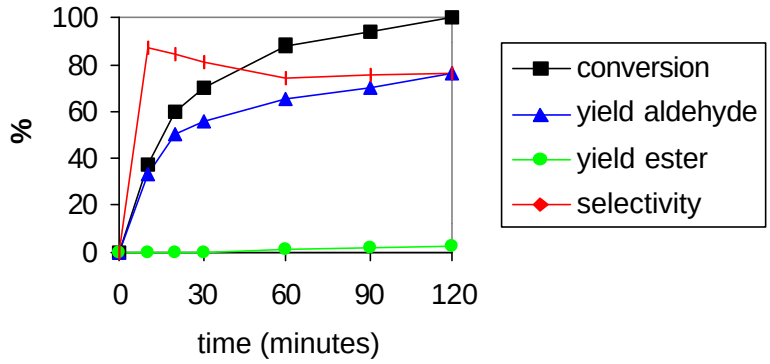
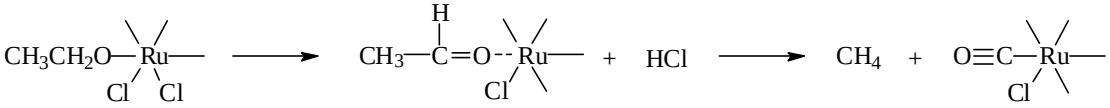


Figure 4.4. *Catalytic oxidation of 1-octanol monitored in time.*

Clearly, the selectivity decreases slowly with time and product loss already occurs from the beginning of the reaction. No other by-products besides octyl ester could be identified in the oxidation of 1-octanol. However, there is some evidence that alcohol and aldehyde molecules

formed during the reaction coordinate to the metal center of the catalyst. In the first attempt to identify ruthenium intermediates, a reaction mixture containing 1-octanol as a substrate was distilled (130°C, 10^{-1} Torr). ^{1}H- and ^{13}C-NMR spectra of the residue did not allow identification of any ruthenium alkoxide species. Subsequently, it was tried to release alcohol or aldehyde from the metal center by adding strong coordinating ligands, like cyanide, a large excess of phosphine ligands or by adding 36% HCl. Unfortunately, also in these cases no alcohol or aldehyde could be identified. Furthermore, to examine the influence of the catalyst on product loss, experiments with different amounts of catalyst were performed. More product loss occurs when a larger amount of catalyst is used. All reaction mixtures were distilled (130°C, 10^{-1} Torr) and again, ^{1}H- and ^{13}C-NMR spectra of the residues did not show ruthenium alkoxide species. However, IR-spectrometry revealed a strong absorption peak at 1960 cm^{-1} for all residues. Since metal carbonyl complexes[43] and metal hydrides[3,44] feature absorptions in this region, an experiment was performed using a larger primary aliphatic alcohol than 1-octanol thus preventing evaporation of the lower molecular weight by-products. When 1-dodecanol was used undecene (6%) could be identified as a by-product. This would imply that dehydroformylation is an important consecutive reaction in the catalytic oxidation of primary aliphatic alcohols. Indeed, Chatt et al.[43b] have reported that decarbonylation of an alcohol occurs in the presence of ruthenium chloride triphosphine complexes to form a ruthenium carbonyl complex and a degraded fragment of the alcohol, e.g., methane from ethanol (eq. 7). Likewise, Crabtree *et al.*[45b] recently reported the decarbonylation of aldehydes catalyzed by rhodium complexes with tridentate phosphine ligands.



(7)

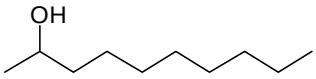
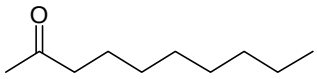
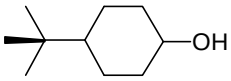
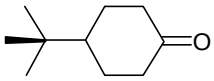
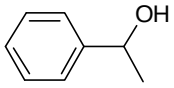
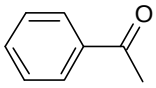
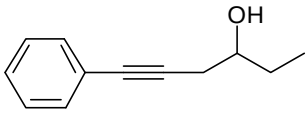
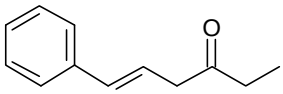
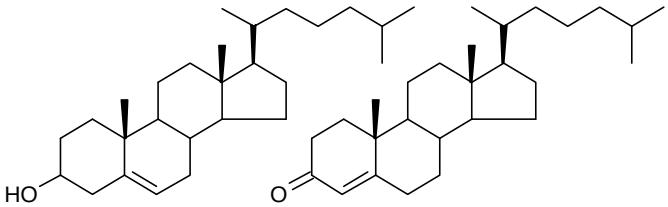
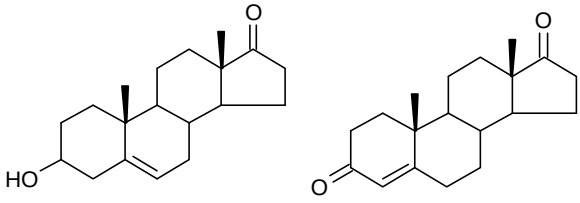
So the oxidation of alcohols use of $RuCl_2$[*S*-BINAP] as a catalyst gave dehydroformylation of an aldehyde into an unsaturated aliphatic compound together with a ruthenium carbonyl species. The dehydroformylation can schematically be presented as depicted in (eq 8).

(8)

The difference in selectivity between primary aliphatic alcohols (80%) and secondary, primary allylic and benzylic alcohols (100%) can be rationalized as follows. When strongly conjugated aldehydes are involved dehydroformylation does not occur (tables 4.1-4.2).

Subsequently, several secondary alcohols were tested. The results reported in table 4.3 indicate that although selectivity is high, the reactions are quite slow. Again experiments were performed in *p*-xylene as a solvent at 130°C in the presence of 2.0 molar equivalents of tolane and 5.0 mol% $RuCl_2$[*S*-BINAP].

Table 4.3. *Catalytic oxidation of a variety of secondary alcohols*.

entry	substrate	product	time (h)	Conv (%)	$Y_{ket.}$ (%)	$S_{ket.}$ (%)
1			24	34	29	85
2			24	47	41	87
3			5	30	21	70
4			24	79	39	50
5			48	100	97	97
6			16	14	7	50[a)]
7			72	30	23	77[b)]
8			170	87	83	96

[a)] The reaction was performed without tolane in 10 ml of refluxing acetone as solvent and hydrogen acceptor.

[b)] The reaction was performed without tolane in 10 ml of refluxing cyclohexanone as solvent and hydrogen acceptor.

When a secondary benzylic alcohol like 1-phenylethanol (entry 3) was used as a substrate, the reactivity increased compared to aliphatic alcohols like 2-decanol and 4-*t*-butyl-hexanol (entries 1 and 2). This increase in reactivity can be attributed to stabilization by conjugation due to the phenyl group. Oxidation of 6-phenyl-5-hexyn-3-ol (entry 4) led to the formation of several products which could be identified with GC/MS: 6-phenyl-5-hexyn-3-one (25%), 6-phenyl-5-hexen-3-ol (16%) and 6-phenyl-5-hexen-3-one (39%). Formation of the latter two could imply that intra- and/or intermolecular hydrogen transfer occurs.

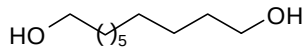
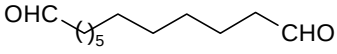
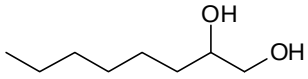
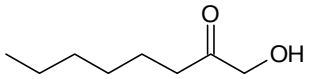
The Δ5(6)-(3-hydroxy)-steroids cholesterol (entries 5-7) and *trans*-dehydroandrosterone (entry 8) could be oxidized in high conversion and yield. Unfortunately, migration of the double bond from the Δ5(6) to the Δ4 position occurred. 4-Cholestene-3-one could be isolated from the reaction mixture in 65% yield by flash chromatography on silica-gel with a mixture of dichloromethane / diethyl ether as eluent in a purity of about 98%, judged from ^{1}H- and ^{13}C-NMR data. Whereas Bäckvall *et al*. [35] reported to be able to selectively oxidize cholesterol into 4-cholestene-3-one with acetone as solvent and hydrogen acceptor, the $RuCl_2$[*S*-BINAP] complex showed little activity towards this reaction (entry 6). When cyclohexanone was used as solvent and hydrogen acceptor, aldol condensation products of cyclohexanone could be identified with GC/MS (entry 7).

The difference in reaction rate between primary and secondary alcohols is quite remarkable. The turnover frequencies for the $RuCl_2$[*S*-BINAP] catalyzed oxidations are typically 4 to 10 h^{-1} for primary alcohols, secondary alcohols are generally oxidized with a rate of 0.1 to 1 h^{-1}. In contrast to the $Ru_3(CO)_{12}$ catalyzed oxidations, described in chapter 3, which showed turn over frequencies of typically 4 to 10 h^{-1} for primary alcohols and 15 to 47 h^{-1} for the oxidation of secondary alcohols. Furthermore, lower concentrations of $Ru_3(CO)_{12}$ could be used for the oxidation in secondary alcohols. The difference in the $RuCl_2$[*S*-BINAP] catalyzed oxidations of primary and secondary alcohols can be rationalized in terms of differences in steric crowding when they have to be incorporated in the catalytic cycle.

Furthermore, the $RuCl_2$[*S*-BINAP] complex was tested as an oxidation catalyst of two diols. Both experiments were performed in *p*-xylene as a solvent at 130°C in the presence of 2.0 molar equivalents tolane as H-acceptor and 5.0 mol% $RuCl_2$[*S*-BINAP].

As indicated in table 4.4, 1,10-decanediol could be oxidized to the dialdehyde in high yield (entry 1) and only 15% 10-hydroxy-decanal could be identified. However, special chemoselectivity was observed compared to the former results in the oxidation of 1,2-octanediol (entry 2). In this reaction not the primary but the secondary hydroxyl group was oxidized selectively. The α-hydroxy ketone, 1-hydroxy-2-octanone, could be characterized in the reaction mixture by GC/MS, IR, ^{1}H- and ^{13}C-NMR. A transition metal catalyst also employed in the regioselective oxidation of 1,2-diols into α-hydroxy ketones is peroxotungstophosphate, used in combination with acidic hydrogen peroxide in a two-phase system (aqueous hydrogen peroxide/chloroform).[36] A possible explanation of the observed chemoselectivity could be that first the primary alcohol is oxidized into the aldehyde and then due to enolization, the thermodynamically more stable ketone is formed.

Table 4.4. *Catalytic oxidation of various diols.*

entry	substrate	product	time (h)	Conv (%)	Y_{ald} (%)	$S_{ald.}$ (%)
1 [a)]			2	100	67	67
2			2	83	70	84

[a)] The reaction was performed with 3.0 molar equivalents tolane relative to the substrate.

4.3.2 Applicability of the $RuCl_2$[*S*-BINAP] complex in kinetic resolutions

It is known that homogeneous ruthenium complexes bearing chiral phosphine ligands are extremely useful in enantioselective hydrogenation processes.[22] The best known examples of such catalysis are displayed by rhodium(I)- and ruthenium(II)-BINAP complexes developed by Noyori *et al*. Here the chiral $RuCl_2$[(S)-BINAP] catalyst was investigated for the enantioselective dehydrogenation of racemic 1-phenylethanol and 1-phenyl-2-propanol. Both reactions were performed in *p*-xylene as a solvent at 130°C in the presence of 2.0 molar equivalents tolane and 5.0 mol% $RuCl_2$[*S*-BINAP]. Furthermore, a small amount of K_2CO_3 was added to accelerate the reaction. After 2 hours both reactions had reached 50% conversion and were then stopped. Disappointingly, no chiral enrichment was observed, indicating that there is no difference in reaction rate between $\mathbf{k_1}$ and $\mathbf{k_2}$ (figure 4.5).

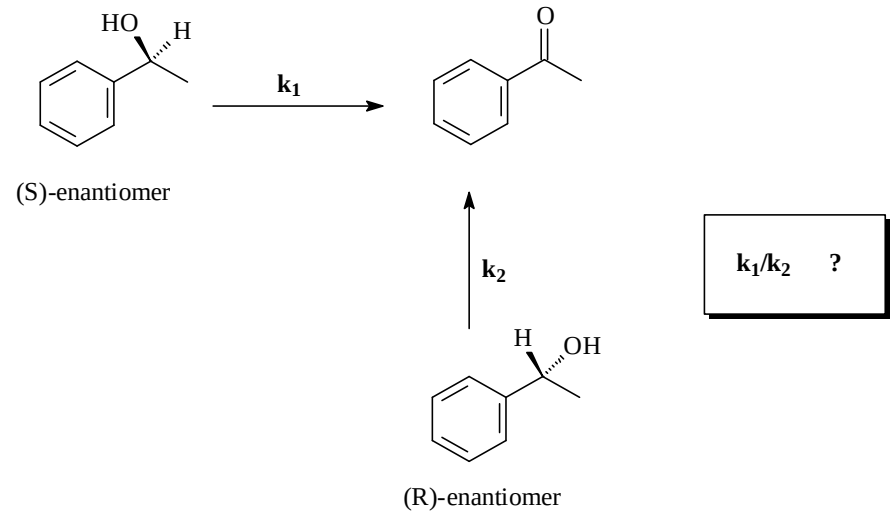


Figure 4.5 : *A difference in reaction rate between* k_1 *and* k_2 *would lead to chiral enrichment.*

4.3.3 Solvent effects

An elaborate screening of the influence of solvent on the catalytic oxidation has been performed. In the experiments always 1-octanol, 2.0 molar equivalents of tolane as H-acceptor and 5.0 mol% $RuCl_2$[*S*-BINAP] as catalyst have been used. Performing the reaction in solvents like *p*-xylene, toluene, decaline and chlorobenzene results in moderate to good conversion and yields. However, small amounts of ester are produced. Polar aprotic solvents like NMP, DMF and DMA tend to inhibit the reaction. Performing the reaction in the polar protic solvent phenol also inhibits the reaction. Better results are obtained in *p*-xylene and toluene than decaline. This could be rationalized by invoking stabilization of the catalytic system by the aromatic solvent. The lower yield and conversion using toluene compared to *p*-xylene can entirely be ascribed to the lower reaction temperature which causes a decrease in reaction rate.

Table 4.5. *Influence of solvent on conversion, yield and selectivity.*

entry	solvent	temperature (^oC)	time (h)	Conv. (%)	$Y_{ald.}$ (%)	$Y_{est.}$ (%)	$S_{ald.}$ (%)
1	*p*-xylene	130	2	100	81	1	81
2	toluene	110	2	85	64	2	75
3	decaline	130	2	61	25	1	41
4	chlorobenzene	130	5	66	52	0	79
5	NMP	130	2	9	1	0	10
6	DMF	130	2	17	2	0	12
7	DMA	130	2	21	6	0	29
8	phenol	130	2	0	0	0	0

4.3.4 Effect of base

In order to investigate the influence of base on the catalytic oxidation of 1-octanol several experiments were performed. All experiments were performed in *p*-xylene at 130^{o}C in the presence of 2.0 molar equivalents of tolane as H-acceptor and 5.0 mol% $RuCl_2$[*S*-BINAP]. When bases like potassium carbonate (K_2CO_3) or potassium acetate (KOAc) were added, reaction rates increased. However, selectivity decreases concomitantly leading to considerable ester formation. Since ruthenium diphosphine trifluoroacetate complexes are active catalysts for the dehydrogenation of alcohols,[37] addition of trifluoroacetic acid (CF_3CO_2H) was attempted to increase the reaction rate and selectivity. Unfortunately, this resulted equally in a decrease in selectivity due to ester formation.

The accelerating effect of K_2CO_3 was also examined when secondary alcohols were used as substrates. The results summarized in table 4.6 indicate that the presence of K_2CO_3 increases the reaction rate drastically. Moreover, selectivities are excellent. As stated before, secondary alcohols are generally oxidized at a rate of 0.1 to 1 h^{-1} without addition of a base. Adding 2.0 molar equivalents K_2CO_3 relative to the catalyst enhanced turnover frequenties to 1 to 5 h^{-1}, implying an accelerating effect of the base in the order of a factor of 10. A 30^{o}C decrease in reaction temperature still results in complete conversion of the alcohol into the corresponding ketone within 20 hours.

Table 4.6. *Influence of base on conversion, yield and selectivity of the catalytic oxidation of secondary alcohols*

entry	substrate	amount of catalyst (mol%)	temperature (^oC)	time (h)	Conv. (%)	$Y_{ket.}$ (%)	$S_{ket.}$ (%)
1	2-decanol	5	130	4	100	100	100
2	2-decanol	5	100	20	100	99	99
3	2-decanol	1	130	72	85	85	100
4	cholesterol	5	130	20	100	100	100

The rate accelerating effect of K_2CO_3 was also examined with cholesterol as substrate. The shorter reaction times with base might prevent migration of the double bond, see entry 4. Unfortunately, ^{13}C-NMR revealed that during the oxidation of cholesterol (Δ5(6)-(3-hydroxy)-steroid) the double bond had migrated to afford 4-cholestene-3-one (Δ4-(3-oxo)-steroid). The migration is probably due to the high temperature and the mildly basic conditions at which this reaction is performed. Much milder reaction conditions have to be found to prevent migration of the double bond. Also, as steroids with the double bond in the Δ5(10) position, the industrially important steroid (**11**) depicted in figure 3.12 was selected as substrate. However, due to the presence of a hydroxyl group next to an acetylene group, capable of acting as a H-acceptor, a very low selectivity was reached. ^{1}H and ^{13}C NMR as well as IR data demonstrated that no hydroxyl and no acetylene groups were present in the products.

4.3.5 Screening of H-acceptors

Since tolane is a relatively expensive hydrogen acceptor, other hydrogen acceptors were investigated in the catalytic oxidation of 1-octanol into octanal. In addition, the influence of the amount of tolane was studied. The results in table 4.7 indicate that acetylene compounds like 1-phenylpropyne or dehydrolinalool are superior to nitro compounds such as nitrobenzene and *m*-dinitrobenzene. At around 2 molar equivalents of tolane relative to the alcohol substrate an optimum appeared to be present. Reducing the amount of tolane decreases the reaction rate and started to favour ester formation. A possible explanation of the latter observation could be the presence of many vacant coordination sites on which ester

formation can occur due to the relative small amount of acceptor molecules. However, increasing the amount of tolane above 2 molar equivalents also decreases the reaction rate, presumably due to the occupation of vacant coordination sites by the acceptor. Furthermore, selectivity decreases with time which is probably due to conversion of the aldehyde into the ester in the presence of the ruthenium catalyst.

Table 4.7. *Catalytic oxidation of 1-octanol into octanal using different H-acceptors and the influence of the amount of tolane.*

entry	hydrogen acceptor	acceptor/ substrate ratio	time (h)	Conv. (%)	$Y_{ald.}$ (%)	$Y_{est.}$ (%)	$S_{ald.}$ (%)
1	1-phenylpropyne	2.0	2	70	59	0	84
2	dehydrolinalool	2.0	2	69	57	0	83
3	nitrobenzene	2.0	2	34	1	0	3
4	*m*-dinitrobenzene	1.0	2	41	1	0	2
5	tolane	1.0	2	78	51	8	65
			7	95	45	17	47
6	tolane	2.0	2	100	81	1	81
			8	100	70	6	70
7	tolane	3.0	2	88	46	1	52

Substituted analogues of tolane have been synthesized also. These compounds can give information about the catalytic mechanism. In the catalytic cycle the H-acceptor has to coordinate to the metal center first. After coordination a hydride is transferred from the metal center to the H-acceptor. Electron rich H-acceptors coordinate well to the metal center but are poor hydride acceptors. The opposite is true for electron poor H-acceptors. These compounds would take up the hydride easily but would not coordinate very well. For this reason the MeO (electron rich) and CF_3 (electron deficient) substituted analogues of tolane have been synthesized and were studied as H-acceptor in the oxidation of 1-octyl alcohol. The oxidation was performed at 130°C in *p*-xylene as solvent and stopped after 2 hours. The results of the experiments with different H-acceptors are depicted in table 4.8.

Table 4.8: *Oxidation of 1-octyl alcohol with tolane and substituted analogues as H-acceptor.*

	$RuCl_2$[(S)-BINAP]	
	Conv (%)	Y (%)
tolane	100	80
4-MeO-tolane	79	64
4-CF_3-tolane	42	29

In the catalytic systems tolane was more efficient than the electron rich 4-MeO-tolane. Both tolane and 4-MeO-tolane coordinate better to the metal center than 4-CF_3-tolane does. Due to the slower complexation of 4-CF_3-tolane, the rate of hydride insertion is lower compared to the other two H-acceptors. The difference between tolane and the electron rich 4-MeO-tolane can be explained by realizing that the electron rich H-acceptor will take up the hydride with some more difficulty than tolane does despite faster complexation. In addition, experiments with equimolar mixtures of two H-acceptors were performed. The results of these experiments are collected in table 4.9.

Table 4.9: *Conversion of 1-octyl alcohol with equimolar mixtures of H-acceptors.*

	$RuCl_2$[(S)-BINAP]	
	Conv (%)	Y (%)
tolane/4-MeO-tolane	77	63
tolane/4-CF_3-tolane	70	57
4-MeO-tolane/ 4-CF_3-tolane	63	50

Compared to the oxidations with tolane, 4-MeO-tolane or the mixture of tolane and 4-MeO-tolane, the reaction with a mixture of 4-MeO-tolane and 4-CF_3-tolane is faster than expected. Surprisingly, the conversion of 4-CF_3-tolane into 4-CF_3-stilbene is faster than the conversion of tolane or 4-MeO-tolane to the corresponding stilbene compounds (table 4.10).

Table 4.10: *Conversions of the H-acceptors in the mixed experiments.*

	$RuCl_2$[(S)-BINAP]
	Conv (%)
tolane/4-MeO-tolane	32/30
4-MeO-tolane/ 4-CF_3-tolane	9/34

The conversion of tolane and MeO-tolane into the corresponding stilbenes is nearly the same indicating that both compounds are comparable in combined coordination and H-acceptance. From the mixture of 4-MeO-tolane / 4-CF_3-tolane the overall conversion was expected to be much slower compared to that of tolane/MeO-tolane. Surprisingly, the conversion of CF_3-tolane is higher than that of 4-MeO-tolane indicating that both H-acceptors play an important role in the oxidation. The asymmetry introduced by the substituents on the hydride acceptor may also influence the coordinating and hydride accepting properties of the H-acceptor. All results obtained with the substituted tolane analogues and the $RuCl_2$[(S)-BINAP] catalyst are comparable to those of the $Ru_3(CO)_{12}$ catalyst with the substituted tolane analogues, see chapter 3.

4.3.6 Effect of a radical scavenger on the catalytic reaction

Furthermore, experiments were performed with a radical scavenger to determine whether the oxidation of alcohols is a one or two electron process. When standard reactions were performed in the presence of equimolar amounts of 2,6-di-tert-butyl-4-methylphenol as a radical scavenger (compared to the substrate), the reactions were even faster than in the absence of radical scavenger. Hence, it can be concluded that the oxidation is not of radical nature (figure 4.6).

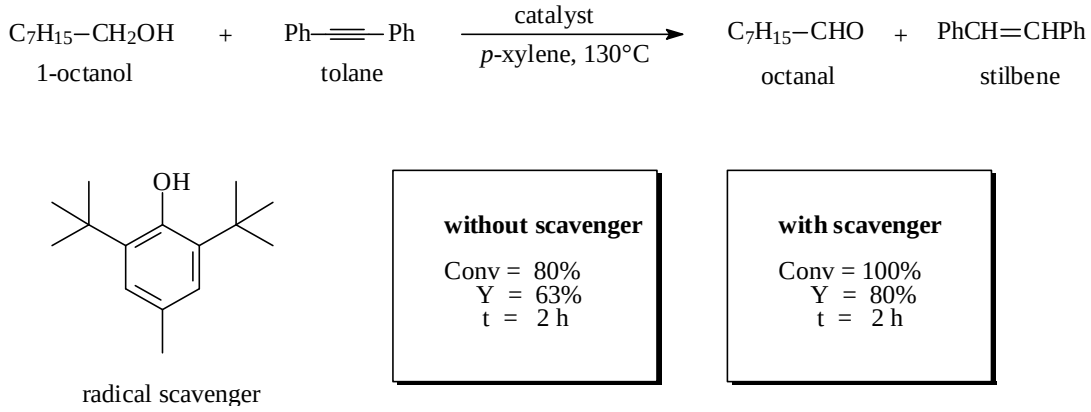


Figure 4.6: *Addition of a radical scavenger revealed the concertedness of the oxidation.*

4.3.7 Towards unraveling the catalytic cycle

A reaction mixture originating from 1-dodecanol as substrate was investigated to elucidate the various ruthenium complexes present during the catalytic oxidation. A light brown powder **7** could be obtained via precipitation in hexane.

^{1}H-NMR, IR and MALDI-TOF were used to characterize the isolated solid. Because the ^{1}H-NMR-spectra did not show any characteristic absorptions in the range from –20 to 0 ppm, the presence of ruthenium hydride complexes was excluded (figure 4.7).[38,39] The small signals at 0.88, 1.25, 1.56 ppm correspond to water and alkyl protons, respectively. The BINAP protons are visible as a broad absorption from 5.2 to 8.4 ppm.

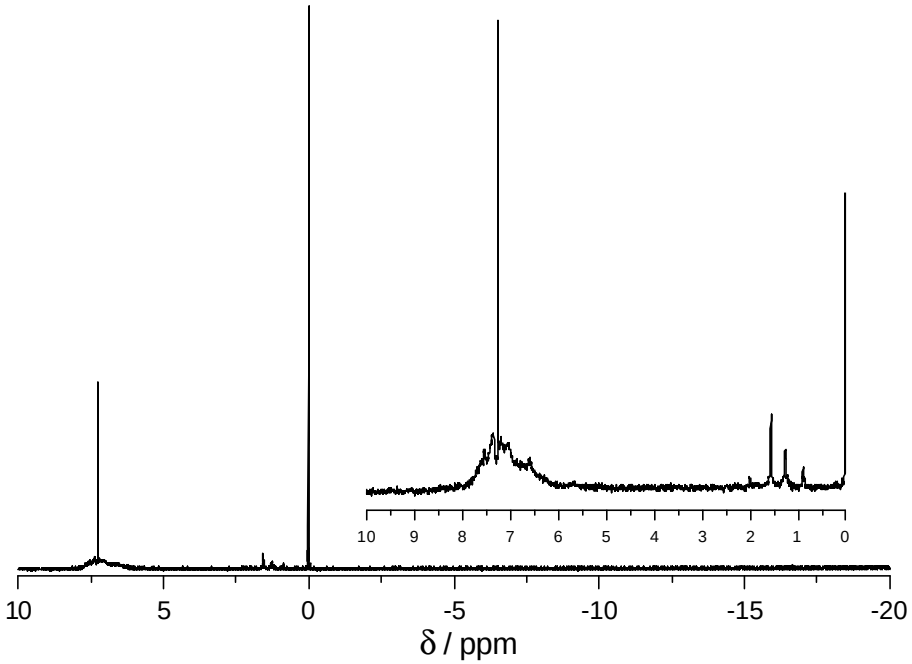


Figure 4.7: *^{1}H-NMR-spectrum of the precipitate **7** obtained from dodecanol in $CDCl_3$.*

However, IR-spectra of the precipitate **7** obtained after the oxidation of 1-dodecanol show one major broad peak at 1963 cm^{-1} that has been assigned to the carbonyl stretching vibration (Figure 4.8). Moreover, since no absorptions between 1900 and 1700 cm^{-1} are observed, bridging carbonyls are absent.[40] The peaks between 1600 and 694 cm^{-1} are characteristic absorptions of the ruthenium BINAP complex. In this region, the strong narrow absorption at 1435 cm^{-1} corresponds to the stretching of the phosphorus-phenyl bond present in the BINAP ligand.

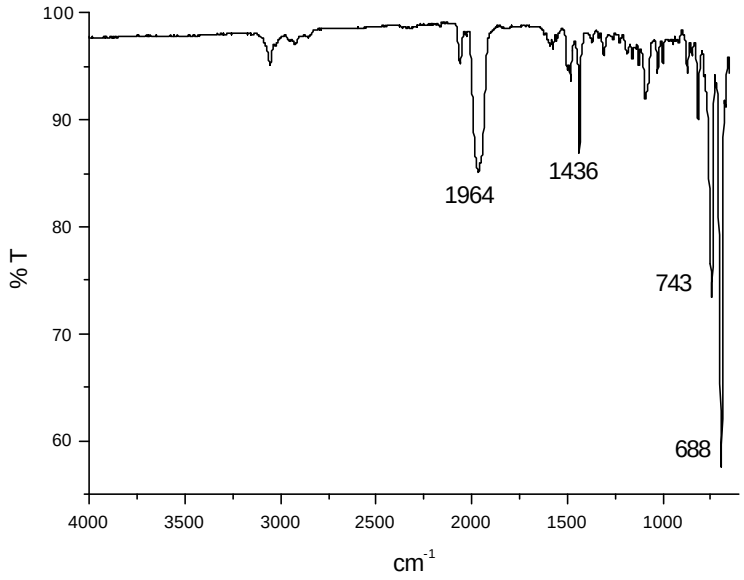


Figure 4.8: *IR-spectrum (neat) of the precipitate **7** obtained from a reaction mixture after oxidation of 1-dodecanol.*

Although the absorption peaks in the IR-spectrum are relatively weak, almost all signals can be attributed to the BINAP ligand or to Ru-carbonyl. This would suggest a simple structure of the complex. However, MALDI-TOF-spectra featured a range of peaks corresponding to various ruthenium BINAP containing species as shown in figures 4.10 and 4.11. Several mononuclear ruthenium species can be assigned to the masses between 750 and 1100 g/mol (figure 4.9).

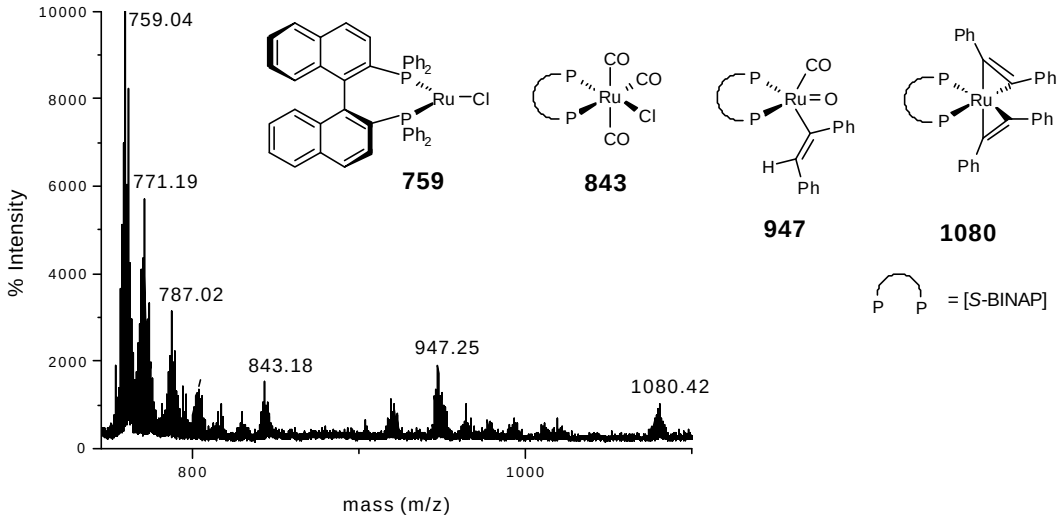


Figure 4.9: *MALDI-TOF-spectrum of **7** in $CDCl_3$: mononuclear ruthenium BINAP complexes.*

The mass of 843 g/mol can be attributed to octahedral $RuCl(CO)_3$[BINAP] which is formed upon dehydroformylation. The peak observed at 947 g/mol could correspond to RuO(CO)(tolane-H)[BINAP], while the mass of 1080 can be attributed to Ru[BINAP](tolane)$_2$. The presence of the latter two species suggest that tolane is coordinated to the ruthenium metal center in at least part of the catalytic cycle. The masses of 1555, 1581 and 1609 g/mol may be assigned to the dinuclear ruthenium complexes Ru_2Cl_3[BINAP]$_2$, $Ru_2Cl_3(CO)_2$[BINAP]$_2$ and $Ru_2Cl_3(CO)_3$[BINAP]$_2$ (figure 4.10). The latter three complexes form two chloride bridges, a phenomenon well known in coordination chemistry.[39,40]

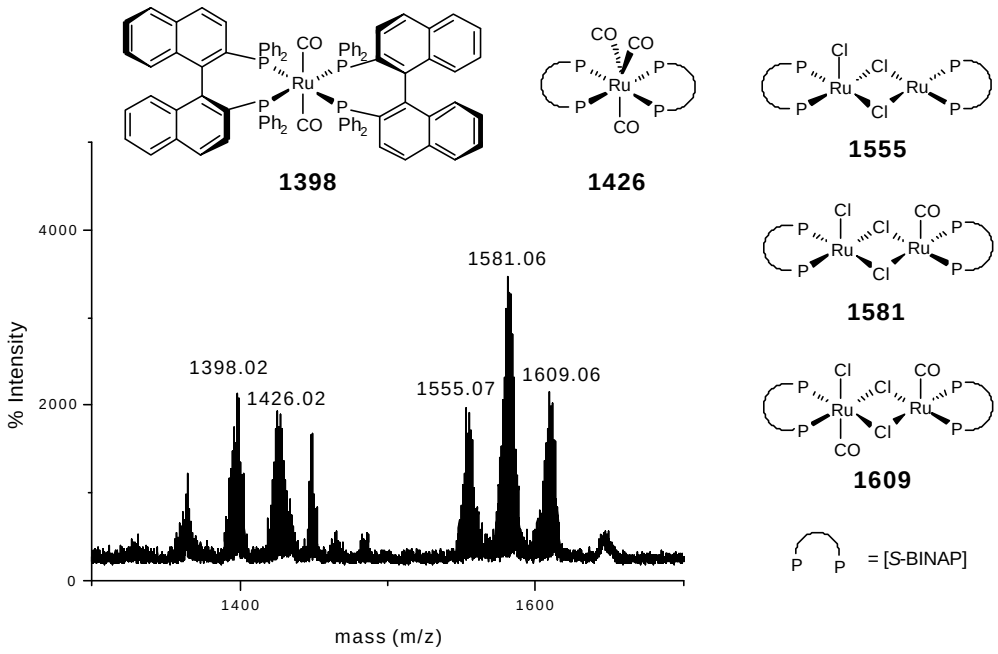


Figure 4.10: *MALDI-TOF-spectrum of **7** in $CDCl_3$: two mononuclear and three dinuclear ruthenium [BINAP] complexes.*

Yellow powders could be obtained by precipitation from reaction mixtures in which 1-octanol was used as a substrate. IR-, ^{1}H-NMR- and MALDI-TOF- data of these solids were similar to the data obtained from 1-dodecanol and confirm the absence of alcohol fragments in the powders. In order to separate and purify the various complexes present in these powders, thin layer chromotography (TLC) was performed with different eluents ranging from hexane to 10% methanol in dichloromethane both on silica and alumina plates. Unfortunately, this attempt to isolate pure catalyst intermediates turned out to be not successful.

The oxygen sensitive $RuCl_2$[*S*-BINAP] catalyst is actually a complex cluster designated as $[RuCl_2[S\text{-BINAP}]]_x$. This property hampers a smooth elucidation of the catalytic cycle for the alcohol oxidation reactions based on MALDI-TOF measurements. So, the MALDI-TOF-spectrum of the pure complex does not show one unequivocal peak but several peaks appear (figure 4.11). In this spectrum the mass of 794 g/mol corresponds to the $RuCl_2$[BINAP] complex, while the masses of 913 and 929 can be attributed to $RuCl_2$[BINAP](chloroform) and the oxidized form $RuOCl_2$-[BINAP](chloroform). Furthermore, dinuclear ruthenium species are clearly present at masses of 1551, 1570 and 1586 g/mol which can be attributed to $Ru_2O_2Cl_2[BINAP]_2$, $Ru_2OCl_3[BINAP]_2$ and $Ru_2O_2Cl_3[BINAP]_2$, respectively. In all these species presumably chloride bridges are present. Although ruthenium and phosphorus can be oxidized. These complexes are probably ruthenium oxo species. In this way 18-electron complexes are formed.

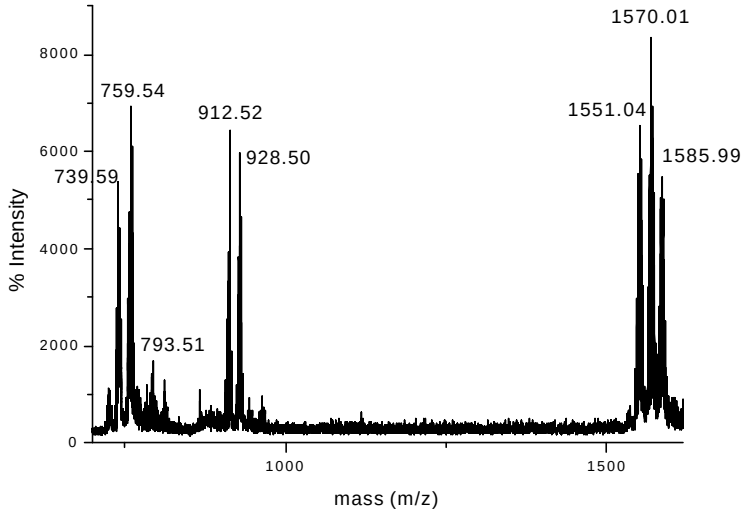


Figure 4.11: *MALDI-TOF-spectrum of* $[RuCl_2[S\text{-BINAP}]]_x$ *in* $CDCl_3$.

Since the $RuCl_2$[BINAP] complex is not a well-defined catalyst and very little mechanistic information is available about ruthenium-BINAP catalyzed reactions, it was difficult to obtain information about the catalytic cycle describing the oxidations of alcohols. Nevertheless, based on the results obtained so far, particularly from the competition experiments with the electron rich and deficient tolane analogues, a tentative catalytic cycle was proposed (figure 4.12).

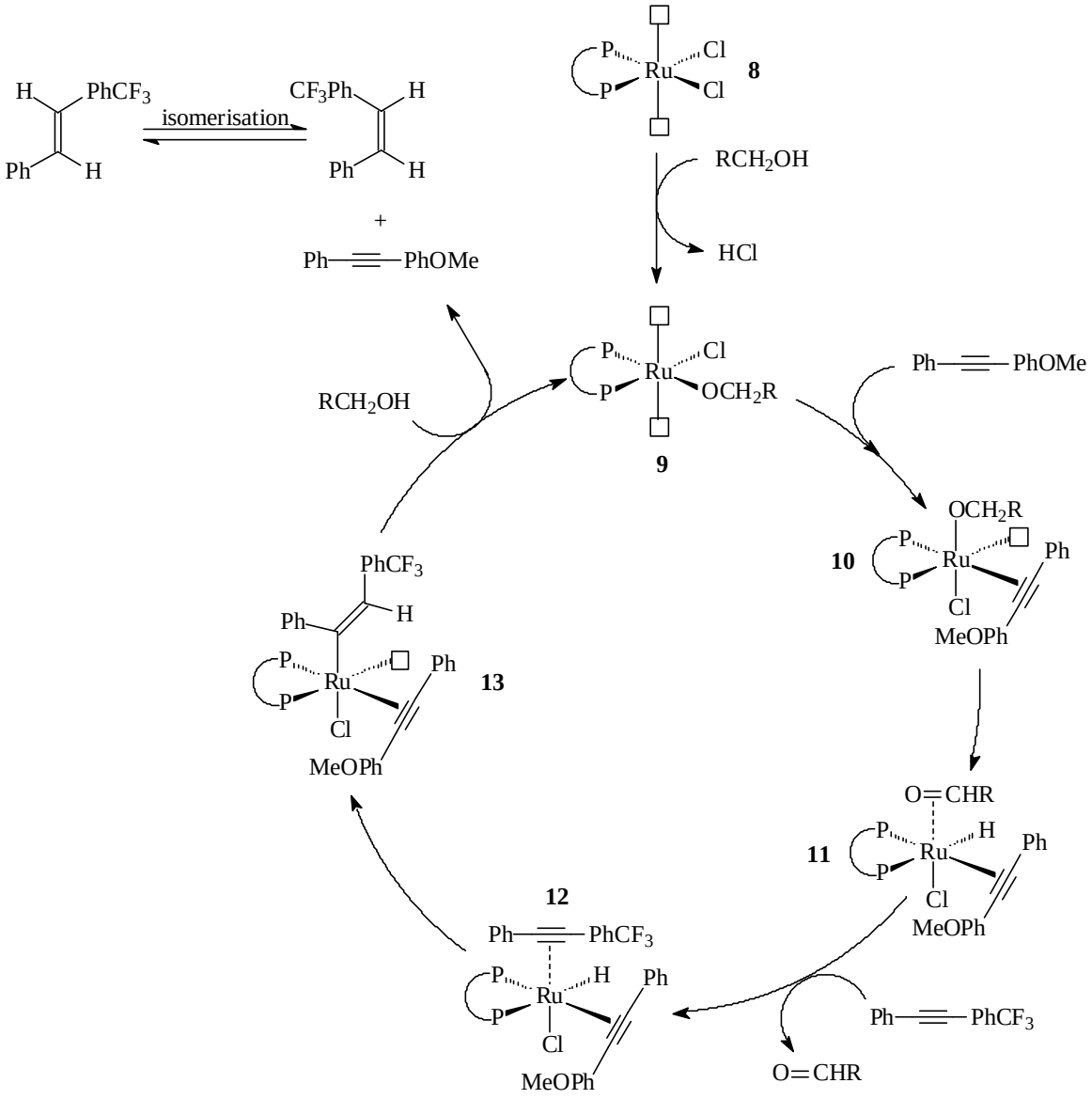


Figure 4.12: *Tentative mechanism for the $[RuCl_2[S\text{-}BINAP]]_x$ catalyzed oxidation of alcohols.*

In this simplified cycle the $[RuCl_2[S\text{-BINAP}]]_x$ complex is proposed to be defragmented into the monometallic ruthenium complex $RuCl_2$[BINAP]. Subsequently, an alcohol inserts into the $RuCl_2$[BINAP] complex **8** liberating hydrogen chloride and giving a coordinatively unsaturated ruthenium alkoxide species **9**. In the next step the electron rich 4-MeO-tolane ligand coordinates with ruthenium affording **10**. Then β-hydrogen elimination from the alkoxide ligand gives rise to a ruthenium hydride species and one aldehyde or ketone molecule **11** which is released from the cycle with concomitant generation of a free

coordination site. Subsequently, the electron deficient 4-CF_3-tolane can coordinate to the metal center due to the enhanced electron density introduced by the electron rich 4-MeO-tolane **12**. Then, the hydride is inserted in the 4-CF_3-tolane, giving the coordinatively unsaturated ruthenium alkoxide species **13**. Finally, oxidative addition of alcohol and concomitant release of 4-MeO-tolane to generate a free coordination site restores the coordinatively unsaturated ruthenium alkoxide species **9** and completes the catalytic cycle. Due to the high reaction temperature partial isomerisation of *cis*-stilbenes occurs into the *trans* isomer. Furthermore, dehydrocarbonylation can occur from **11** to give a ruthenium carbonyl species and a free alkene.

About the catalytic cycle a few remarks need to be made:

1) since none of the intermediates proposed has been isolated, the suggested cycle is merely plausible.
2) it is not unlikely that dinuclear ruthenium complexes could participate in the cycle since they are initially present in the catalyst.
3) several catalytically active ruthenium carbonyl species could be formed during dehydroformylation.

4.4 Conclusions

The thermodynamic uphill oxidation of various primary and secondary alcohols is catalyzed with $RuCl_2$[BINAP], when simple organic molecules like tolane are used as H-acceptor. The turnover frequencies for primary allylic and benzylic alcohols are typically 4 to 10 h^{-1}, while secondary alcohols are generally oxidized at a rate of 0.1 to 1 h^{-1}. The difference in reaction rates between primary and secondary alcohols can be rationalized in terms of differences in stereochemical crowding in the complex. In contrast to the $Ru_3(CO)_{12}$ catalyzed oxidations of primary alcohols, described in chapter 3, no additional ligand is needed to suppress consecutive reactions such as ester formation. The product loss of about 20% which is observed when primary aliphatic alcohols in the absence of a conjugated system are used as substrates, can be partly attributed to dehydroformylation. Furthermore, $Ru_3(CO)_{12}$ catalyzed oxidations of secondary alcohols are fast compared to those catalyzed by $RuCl_2$[BINAP]. The opposite is true for the oxidation of primary alcohols. Addition of a base has a strongly

accelerating effect on the catalytic oxidation ensuring that secondary alcohols could be oxidized to completion within a few hours.

From all H-acceptors screened in the catalytic hydrogen transfer reaction from alcohol, tolane gave the best results. Competition experiments of electron rich 4-MeO-tolane and the electron deficient 4-CF_3-tolane revealed cooperativity between the ligating H-acceptors. Addition of a radical scavenger to the reaction showed that the oxidation reaction is not a radical process.

It was found that (Δ5(6)-(3-hydroxy)-steroids) like cholesterol and *trans*-dehydro-androsterone could not be oxidized to the corresponding (Δ5(6)-(3-oxo)-steroids) without double bond migration. 4-Cholestene-3-one could successfully be isolated in moderate yield. Oxidation of cholesterol in the presence of acetone or cyclohexane as H-acceptors was unsuccessful. Double bond migration is presumably due to the drastic reaction conditions.

Though, Noyori *et al*. reported that BINAP catalysts are very effective in the enantioselective hydrogenation processes,[20] no enantioselective dehydrogenation of racemic 1-phenylethanol and 1-phenyl-2-propanol could be achieved.

Attempts to isolate catalytic intermediates were not successful. Although the detailed mechanism of the catalytic dehydrogenation of alcohols still remains unclear, a plausible catalytic cycle is proposed. The assumption that the H-acceptor also plays an important role as ligand seems justified. In order to elucidate the catalytic cycle spectroscopic data about catalytic intermediates have still to be collected.

In summary, the present $[RuCl_2[S\text{-BINAP}]]_x$ system has proven its potential in the selective transformation of a variety of alcohols into fine chemical aldehydes and ketones. Although a corner of the veil has been raised, more efforts have to be made to elucidate the structure of the intermediates and unravel the exact mechanism of the catalytic cycle.

4.5 Experimental

General:

For all general remarks, see the experimental section of chapter 3.

$RuCl_2$[BINAP] catalyzed oxidations, general procedure:

All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment consisted of the following. An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with $RuCl_2$[BINAP] (71.5 mg, 0.090 mmol) and tolane (700 mg, 3.90 mmol). Alcohol (2.00 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 ml) was added to the mixture. A small aliquot was taken from the alcohol/internal standard solution for GC analysis. The reaction tube was placed in a 12 Tube Radley Reaction Carousel and the mixture was heated and stirred with a magnetic stirrer for several hours. Small aliquots of reaction mixture could be taken for GC analysis. The conversions and yields were determined with GLC. The products were characterized (GLC) by comparison with authentic samples.

Octanal:

Octanol was oxidized according to the general procedure described above (table 4.1, entry 1). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC. The reaction mixture was purified by was purified by bulb-to-bulb distillation yielding (81 %) octanal. The spectral data was in accordance with literature.[44] ^{1}H-NMR ($CDCl_3$): δ = 9.85 (s, 1H); 2.41 (t, 2H); 1.62 (m, 2H); 1.30 (m, 8H); 0.88 (t, 3H). ^{13}C-NMR ($CDCl_3$): δ = 203.1; 44.3; 31.9; 29.5; 29.3; 23.0; 22.4;14.5; GC/MS *m/z* M^+: 128.

Phenylacetaldehyde:

2-Phenylethanol was oxidized according to the general procedure described above (table 4.1, entry 9). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (32 %). The spectral data was in accordance with literature.[41] ^{1}H-NMR ($CDCl_3$): δ = 9.72 (d, 1H), 7.30 (m, 5H), 3.66 (d, 2H). ^{13}C-NMR ($CDCl_3$): δ = 199.4, 131.9, 129.9, 129.6, 127.4, 50.5.

(*E,Z*)-3,7-Dimethyl-2,6-octadienal (Geranial):

Geraniol was oxidized according to the general procedure described above (table 4.2, entry 1). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (81 %). The spectral data was in accordance with literature.[42] ^{1}H-NMR ($CDCl_3$): δ = 9.97 (d, 1H), 5.85 (dd, 1H), 5.05 (m, 1H), 2.32-2.12 (m, 7H), 1.76-1.59 (2s, 6H). ^{13}C-NMR ($CDCl_3$): δ = 191.2, 190.7, 163.72, 163.70, 133.6, 132.8, 128.6, 127.4, 122.5, 122.2, 40.6, 32.6, 27.0, 25.7, 25.6, 25.0, 17.7, 17.6.

3-Phenyl-2-propenal:

Cinnamyl alcohol was oxidized according to the general procedure described above (table 4.2, entry 2). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (100 %). The spectral data was in accordance with literature.[43] ^{1}H-NMR ($CDCl_3$): δ = 9.73 (d, 1H), 7.59-7.43 (m, 6H), 6.77-6.68 (dd, 1H). ^{13}C-NMR ($CDCl_3$): δ = 193.8, 152.9, 131.3, 129.1, 128.9, 128.5, 127.2

Benzaldehyde:

Benzyl alcohol was oxidized according to the general procedure described above (table 4.2, entry 3). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (92 %). The spectral data was in accordance with literature.[44] For spectral data see chapter 2.

2-Decanone:

2-Decanol was oxidized according to the general procedure described above (table 4.3, entry 1). The product was characterized (GLC) by comparison with an authentic sample. The yield was determined with GLC (29 %). The spectral data was in accordance with literature.[44] For spectral data see chapter 2.

4-Cholestene-3-one:

Cholesterol was oxidized according to the general procedure described above (table 4.3, entry 6). The product was characterized (GLC) by comparison with an authentic sample. The yield was determined with GLC. Purification of the reaction mixture by flash column chromatography (silica, with dichloromethane/ether (20:1)) yielded 4-cholestene-3-one as a light brown/white powder (97 %). The spectral data were in accordance with literature.[35] ^{1}H-NMR ($CDCl_3$): δ = 5.75 (s, 1H); 2.48-2.22 (m, 2H); 2.05-1.95 (m, 2H); 1.88-1.75 (m, 2H), 1.74-1.22 (m, 12H), 1.20 (s, 3H), 1.19-0.94 (m, 8H), 0.91 (d, 3H), 0.86 (dd, 6H), 0.71 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ = 199.7, 171.7, 123.7, 56.1, 55.8, 53.9, 42.4, 39.6, 39.5, 38.6, 36.1, 35.7, 35.7, 35.6, 34.0, 32.9, 32.0, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.0, 18.6, 17.4, 11.9.

Androst-4-ene-3,17-dione:

3-Hydroxyandrost-5-en-17-one was oxidized according to the general procedure described above (table 4.3, entry 8). The product was characterized (GLC) by comparison with an authentic sample. The yield was determined with GLC. Purification of the reaction mixture by flash column chromatography (silica, with dichloromethane/diethyl ether (20:1)) yielded androst-4-ene-3,17-dione

as a white powder (83 %). The spectral data was in accordance with literature.[35] ^{1}H-NMR ($CDCl_3$): δ = 5.73 (s, 1H), 2.51-2.28 (m, 5H), 2.15-1.33 (m, 10H), 1.20 (s, 3H), 1.31-0.93 (m, 4H), 0.90 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ = 220.4, 199.3, 170.3, 124.1, 53.8, 50.8, 47.5, 38.6, 35.7, 35.6, 35.1, 33.9, 32.5, 31.21, 30.7, 21.7, 20.3, 17.3, 13.7.

1,10-Decanedial:

1,10-decanediol was oxidized according to the general procedure described above (table 4.4, entry 1). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (67 %). The spectral data was in accordance with literature.[45] ^{1}H-NMR ($CDCl_3$): δ = 9.76 (t, 2H), 2.43 (m, 4H), 1.65-1.60 (m, 4H), 1.43-1.26 (m, 8H). ^{13}C-NMR ($CDCl_3$): δ = 202.9, 43.9, 29.1, 29.1, 22.0.

1-Hydroxy-2-octanone:

1,2-Octanediol was oxidized according to the general procedure described above (table 4.4, entry 2). The product was characterized (GLC) by comparison with authentic samples. The yields were determined with GLC (70 %). The spectral data was in accordance with literature.[46] ^{1}H-NMR ($CDCl_3$): δ = 4.22 (s, 2H), 2.67 (t, 2H), 1.33-1.32 (m, 8H), 0.93 (t, 3H).

Solvent effects:

Analogous to the general procedure, the oxidation of 1-octanol was performed with 2.50 ml of the solvent at 130 °C. The conversion was monitered by GC analysis. The results are depicted in scheme 4.5.

Screening of H-acceptors:

Analogous to the general procedure, the oxidation of 1-octanol was performed with 2 equivalents of the alternative H-acceptor. All reactions were stopped after 5 h. The conversion was monitered by GC analysis.

1-Phenylethynyl-4-trifluoromethyl-benzene:

1-Phenylethynyl-4-trifluoromethyl-benzene was synthesized as described in chapter 3.

1-Methoxy-4-phenylethynyl-benzene:

1-Methoxy-4-phenylethynyl-benzene was synthesized as described in chapter 3.

Oxidation with equimolar mixtures of H-acceptors:

Analogous to the general procedure, the oxidation of 1-octanol was performed with a 1 to 1 mixture of H-acceptors (total 2 equivalents of H-acceptor). All reactions were stopped after 2 hours. The conversion was monitered by GC analysis (tables 4.8-4.10).

Oxidation with radical scavenger:

The oxidation of 1-octanol was performed according to the general procedure in the presence of 2,6-di-tert-butyl-4-methylphenol (427 mg, 1.94 mmol). The conversion was monitered by GC analysis (figure 4.7).

Precipitation and characterization of dodecanol reaction mixture (figures 4.7-4.9):

An oven-dried 40 ml reaction tube was flushed with argon before it was charged with $[RuCl_2[$*S*-BINAP$]]_x$ (79.7 mg, 0.10 mmol) and tolane (696.0 mg, 3.91 mmol). 1-dodecanol (372.1 mg, 2.0 mmol) and internal standard (1,3,5,-tri-*tert*-butylbenzene; 73.5 mg, 0.30 mmol) dissolved in *p*-xylene (2.5 ml) was added to the mixture. A small aliquot was taken from the 1-dodecanol solution for GC analysis beforehand. The reaction tube was placed in the carousel and the mixture was allowed to reflux and magnetically stirred for 5 h. The reaction mixture was allowed to cool to room temperature. Tolane, cis- and trans-stilbene, internal standard and dodecanal were distilled from the reaction mixture in a Kugelrohr at 130°C and 10^{-1} Torr. The residue taken up in a minimal amount of chloroform was precipitated with hexane, affording a light brown powder (**7**) (218.6 mg). ^{1}H-NMR ($CDCl_3$): δ = 8.4-5.2 (m, *H*-BINAP), 1.56 (s, water), 1.25 (m, C*H*$_2$-alkyl), 0.88 (t, C*H*$_3$-alkyl). IR (ATR): ν = 3055, 2925, 2855, 2062, 1963 (CO, carbonyl), 1600, 1574, 1554, 1497, 1482, 1435 (P-Ph, BINAP), 1370, 1307, 1260, 1186, 1158, 1092, 1072, 1028, 1000, 871, 845, 815, 744, 694. MALDI-TOF: 759, 771, 789, 845, 947, 1080, 1398, 1426, 1555, 1581, 1609.

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Chapter 5

Highly sustainable catalytic dehydrogenation of alcohols in the absence of H-acceptors.

Abstract

The catalytic dehydrogenation of alcohols into aldehydes and ketones in the absence of a H-acceptor was studied using several transition metal catalysts. In contrast to the $Ru_3(CO)_{12}$ and the $RuCl_2$[(S)-BINAP] catalyzed oxidations described in chapters 3 and 4 ¾ in which the catalysts give rise to oxidation of primary alcohols into aldehydes in high selectivity with the aid of stoichiometric amounts of H-acceptor¾ the catalytic dehydrogenation of primary alcohols in the absence of a H-acceptor is problematic due to decarbonylation with concomitant catalyst deactivation and aldol condensation under the strong acid or basic conditions applied. However, several secondary alcohols could be dehydrogenated with high selectivity into the corresponding ketones in relatively short reaction times. In this way highly effective atom utilization could be realized avoiding solvents and giving hydrogen gas as the sole by-product. The described catalytic application is known in the production of hydrogen gas, but to our surprise has not been systematically studied with respect to the fate of the alcohols used. The catalysts used in these reactions could be prepared in situ from commercially available chemicals.

5.1 Introduction

The development of catalytic oxidations under mild reaction conditions is very appealing. The fine chemical industry needs the development of sustainable technologies, based on environmental acceptability. The criteria include high atom efficiency, formation of little inorganic waste and selective synthesis of the desired products. Usually, salts represent the main waste, accounting for 70 wt %.[1,2] Moreover, the reactions are often performed in environmentally unfriendly solvents, typically chlorinated hydrocarbons.[3] Therefore, an environmentally friendly catalytic oxidation methodology using transition metal catalysts that will not produce such waste needs to be developed.[4,5]

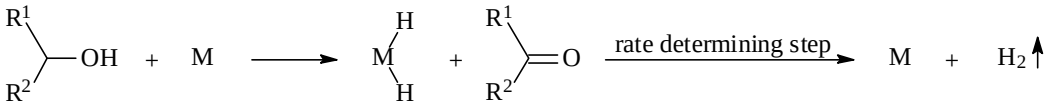
The catalytic production of hydrogen in which alcohols are used as hydrogen donor has been the subject of substantial research interest during recent years since it may give access to fuel from industrial waste alcohols or from biomass derived materials. Several homogeneous catalysts are able to dehydrogenate small alcohols like ethanol or 2,3-butanediol, giving rise to carbonyl derivatives and hydrogen gas.[6,7,8]

A major problem encountered is that many of the coordinatively unsaturated or potential coordinatively unsaturated transition metal complexes also decarbonylate alkanals and this reaction is seldom catalytic, see eq 1. Since secondary alcohols are not susceptible to decarbonylation poisoning of the catalyst does not occur and efficient hydrogen production is observed.

$$RCH_2OH \xrightarrow{\text{catalyst}} RH + CO + H_2 \qquad (1)$$

The retarding effects of accumulated aldehyde or ketone are presumably attributable to competition between the alcohol and the carbonyl product in the initial coordination step.[6,8,9,10] This reaction has often been used for the synthesis of hydrido and/or carbonyl metal complexes of several metals.[11]

Although the stoichiometric dehydrogenation of alcohols by transition metal species is a common place phenomenon, extensively employed in the synthesis of metal hydride complexes, homogeneous systems capable of catalyzing these reactions are rare.[12] In addition, the rate determining step for alcohol dehydrogenation is loss of H_2 from the metal species as depicted in eq. 2.[6,13]



(2)

M = catalyst

Two systems for the dehydrogenation of alcohols catalyzed by transition metal complexes are well known.[14] The first, containing rhodium(III) - tin(II) chloride is known as Charman's [15]

system see section 5.7 and the second involving $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ has been reported by Dobson and Robinson see section 5.2.[12,17]

5.1.1 Acid catalyzed hydrogen elimination by $Ru(OCOCF_3)_2(CO)(PPh_3)_2$

The dihydrido-complex $Ru(H)_2(CO)(PPh_3)_3$ reacts with weak carboxylic acids ($pK_a > \sim 4.2$) in boiling 2-methoxyethanol to form hydrido(mono-carboxylato) derivatives.[17] In each instance a molecule of triphenylphosphine is displaced to accommodate the chelate carboxylate ligand. These complexes are air sensitive: they decompose in the solid state and even more rapidly when dissolved in chlorinated solvents. Carboxylic acids with $pK_a < \sim 4.2$ (R = *p*-C_6H_4Cl, *p*-$C_6H_4NO_2$) react with $Ru(H)_2(CO)(PPh_3)_3$ in boiling methoxyethanol to form dicarboxylato-derivatives $Ru(OCOR)_2(CO)(PPh_3)_2$. In contrast, perfluorocarboxylato-complexes are air-stable crystalline solids and dissolve in common organic solvents to form air stable solutions. All are monomeric in chloroform solution and some representatives of this type of catalyst show evidence of appreciable dissociation. The air stable crystalline product obtained from the dihydride $Ru(H)_2(CO)(PPh_3)_3$ with a perfluorocarboxylic acid in boiling benzene or toluene contains one uni- and one bidentate perfluorocarboxylate ligand. The unidentate perfluorocarboxylate ligands are susceptible to alcoholysis when located trans with respect to good σ-donors such as triphenylphosphine, but inert to alcohols when trans to poor σ-donors such as carbonyl or perfluorocarboxylate ligands. So, the susceptibility to alcoholysis shown by the complex $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ is indicative of the *fac*-stereochemistry with the perfluorocarboxylate ligands trans to PPh_3, see figure 5.1. In contrast, the reluctance of the complex $Ru(OCOCF_3)_2(CO)_2(PPh_3)_2$ to undergo a similar process is consistent with the presence of perfluorocarboxylate ligands trans to poor σ-donors groups.[18]

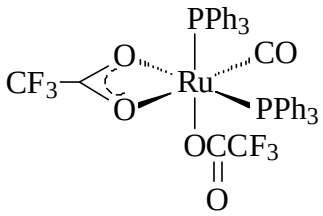


Figure 5.1: *Remaining three coordination sites shared by two $CF_3CO_2^-$ ligands in the fac complex.*

The mechanism proposed for the catalytic dehydrogenation process involves solvolysis of the ruthenium perfluorocarboxylate catalyst $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ to afford alkoxides $Ru(OR)(OCOCF_3)(CO)(PPh_3)_2$ which subsequently undergo β-hydride elimination to generate aldehyde or ketone and the hydride $RuH(OCOCF_3)(CO)(PPh_3)_2$. Attack of trifluoroacetic acid on the hydride would then liberate H_2 and regenerate the catalyst, see figure 5.2.[12,19]

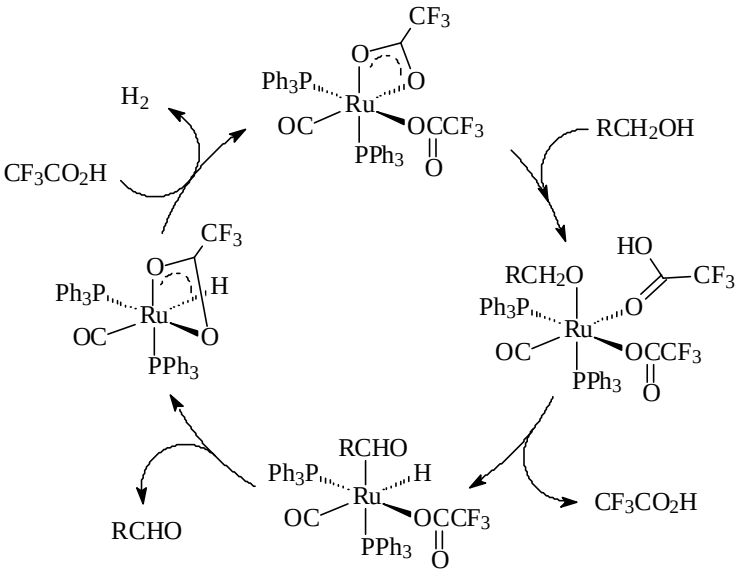


Figure 5.2: *Acid catalyzed dehydrogenation of alcohols.*

The dehydrogenation has been observed with a broad range of primary and secondary alcohols by following the production of hydrogen but surprisingly not the products. Kinetic data indicate that the rate of hydrogen production increases with increasing boiling point of the alcohol and ranges from 7.5 10^{-3} mol s^{-1} (mol of catalyst)$^{-1}$ (ethanol) to 2.27 mol s^{-1} (mol of catalyst)$^{-1}$ (benzyl alcohol) for $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ as catalyst under optimum reaction conditions. Catalyst efficiency decreases in the series Ru > Os and CF_3 ~ C_2F_5 > C_6F_5.[12] The catalysis is promoted by free acid (CF_3CO_2H) up to an optimum concentration of ca. 12 mol / mol of catalyst but is progressively inhibited by higher concentrations.[20]

5.1.2 Immobilization of the $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ catalyst

The last decade has seen an increase in studies on the application of transition metal complexes as heterogenized catalysts. The main advantages of the heterogenized catalysts are

(a) the high selectivity, comparable with that of homogeneous processes, (b) the ease of separation of the catalyst from the reaction products, (c) the possibility of modification of the chemical affinity of the heterogenized catalyst to reagent and (d) the possibility of performing the reaction under mild non-corrosive conditions. These advantages led to the attempts to immobilize the ruthenium complex on polystyrene-divinylbenzene resins, functionalized with phosphine and carboxylic groups, see figure 5.3.[21]

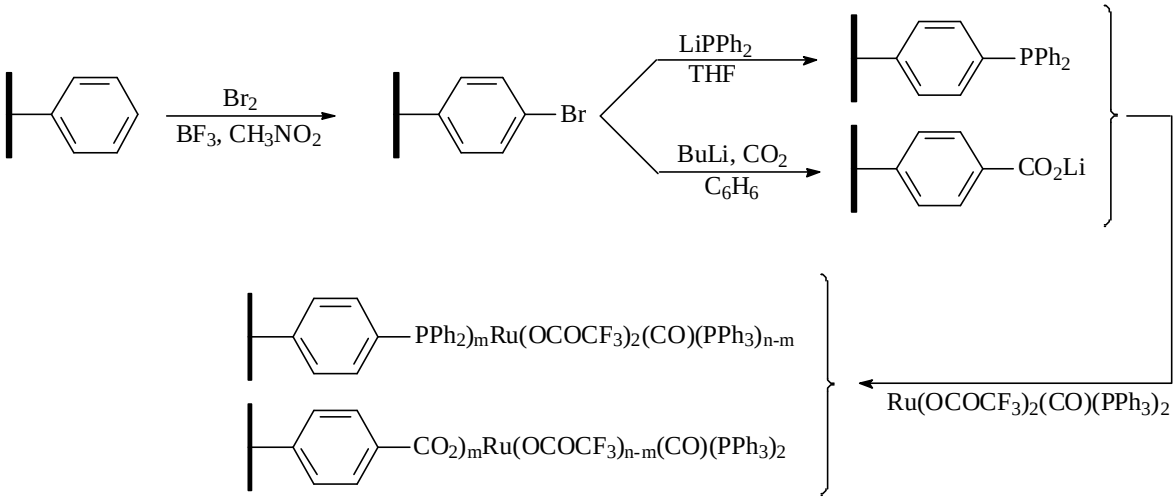


Figure 5.3: *Synthesis of immobilized ruthenium complexes on polystyrene-divinylbenzene resins*

Mixed polystyrene-divinylbenzene resins containing diphenylphosphine and carboxylate have also been synthesized. However, in all of the supported systems a considerable reduction in activity compared with the homogeneous catalyst was observed, probably resulting from diffusion limitations. An influence of the spatial structure of the polymeric ligand on the catalytic activity is also observed. The random arrangement of the carboxylate ligands in the polymer is an additional factor contributing to the decrease in catalytic performance. Nevertheless, the heterogenized catalyst preserved its activity after repeated applications, indicating the high stability of the heterogenized catalyst.

5.1.3 Optimalization by chelating ligands

The $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ catalyzed dehydrogenation described by Dobson and Robinson and more recently the polystyrene supported analogues by Rybak and Ziolkowski can be optimized by chelating ligands.[22-24] The mechanism originally proposed by Robinson

requires an isomerization whereby the two trans located phosphine ligands must rearrange into a *cis* configuration in order to complete the catalytic cycle. Locking the phosphine ligands into a *cis* configuration by means of a chelating diphosphine affected the rate of the overall reaction. The diphosphine ruthenium perfluorocarboxylate complexes are reported to be more efficient dehydrogenation catalysts. However, they are deactivated by decarbonylation of aldehyde and seem to be specific for the dehydrogenation of secondary alcohols.[25]

5.1.4 Base catalyzed hydrogen elimination by $Ru(H)_2(N_2)(PPh_3)_3$

After N_2 elimination the $Ru(H)_2(N_2)(PPh_3)_3$ complex, catalyzes the production of hydrogen from a range of alcohol containing substrates with rates exceeding 1000 catalyst turnovers per hour. Furthermore, an increase in rate was observed up on irradiation. This may arise from a photochemical enhancement of the rate of H_2 evolution from the intermediary species $RuH_4(PPh_3)_3$, *vide infra* at the end of the catalytic cycle. Base is required to make this reaction proceed, suggesting that the first step of the reaction involves attack of alkoxide ion on the ruthenium complex to give an anionic species from which aldehyde is lost to give the known $[Ru(H)_3(PPh_3)_3]^-$ species, see figure 5.4. Halpern has demonstrated that this anionic complex is an efficient ketone hydrogenation catalyst precursor, but that the reaction involves initial protonation by the alcohol to give the known active catalytic species $Ru(H_2)(H)_2(PPh_3)_3$.[26] This latter complex contains molecular hydrogen, which is readily replaced by neutral or anionic donors to release H_2.[27]

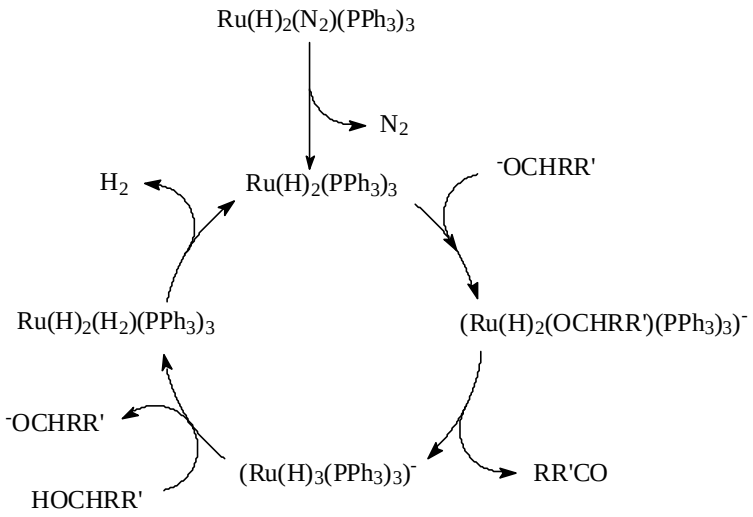


Figure 5.4: *$Ru(H)_2(N_2)(PPh_3)_3$ catalyzed hydrogen production from alcohols.*

The high rates of hydrogen production can be rationalized by various aspects, such as (a) the facile formation of the alkoxide complex due to the lability of the N_2 molecule as a ligand, (b) the facile protonation of the trihydrido species owing to its negative charge and (c) the lability of H_2 as a ligand in $Ru(H_2)(H)_2(PPh_3)_3$ due to its presence as coordinated dihydrogen. In almost every dehydrogenation, the rate of hydrogen production using $Ru(H)_2(N_2)(PPh_3)_3$ as catalyst is significantly higher compared to other catalysts like $Ru(H)_2(PPh_3)_4$ or to the best of the rhodium catalysts $[Rh(bipy)_2Cl$ (bipy = bipyridine)].[27] Rates of about 100 catalyst turnovers per hour could be obtained for various rhodium catalysts. Furthermore, production of hydrogen gas from species of this kind is known to depend significantly on the nature of the ligands in the coordination sphere. For instance, hydrogen does not evolve thermally from $[Rh(H)_2(py)_2(P^iPr_3)_2]^+$ but when one pyridine (py) molecule is replaced by CO, smooth hydrogen evolution is observed in the dark at room temperature.[28]

5.1.5 Acceleration of the rate limiting hydrogen elimination by irradiation

Although a lot of transition metal hydrides will not lose hydrogen under a variety of thermal conditions, irradiation with ultraviolet light readily induces elimination of H_2 from di- and poly-hydride metal complexes (figure 5.5).[27-30] This reaction has provided one of the key entries to transform 18 electron precursors into highly reactive 16 electron intermediates. The reverse reaction will usually proceed thermally.[31] The elimination of hydrogen from di- and polyhydrides has been demonstrated for V, Mo, W, Re, Fe, Ru, Co and Ir-derivatives containing a diverse array of ligands.[13]

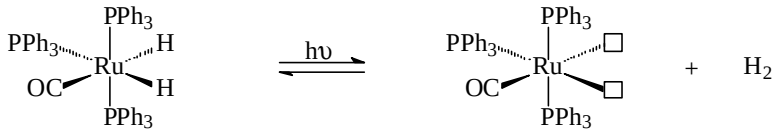
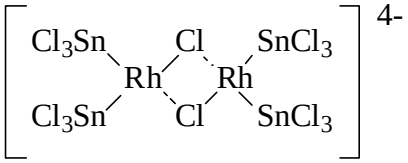


Figure 5.5: *Photochemical reductive elimination of hydrogen.*

5.1.6 Rhodium-tin catalyzed dehydrogenation

Chloro complexes of rhodium (III) catalyze the dehydrogenation of isopropyl alcohol.[32] During the reaction Rh(0) is formed and the rate of hydrogenation decreases as the rhodium complex is withdrawn from the reaction medium by precipitation. The rhodium chloride catalyzed dehydrogenation has also been examined in the presence of tin (II) chloride, to

investigate whether the rhodium hydride intermediate is protected against metal precipitation by replacing chloride with $SnCl_3^-$ ligands. It has been reported that platinum-tin chloride complexes are stable with respect to reduction to platinum metal by molecular hydrogen. Wilkinson *et al.* examined the complex formed between rhodium chloride and tin (II) chloride and assigned it formula **1**.[33]



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Lithium chloride and hydrogen chloride also affect the rate of dehydrogenation by changing the coordination state of the catalyst. The reduced rate of dehydrogenation caused by the gradual accumulation of the product acetone can be explained by assuming that the reverse reaction is significant.[32] Furthermore, Saito and co-workers were able to photo enhance the catalytic dehydrogenation of isopropyl alcohol with the homogeneous rhodium-tin complex.[34] However, the catalytic system for alcohol dehydrogenation based on rhodium-tin species is approximately 10-60 times less efficient than the $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ system.

5.1.7 Iridium catalyzed dehydrogenation of alcohols

Bennett and Milner have reported that $IrCl(PPh_3)_3$ dehydrogenates ethanol to produce acetaldehyde and $IrCl(H)_2(PPh_3)_3$.[35] Geoffroy and Pierantozzi have attempted to render this dehydrogenation reaction cyclic by irradiating $IrCl(H)_2(PPh_3)_3$ in the presence of ethanol with the aim of catalytically dehydrogenating primary alcohols through continuous photolysis.[36] However, irradiation of $IrCl(H)_2(PPh_3)_3$ in refluxing ethanol only led to less than stoichiometric amounts of acetaldehyde and not the expected catalysis. Geoffroy and Pierantozzi subsequently discovered that both $IrCl(PPh_3)_3$ and $IrCl(H)_2(PPh_3)_3$ react with acetaldehyde to produce catalytically inactive species like $IrCl(CO)(PPh_3)_2$.

5.2 Outline of this chapter and objectives

Several homogeneous transition metal catalysts are known to dehydrogenate low molecular weight alcohols like ethanol or 2,3-butanediol in order to produce hydrogen gas.

However, except for hydrogen gas, the dehydrogenation products have never been characterized. In this chapter the catalytic dehydrogenation of alcohols, as described by Dobson and Robinson, is investigated to produce ketones/aldehydes in the absence of H-acceptors. In contrast to the $Ru_3(CO)_{12}$ and $RuCl_2$[BINAP] systems described in chapter 3 and 4 respectively, in this case no H-acceptor is needed. For the acid catalyzed dehydrogenation an optimum in the amount of trifluoroacetic acid has been found. Several acids have been screened for their activity. The major challenge in dehydrogenating primary alcohols appeared to be preventing the decarbonylation reaction and the aldol condensation of the initially formed aldehyde. The hydrogen gas evolved during the reaction shifts the equilibrium favorably. Furthermore, the dehydrogenation could be performed with smaller amounts of catalyst and no solvent is needed in the case of liquid alcohols. Advantages of the catalytic dehydrogenation over other catalytic systems are:

- **Sustainability (no waste)**
- **High atom efficiency** **~ 50%** ⟶ **98%**
- **No solvent needed**

5.3 Results and discussion

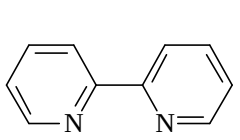
Compared to classical oxidations, the catalytic oxidation accompanied by elimination of hydrogen gas will enhance the atom efficiency from ~ 50% up to ~ 98%. Although thermodynamically an uphill reaction ($\Delta_r G° \cong$ 30-40 kJ mol^{-1}) the elimination of hydrogen gas shifts the equilibrium in the direction of aldehyde/ketone products. The catalytic dehydrogenation of secondary alcohols described in this chapter can schematically be represented by equation 3.

$$\textit{sec}\text{-alcohol} \xrightarrow[130^{\circ}C]{\text{1 mol \% catalyst}} \text{ketone} + H_2\uparrow \qquad (3)$$

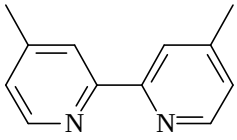
5.3.1 Late transition metals screened for base catalyzed dehydrogenation of alcohols

Various commercially available late transition metal complexes like $RhCl(CO)(PPh_3)_2$, $RhH(CO)(PPh_3)_3$, $Pd(OAc)_2(PPh_3)_2$, $IrCl(CO)(PPh_3)_2$, $IrH(CO)(PPh_3)_3$ and $RuH_2(N_2)(PPh_3)_3$ were screened in the catalytic dehydrogenation of 2-decanol. Exploratory experiments were

performed with 5 mol% of catalyst, 20 mol% of K_2CO_3 as base and all experiments were performed at 130°C in *p*-xylene as solvent. Furthermore, experiments with $RuH_2(CO)(PPh_3)_3$, $RuCl_2(bpy).H_2O$ and $Rh_2(bpydiMe)(COD)Cl_2$ were performed with 1 mol% of catalyst, 6 mol% K_2CO_3 and without solvent.



bpy



bpydiMe

The $RuCl_2(bpy).H_2O$ and $Rh_2(bpydiMe)(COD)Cl_2$ catalyzed dehydrogenation was performed with 2-octanol as substrate. All reactions were stopped after 5 hours. The results of these exploratory experiments are collected in table 5.1.

Table 5.1: *Catalysts screened for dehydrogenation of secondary alcohols.*

Entry	Catalyst	Conv (%)	Y (%)
1	$Pd(OAc)_2(PPh_3)_2$	4	4
2	$IrCl(CO)(PPh_3)_2$	5	5
3	$IrH(CO)(PPh_3)_3$	4	4
4	$RhCl(CO)(PPh_3)_2$	6	6
5	$RhH(CO)(PPh_3)_3$	13	13
6	$Rh_2(bpydiMe)(COD)Cl_2$	54	54
7	$RuH_2(CO)(PPh_3)_3$	47	38
8	$RuCl_2(bpy).H_2O$	45	43
9	$RuH_2(N_2)(PPh_3)_3$	80	26

Although the catalysts in entries 1 to 4 are well known for dehydrogenation and hydrogenation respectively and have good β-hydrogen elimination properties, they display no activity towards the catalytic dehydrogenation from 2-decanol under the elimination of hydrogen gas. The very active $RuH_2(N_2)(PPh_3)_3$ catalyst (entry 9) described in section **5.5** produces a lot of hydrogen gas but the selectivity to the ketone is low. Nevertheless, four

catalysts in entries 5 to 8, produce the ketone more than stoichiometrically with respect to the catalyst and in high selectivity. Very low conversions and selectivities were observed when these catalysts were applied in the dehydrogenation of primary alcohols. This is probably due to decarbonylation of the produced aldehyde. As carbon monoxide poisons the catalyst the dehydrogenation of primary alcohols was not further investigated. The mechanism described by Cole-Hamilton (figure 5.4) rationalizes the base catalyzed dehydrogenation of secondary alcohols.[27]

5.3.2 Acid catalyzed dehydrogenation of alcohols

Recently, $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ was found to catalyze hydrogen elimination from long chain aliphatic secondary alcohols. Ketones are produced, in high yields and in relatively short reaction times using 1 mol% of catalyst, 12 mol% CF_3CO_2H and at a temperature of 130°C. No solvent was used. The catalyst was prepared *in situ* from commercially available $RuH_2(CO)(PPh_3)_3$ and trifluoroacetic acid. All reactions started as a bright yellow solution and after a few minutes turned dark red and changed to bright yellow again at the end of the reaction. The catalyst could be recycled several times without loss in catalytic activity. Furthermore, no loss in catalytic activity was observed when the catalyst came in contact with water. The turnover number could well exceed 200 in the case of the oxidation of 2-octanol. The results are depicted in table 5.2.

Table 5.2: *$Ru(OCOCF_3)_2(CO)(PPh_3)_2$ catalyzed hydrogen elimination from secondary alcohols.*

Entry	Substrate	Time (h)	Conv (%)	Y (%)	Sel (%)
1	2-octanol	5	84	81	96
2	2-decanol	5	86	82	95
3	1-phenylethanol	8	100	99	99
4	4-tert-butylcyclohexanol	5	53	34	64
5	menthol	25	73	51	70
6	cyclohexanol	5	85	80	94

The very low concentrations of H_2 in boiling alcohol as a result of immediate removal ensure that the back-reaction — hydrogenation of the ketone or aldehyde — does not play a

significant role. The dehydrogenation of secondary alcohols in the absence of a H-acceptor to produce ketones can be rationalized with the catalytic cycle for the production of hydrogen gas from simple alcohols like ethanol or 2,3-butanediol as proposed by Dobson and Robinson. These authors stated that the catalysis is promoted by the addition of small amounts of free acid (CF_3CO_2H) and is inhibited by aldehyde or ketone and large amounts of acid.[12] However, in our hands, *in situ* preparation from $RuH_2(CO)(PPh_3)_3$ and 18 equivalents of CF_3CO_2H yielded the highest selectivities in the dehydrogenation of secondary alcohols. In trying to get mechanistic information a ruthenium complex formed during the dehydrogenation of 2-octanol with 12 equivalents of CF_3CO_2H was isolated after distillation of the reaction mixture. The mass (m/z) of 877 obtained from MALDI-TOF measurements was assigned to $Ru(OCOCF_3)_2(CO)(PPh_3)_2$. This compound was also found by Robinson as a result of synthesizing perfluorocarboxylato derivatives.[18]

Low conversions and selectivities were observed when primary alcohols were dehydrogenated. The aldehydes decarbonylate and produce CO that poisons the catalyst as was demonstrated by Geoffroy and Pierantozzi.[36] Furthermore, the strong acidic conditions employed catalyze aldol condensation. Milder reaction conditions have to be found to render the oxidation of primary alcohols successful. These milder reaction conditions can probably be achieved by varying the type of either ligands or acids.

5.3.3 Influencing the dehydrogenation by variation of the acids

Four different acids were investigated in the $Ru(H)_2(CO)(PPh_3)_3$ catalyzed dehydrogenation of 2-decanol and 2-octanol. The results obtained from 2-decanol and 2-octanol are comparable, see table 5.2. The experiments were performed with 1 mol% $Ru(H)_2(CO)(PPh_3)_3$, with different amounts of acid compared to the catalyst and at a temperature of 130°C in the absence of solvent. All experiments were stopped after 5 hours. The results of these experiments are collected in table 5.3.

Table 5.3: *Effect of acid and amount of acid on the catalytic dehydrogenation of 2-decanol and 2-octanol.*

Acid	pK_a	eq acid	Conv (%)	Y (%)	Sel (%)
p-$CH_3C_6H_4SO_3H$	-6.5	1	77	55	71
		2	97	64	66
		4	100	44	44
CF_3CO_2H*	0.23	0	58	24	41
		2	52	33	63
		6	79	54	68
		12	86	82	95
		18	84	81	96
CCl_3CO_2H	0.65	5	40	33	83
CH_3CO_2H	4.76	12	62	49	79

* 2-decanol was used as substrate.

Due to the high volatility of CF_3CO_2H — it evaporates from the reaction mixture — other acids with higher boiling points were investigated. Small amounts of *p*-toluenesulfonic acid as relatively strong acid are needed. With an increasing amount of the acid the dehydrogenation rate increases but the selectivity to ketone decreases; presumably due to acid catalyzed aldol condensation of the ketone. In contrast, the selectivity and rate of dehydrogenation increase with increasing amounts of the weaker acid CF_3CO_2H with an optimum amount of ~12 equivalents compared to the catalyst. When even weaker acids are used, the dehydrogenation becomes slower. This can be rationalized by the weaker ability to protonate the metal hydride compared to CF_3CO_2H and *p*-TsOH. For this reason hydrogen gas is released at a lower rate from the metal center and consequently the overall dehydrogenation is slower. The optimum reaction conditions were found when 12 equivalents of CF_3CO_2H were used.

5.4 Conclusions

An environmentally benign dehydrogenation methodology using transition metal catalysts like $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ has been developed. The criteria include high atom efficiency as well as formation of little inorganic waste. Several secondary alcohols have been selectively dehydrogenated into the corresponding ketones in relatively short reaction times.

Furthermore, the catalysts used in these reactions could be prepared *in situ* from commercially available chemicals. In comparison to the classical Oppenauer oxidation, and the $Ru_3(CO)_{12}$ or $RuCl_2$[BINAP] catalyzed oxidations, the $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ catalyzed dehydrogenation can be performed with less catalyst, in the absence of solvents and with a high selectivity. The catalyst could be recycled several times without observing any loss in catalytic activity. For the oxidation of 2-octanol the obtained turnover number could well exceed 200. The acid catalyzed dehydrogenation is more active and selective than the base catalyzed dehydrogenation. The best acid for the dehydrogenation has been found to be CF_3CO_2H. However, small amounts of *p*-TsOH could also be used. Probably there is an optimum pK_a value around 0.2.

A ruthenium complex formed during the dehydrogenation of 2-octanol was isolated. The mass (m/z) of 877 obtained from MALDI-TOF measurements was assigned to $Ru(OCOCF_3)_2(CO)(PPh_3)_2$. Similar compounds were also found by Robinson as a result of synthesizing perfluorocarboxylato derivatives. Unfortunately, the oxidation of primary alcohols with spontaneous release of hydrogen remains problematic due to side reactions like aldol condensation of the aldehyde formed and decarbonylation with concomitant deactivation of the catalyst.

5.5 Experimental

Screening transition metal complexes as catalysts, general procedure:

All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment consisted of the following. An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with catalyst (0.10 mmol) and K_2CO_3 (55.3 mg, 0.40 mmol). Alcohol (2.00 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 ml) were added to the mixture. A small aliquot was taken from the alcohol/internal standard solution for GC analysis. The reaction tube was placed in a 12 Tube Radley Reaction Carousel and the mixture was heated and stirred with a magnetic stirrer for several hours. Small aliquots of reaction mixture were taken for GC analysis. The conversions and yields were determined with GLC. The products were characterized (GLC) by comparison with authentic samples (table 5.1).

Dinitrogen(dihydro)tris(triphenylphosphino)ruthenium ($RuH_2(N_2)(PPh_3)_3$):

$RuH_2(N_2)(PPh_3)_3$ was prepared according to a literature procedure.[6]

$RuCl_2(PPh_3)_3$ (0.5 g, 0.44 mmol) was dissolved in a mixture of toluene (30 ml) and methanol (50 ml) under N_2. Dry, finely ground sodium borohydride (0.75 g, 20 mmol) was added with rapid stirring. After 30 min the complex precipitated as off-white powder. Degassed methanol (50 ml) was added and the product filtered off and dried in vacuo. The product was identified as $RuH_2(N_2)(PPh_3)_3$ by its IR (ATR) spectrum: υ = 2140, 1935, 1920 cm^{-1}.

Carbonyl(dihydrido)tris(triphenylphosphino)ruthenium (II) ($RuH_2(CO)(PPh_3)_3$):

$RuH_2(CO)(PPh_3)_3$ was prepared according to a literature procedure.[37]

To a suspension of $RuCl_2(PPh_3)_3$ (1.0 g, 0.88 mmol) in toluene and methanol (75 ml) was added sodium borohydride (0.2 g, 5.33 mmol). After being refluxed under hydrogen for *ca* 2 h, the complex dissolved and the initial dark-brown suspension becomes light orange. On cooling in a hydrogen stream a white solid precipitated. After filtration the solid was washed with diethyl ether and dried in vacuo (418 mg, 42 %). ^{1}H-NMR ($CDCl_3$): δ = 7.3-6.8 (m, 45H), -6.8 (m, 1H), -8.8 (m, 1H). ^{31}P-NMR ($CDCl_3$): δ = 58.23, 58.19, 58.10, 45.83, 45.71. IR (ATR): υ = 1963, 1941, 1915 cm^{-1}.

Carbonyl(trifluoroacetato-O)(trifluoroacetato-O,O')bis(triphenylphosphino)ruthenium ($Ru(OCOCF_3)_2(CO)(PPh_3)_2$):

$Ru(OCOCF_3)_2(CO)(PPh_3)_2$ was prepared according to a literature procedure.[18]

Trifluoroacetic acid (1 ml, 13.5 mmol) was added to a solution of carbonyldihydrido-tris(triphenylphosphine) ruthenium (0.46 g) in toluene (10 ml). The mixture was heated under reflux for 1 h and then evaporated under reduced pressure. The residual yellow oil was crystallized from dichloromethane-methanol and the product filtered off, washed successively in methanol, water, and methanol, then dried in vacuo as yellow crystals (338 mg, 77%). ^{31}P-NMR ($CDCl_3$): δ = 39.6. IR (ATR): υ = 3057, 2963, 1973, 1669, 1648, 1482, 1434, 1260, 1190, 1136, 1089, 1016, 793, 741, 726, 650 cm^{-1}.

Di-μ-chloro(η^4–1,5-cyclooctadiene)(4,4'-dimethyl-2,2'-dipyridyl)dirhodium ($Rh_2(bpydiMe)(COD)Cl_2$):

$Rh_2(bpydiMe)(COD)Cl_2$ was prepared analogously as described for $RuCl_2(bpy).H_2O$ [38].

A solution of 4,4'-dimethyl-2,2'-dipyridyl (748 mg, 4.06 mmol) in toluene (30 ml) was added to an orange solution of $[RhCl(C_8H_{12})_2]_2$ (493 mg, 1.0 mmol) in toluene (10 ml). After stirring the mixture and heating to 60 °C for 30 min the orange suspension was filtered, the solid was washed 3 times with toluene and dried in vacuo (~ 90%). ^{1}H-NMR ($CDCl_3$): δ = 9.08 (s, 2H), 7.58 (d, 2H), 7.30 (d, 2H), 4.48 (s, 4H), 2.72 (s, 6H), 2.59 (m, 4H), 2.12 (d, 4H). IR (ATR): υ = 3048, 3012, 2939, 2914, 2873,

2827, 1618, 1557, 1492, 1480, 1428, 1328, 1308, 1244, 1221, 1176, 1135, 1116, 1077, 1037, 1023, 994, 963, 921, 890, 868, 834, 818, 774, 562 cm^{-1}.

Acid catalyzed dehydrogenations, general procedure:

All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment consisted of the following. An oven-dry 40 ml Radley Carousel Reaction Tube was flushed with argon before it was charged with $RuH_2(CO)(PPh_3)_3$ (91.8 mg, 0.10 mmol) and CF_3CO_2H (205 mg, 1.8 mmol). A mixture of alcohol (2.00 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) was added to the *in situ* prepared catalyst. The reaction tube was placed in a 12 Tube Radley Reaction Carousel and the mixture was heated to 130 °C and stirred stirrer for several hours. Small aliquots of reaction mixture were taken for GC analysis. The conversions and yields were determined with GLC. The products were characterized (GLC) by comparison with authentic samples (table 5.2).

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Summary

The development of catalytic oxidations proceeding under mild reaction conditions is very appealing in various industrial sectors like pharmaceuticals, agrochemicals and food and flavors. The fine chemical industry needs sustainable technology which is based on environmental acceptability. The criteria include atom efficiency, formation of little inorganic waste and selective synthesis of the desired products. Usually salts are the main waste. Moreover, the reactions are often performed in environmentally undesirable solvents, typically chlorinated hydrocarbons. Therefore, an environmentally benign catalytic oxidation methodology using transition metal catalysts that will not produce such waste needs to be developed. In this thesis the development of catalytic oxidation methodologies of alcohols into aldehydes and ketones is described.

Classical Oppenauer oxidations of secondary alcohols are chemoselective and can be performed under mild reaction conditions. However, low selectivities are observed for the corresponding oxidation of primary alcohols. Furthermore, high concentrations of H-acceptor are needed and the *"catalyst"* is needed in stoichiometric amounts. Metal containing silsesquioxanes in combination with strong H-acceptors were investigated to overcome the hurdles of the classical Oppenauer oxidation. Unfortunately, the metal silsesquioxane complexes do not tend to accelerate the H-transfer. This might be due to either steric effects of the silsesquioxane framework or to strong coordination of the substrate / product to the electron deficient metal center created by the silsesquioxane framework.

Two catalysts ($Ru_3(CO)_{12}$, $RuCl_2$[(S)-BINAP]) were found — which in contrast to the classical Oppenauer oxidation — are able to oxidize primary as well as secondary alcohols into the corresponding aldehydes and ketones. To accelerate the dehydrogenation and to stop the $Ru_3(CO)_{12}$ catalyzed oxidation of primary alcohols at the aldehyde stage, a systematic study of mono- and bidentate ligands was performed. A screening demonstrated that the cone angle of the ligand-metal system considerably influences the conversion rate of the alcohol and the selectivity towards the aldehyde. Triphenylphosphine was selected as the best ligand. The common formation of ester could thus be avoided. This result is unprecedented. In the $RuCl_2$[(S)-BINAP] catalyzed oxidation no additional ligand is needed to suppress side reactions. In addition the chiral $RuCl_2$[(S)-BINAP] catalyst was tested in the oxidation of racemic alcohols to investigate the possibility of kinetic resolution. Among many H-acceptors

screened tolane was found to be the best for both catalysts. Furthermore, electron rich and deficient analogues of tolane have been synthesized and investigated in their performance as H-acceptor. Competition experiments between these acceptors demonstrated that cooperativity between the electron rich and deficient analogues exists and that the H-acceptor is also acting as a ligand. Based on MALDI-TOF, NMR, IR and the results of the competition experiments, tentative catalytic cycles are proposed for both catalytic systems.

Several homogeneous catalysts are known to dehydrogenate small alcohols like ethanol or 2,3-butanediol in order to produce hydrogen gas. However, except for hydrogen gas, the dehydrogenation products have never been investigated. In this thesis the catalytic dehydrogenation process of secondary alcohols into ketones in the absence of H-acceptor was investigated. Several secondary alcohols could be dehydrogenated into the corresponding ketones in relatively short reaction times. In this way highly effective atom utilization can be realized avoiding solvents and giving hydrogen gas as the sole by-product. The catalyst in these reactions has been prepared *in situ* from commercially available chemicals. For the acid catalyzed dehydrogenation an optimal stoichiometry with respect to the amount of trifluoroacetic acid was found. Several other acids were screened for their activity as well. Compared to traditional oxidations, the catalytic oxidation proceeding under the elimination of hydrogen gas enhances the atom efficiency from ~ 50% up to ~ 98% without producing waste. Although thermodynamically an uphill reaction, the removal of hydrogen gas shifts the equilibrium favorably.

Within the framework of IOP-Catalysis the original objective of the project described in this thesis as defined in 1998 has partly been realized. Two oxidation methodologies have been developed which in contrast to the classical Oppenauer oxidation can oxidize primary alcohols into the corresponding aldehydes with high selectivity. The atom efficiency of both systems is, however, low and the H-acceptor used is difficult to remove from the product. Furthermore, both catalytic systems are unable to oxidize steroids without double bond migration. A promising start has been made with the catalytic dehydrogenation of secondary alcohols in the absence of H-acceptor. Several secondary alcohols can now be oxidized with very high atom efficiency and with high TOF/TON. The method is not appropriate for the oxidation of primary alcohols since catalyst deactivation occurs due to decarbonylation of the aldehyde produced. Additional research in this direction is desirable.

Samenvatting

Het promotieonderzoek betreft een zoektocht naar breed toepasbare, chemoselectieve en katalytische oxidatieprocessen voor de omzetting van alcoholen tot voor de fijnchemie relevante aldehyden en ketonen. Aanleiding daartoe is de noodzaak voor de fijnchemische industrie om de klassieke stoichiometrische oxidaties — met vorming van grote hoeveelheden vaak giftig metaal houdend afval en dikwijls uitgevoerd in chloorhoudende oplosmiddelen — te vervangen door meer duurzame technologie met hoge selectiviteit en met weinig afval, kortom met grote *atom efficiency*.

Oppenauer-oxidaties van secundaire alcoholen verlopen in het algemeen met hoge selectiviteit; daarentegen die van primaire alcoholen met geringe selectiviteit. Bovendien zijn zeer hoge concentraties waterstofacceptor en stoichiometrische hoeveelheden "*katalysator*" nodig. Om deze problemen te omzeilen zijn metaalhoudende silsesquioxanen als katalysator in combinatie met sterke waterstofacceptoren onderzocht. Uit de resultaten van dit onderzoek kan geconcludeerd worden dat metaalhoudende silsesquioxanen de waterstofoverdracht naar sterke waterstofacceptoren niet kunnen bewerkstelligen. Dit kan verklaard worden door de vermoedelijke grote sterische hinder van het silsesquioxaan skelet in combinatie met de sterke coördinatie van substraat of product aan de katalysator.

Twee katalysatoren ($Ru_3(CO)_{12}$, $RuCl_2$[(S)-BINAP]) zijn gevonden waarmee — in tegenstelling tot de klassieke Oppenauer-oxidatie — zowel primaire als secundaire alcoholen selectief geoxideerd kunnen worden. Er zijn betrekkelijk geringe hoeveelheden katalysator (5 mol%) nodig. De hoeveelheid waterstofacceptor is eveneens veel kleiner dan bij de klassieke Oppenauer-oxidaties. Om de $Ru_3(CO)_{12}$ gekatalyseerde oxidatie van primaire alcoholen selectief uit te voeren is een studie uitgevoerd naar het effect van de *cone*- en *bite angle* op de selectiviteit en reactiesnelheid. Het onderzoek geeft aan dat de *cone angle* van het ligand metaal systeem een grote invloed heeft op de omzettingssnelheid en de selectiviteit. Als beste ligand kwam uiteindelijk triphenylphosphine uit de bus. Deze vondst is nieuw. Voor de $RuCl_2$[(S)-BINAP] gekatalyseerde oxidaties is geen additioneel ligand nodig om een hoge selectiviteit te garanderen. Ook is deze chirale katalysator getest in de oxidatie van racemische alcoholen met de gedachte om een kinetische resolutie te bewerkstelligen. Voorts is met behulp van MALDI-TOF, NMR, IR en experimenten, waarin uiteenlopende

waterstofacceptoren zijn gebruikt, de katalytische cyclus voor zowel $Ru_3(CO)_{12}$ als voor $RuCl_2$[BINAP] ontrafeld. Ondanks de hoge selectiviteit van beide systemen is de *atom efficiency* laag en de gebruikte waterstofacceptoren zijn moeilijk van de gevormde producten te scheiden.

Van verschillende katalysatoren is beschreven dat ze alcoholen dehydrogeneren onder vorming van waterstofgas. Hierbij heeft men echter nooit het lot van het alcohol onderzocht. In dit proefschrift is deze methode onderzocht om secundaire alcoholen te oxideren zonder gebruik te maken van waterstofacceptoren. Ondanks het feit dat de oxidatie van alcoholen een thermodynamisch ongunstige reactie is ($\Delta_r G° \cong$ 30-40 kJ mol^{-1}) worden toch hoge omzettingsgraden bereikt, omdat waterstofgas als een reactieproduct ontwijkt. Hierbij kunnen ketonen met hoge selectiviteit gesynthetiseerd worden in de aanwezigheid van slechts 1 mol% katalysator en zonder oplosmiddel. De katalysator kan *in situ* gegenereerd worden uit het commercieel verkrijgbare $RuH_2(CO)(PPh_3)_3$ en trifluorazijnzuur. In vergelijking tot andere oxidaties doet de katalytische eliminatie van waterstofgas de *atom efficiency* stijgen van ~ 50% tot vrijwel 100%.

Het onderzoeksvoorstel zoals in 1998 gepresenteerd aan de IOP-Katalyse programma commissie is gedeeltelijk gerealiseerd. Twee nieuwe oxidatiemethoden zijn ontwikkeld waarmee in tegenstelling tot de klassieke Oppenauer oxidatie zowel primaire als secundaire alcoholen met hoge selectiviteit geoxideerd kunnen worden. Desondanks is de *atom efficiency* laag en is de gebruikte waterstofacceptor moeilijk van het gevormde product te scheiden. Pogingen om steroiden te oxideren zonder verschuiving van de dubbele binding waren niet succesvol. Echter, oplosmiddelvrije oxidatie van secundaire alcoholen onder de afsplitsing van waterstofgas werd gerealiseerd met zeer hoge *atom efficiency* en goede TOF/TON. De methode is echter nog niet geschikt voor de oxidatie van primaire alcoholen. Decarbonylering van het gevormde aldehyde genereert namelijk koolmonoxide dat de katalysator vergiftigt. Verder onderzoek is daarvoor nodig en gewenst.

Curriculum Vitae

Renzo Meijer werd geboren op 23 februari 1971 te Winschoten. Na het doorlopen van eerst een HAVO-opleiding en vervolgens een VWO-opleiding aan de Winschoter Scholengemeenschap te Winschoten, werd in 1992 begonnen met de studie Scheikunde aan de Rijksuniversiteit Groningen. Het propedeutisch examen werd in 1994 behaald en het afstudeerproject binnen de vakgroep Organische Chemie (Prof. dr. R.M. Kellogg) werd, na een verblijf van 8 maanden bij DSM-Andeno, in februari 1998 afgerond. Vanaf maart 1998 was hij werkzaam in het kader van het IOP-Katalyse programma als promovendus in de capaciteitsgroep Macromoleculaire en Organische Chemie aan de Technische Universiteit Eindhoven, onder leiding van Prof. dr. L.A. Hulshof en Dr. J.A.J.M. Vekemans. De resultaten van dit onderzoek staan beschreven in dit proefschrift. Vanaf 1 september 2002 treedt hij in dienst by Syncom BV. als Research Chemist.

Renzo Meijer was born in Winschoten, the Netherlands on Februari 23th, 1971. In 1992 he obtained his high school degree at the 'Winschoter Scholengemeenschap' in Winschoten. In the same year, he started the Chemistry study at the University of Groningen. After a traineeship at DSM-Andeno for 8 months in 1997, he graduated in February 1998 at the laboratory of Organic Chemistry (Prof. dr. R.M. Kellogg). In March 1998 he started as a Ph. D. student in the IOP-Catalysis Program, in the laboratory of Macromolecular and Organic Chemistry at the Eindhoven University of Technology under the supervision of Prof. dr. L.A. Hulshof and Dr. J.A.J.M. Vekemans. The results of the project are described in this thesis. From September 1 st, 2002 he will be employed as a Research Chemist at Syncom BV.

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