Ruthenium-catalyzed homogeneous hydrogenolysis of esters to alcohols
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1 Hydrogenation; definitions

Hydrogenation reactions are used to produce a wide variety of both bulk and fine organic chemicals. The term “hydrogenation” refers to a chemical reaction in which one or more hydrogen atoms (and only those) are incorporated into the product(s) of the reaction. In addition, hydrogenation is often used in various purification processes (e.g., selective reduction of trace amounts of acetylene in an ethylene stream or butadiene in a butene stream, and removal of undesired oxygen, hydrogen or carbon oxides from a variety of systems).

Catalytic hydrogenation refers to the addition of hydrogen to an organic molecule in the presence of a catalyst. If the substrate molecule undergoes cleavage, the reaction is referred to as hydrogenolysis. In that case, fragments may be reductively split off the original substrate during or subsequent to the reaction with hydrogen.

![Figure 1: Different hydrogenation routes](image-url)
Hydrogenation catalysts can be distinguished in two types, heterogeneous and homogeneous. Heterogeneous catalysts are solids that form a distinct phase in the gas or liquid environment. Homogeneous catalysts on the contrary dissolve in the liquid or the gas phase medium, forming only one single (homogeneous) phase. Finally hydrogenation can occur without the need of a catalyst using stoichiometric methods, such as application of hydrides like LiAlH₄.

1.1 Transfer hydrogenation

The hydrogen necessary for the hydrogenation reaction can be provided by different sources. One possibility is hydrogenation using dihydrogen gas directly as the source of hydrogen required by the reduction reaction. A second possibility is the application of a transfer hydrogenation catalyst, using, for example, mixtures of 2-propanol and NEt₃ or formic acid and NEt₃ as the hydrogen donor; in these cases the solvent (2-propanol or formic acid respectively) acts as the source of hydrogen. It is, however, not a prerequisite that the donor should be the solvent; the essential feature of transfer hydrogenation is that there are compounds that are able to provide hydrogen to the substrate. The main difference between hydrogenation and transfer hydrogenation is that in the latter, there is no change in the overall unsaturation of the system in its simplest form (scheme 1).¹

![Scheme 1: General scheme for transfer hydrogenation using a secondary alcohol as hydrogen donor. A is the acceptor molecule, M is the hydrogenation catalyst](attachment://scheme_1.png)

1.2 Functional groups in hydrogenation

A large number of catalysts is now available, and the scope of substrates that can be converted by hydrogenation has become very large. Most functional groups can be reduced readily, often under mild conditions and frequently with high chemo-, regio-, and stereoselectivity and excellent yields. Some examples of functional groups that can readily be converted by hydrogenation are given below:
- Acids, aldehydes, ketones and esters give alcohols (addition of hydrogen across C=O, *vide infra*).

\[
\text{R}\text{O} \xrightarrow{\text{hydrogen source}} \text{R}\text{OH}
\]

- Alkenes give alkanes (addition of hydrogen across C=C).\(^3\)

\[
\text{RuH(PCy}_3\text{)(CO)}_2\text{Cl} / \text{HBF}_4\cdot\text{OEt} \xrightarrow{\text{R.T., 1 bar } \text{H}_2} \text{alkane}
\]

- Alkynes give alkenes (addition of hydrogen across C=C).\(^4\)

\[
\text{R}^1\equiv\equiv \text{R}^2 \xrightarrow{\text{Pd(bian)(dmfu)}} \text{H}_2, \text{THF, 20°C} \rightarrow \text{R}^1\equiv \text{R}^2
\]

- Imines give amines (addition of hydrogen across C=N).\(^5,6\)

\[
\text{R}\text{H}^\equiv\equiv \text{N} \xrightarrow{\text{RuCl}_2(\text{PPh}_3)_2 / \text{K}_2\text{CO}_3} \text{PrOH, 82°C} \rightarrow \text{R}^1\text{H}^\equiv \text{R}^2
\]

- Aromatics give cyclohexanes (saturation of the benzene ring).\(^7\)

\[
\text{[Nb(OC}_6\text{HPh}_4\cdot2,3,5,6\text{)Cl}_3]} / \text{^7}\text{BuLi, 80°C, 80 bar } \text{H}_2 \rightarrow \text{cyclohexane}
\]

Hydrogenation is not only applied on a laboratory scale, it also plays an important role in modern day industry and several large scale processes depend on this reaction. The most common process that applies hydrogenation on a large scale is the hydrogenation of vegetable oils to produce margarine; hydrogen is added to the carbon-carbon double bond in...
the unsaturated fatty acid portion of the fat or oil molecule over a nickel catalyst to produce waxes and other (non) edible products (fat hardening). Fat hardening is used in order to make fats solid at room temperature and to improve their thermal stability. Other processes where hydrogenation reactions can be found are the synthesis of fine chemicals and the production of methanol from carbon monoxide.

Catalytic hydrogenation reactions are influenced by a number of factors, including type of catalyst, the solvent in which the reaction is performed, substrate purity, and operating conditions. Temperature, pressure, agitation and catalyst loading can all influence both the rate and selectivity of hydrogenation.

1.3 Hydrogen activation

Under ambient conditions dihydrogen is an unreactive molecule (bond dissociation energy 432 kJ/mol); therefore catalytic hydrogenations — either homogeneous or heterogeneous — always involve steps of H₂ activation. Activation results in a substantial transformation of molecular hydrogen, either to H⁺ (hydrogen radicals; homolytic splitting of the dihydrogen molecule) or to H⁻ (hydride) and H⁺ (proton; heterolytic splitting of the dihydrogen molecule).¹,¹⁰

Homolytic splitting of the dihydrogen molecule can occur in two different ways, either inter-, or intramolecularly and is observed with metals in low oxidation states. Intramolecular homolytic splitting involves a formal two electron oxidative addition of the dihydrogen molecule to the metal center in which the oxidation state of the metal is increased by two.⁸

\[
\begin{align*}
L_nM&+H_2 \leftrightarrow L_nM-H \\
L_nM&+L_nM-\bigcirc \rightarrow 2 L_nM-H
\end{align*}
\]

Scheme 2: Modes of homolytic splitting of dihydrogen
Intermolecular homolytic splitting involves two separate metal centers, each undergoing a one-electron change (scheme 2). Heterolytic splitting or activation of the dihydrogen molecule is associated with metals in higher oxidation states and occurs without a formal change in oxidation state of the metal center, giving rise to hydridic (H\(^-\), usually attached to a metal) and protic (H\(^+\)) centers. Complexes containing coordinated dihydrogen molecules are strong Bronsted acids, and heterolytic splitting of the dihydrogen molecule is therefore promoted by the presence of a base.

\[
\begin{align*}
M(H_2)L_x &+ \text{Base} \rightarrow [M(H)L_x^-] + \text{BaseH}^+ \\
M(H_2)L_x &\rightarrow M(HL)(H)L_{x-1}
\end{align*}
\]

Scheme 3: Modes of heterolytic dihydrogen activation

Similar to homolytic splitting, heterolytic hydrogen cleavage can occur by either an inter-, or an intramolecular pathway. In intermolecular heterolytic dihydrogen splitting, the dihydrogen molecule produces a hydride and the conjugate acid of an external base. In the intramolecular cleavage of dihydrogen, the base is provided by a coordinated ligand (scheme 3).

An example of intramolecular splitting of dihydrogen is shown in scheme 4 where a coordinated amine ligand is acting as a base for the heterolytic splitting of a coordinated dihydrogen molecule.
1.4 Substrates in hydrogenation

The previous section dealt with the general principles involved in metal-catalyzed hydrogenation reactions. Among the catalysts employed to date, besides rhodium, palladium and platinum, especially systems based on ruthenium have been widely used in a variety of homogeneous hydrogenation reactions.\(^{15}\)

The tables 1, 2 and 3 give some examples of ruthenium catalysts used in the hydrogenation of a variety of substrates. The overview given here is by no means complete and new complexes and insights on hydrogenation appear almost daily.

### Table 1: Examples of homogeneous catalyzed hydrogenation reactions\(^{16}\)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(<a href="%5Ctext%7BPP%7D_3">\text{RuH}(\eta^2-H_2)</a>]^* (a)</td>
<td>Phenyl acetylene</td>
<td>17</td>
</tr>
<tr>
<td>(\text{RuH}_2(\eta^2-H_2)_2(\text{PCy}_3)_2)</td>
<td>Dimethyl fumarate</td>
<td>18</td>
</tr>
<tr>
<td>(\text{RuH}_2(\eta^2-H_2)(\text{PPH}_3)_3)</td>
<td>Ketones, arenes</td>
<td>19</td>
</tr>
<tr>
<td>([\text{RuH}(\eta^2-H_2)]P_4]^* (b)</td>
<td>Alkynes</td>
<td>20</td>
</tr>
<tr>
<td>([\text{RuH}(\eta^2-H_2)(\text{binap})]_2]^* (c)</td>
<td>Carboxylic acids</td>
<td>21</td>
</tr>
<tr>
<td>([\text{Ru}(\text{HBpz}_3)(\eta^2-H_2)(\text{PPH}_3)L]BF_4)^ (d)</td>
<td>Alkenes</td>
<td>22</td>
</tr>
<tr>
<td>(\text{RuH}<a href="%5Ceta%5E2-H_2">\text{HB}(3,5-\text{Me}_2\text{Pz})_3</a>)^ (e)</td>
<td>Ketones</td>
<td>23</td>
</tr>
<tr>
<td>((\eta^2-H_2)(\text{dppb})\text{Ru}(\mu-\text{Cl})_3\text{RuCl(dppb)}) (f)</td>
<td>Alkenes</td>
<td>24,25</td>
</tr>
<tr>
<td>((\eta^2-H_2)(\text{dppb})\text{Ru}(\mu-\text{Cl})_3\text{RuCl(PPH}_3)_2) (g)</td>
<td>Hexene</td>
<td>26</td>
</tr>
<tr>
<td>((\eta^2-H_2)(\text{PR}_3)\text{Ru}(\mu-\text{Cl})_3\text{RuCl(PR}_3)_2)</td>
<td>Alkenes</td>
<td>27</td>
</tr>
</tbody>
</table>

\(a\) \(\text{PP}_3=P(\text{CH}_2\text{CH}_2\text{CH}_2\text{PPH}_2)_3\). \(b\) \(P(\text{PhH})_3\), \(P(\text{OME})_3\). \(c\) binap=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. \(d\) \(\text{HBpz}_3=\text{hydridotrispyrazolylborate}\); \(L=\text{PPH}_3,\ \text{CH}_3\text{CN}\). \(e\) \(\text{HB}(3,5-\text{Me}_2\text{Pz})_3=\text{hydridotris}-(3,5-\text{dimethyl})-\text{pyrazolylborate}\). \(f\) \(\text{dppb}=\text{Ph}_2\text{P(\text{CH}_2)_4}\text{PPH}_2\). \(g\) \(\text{P-N}=(\text{Ti-C}_5\text{H}_5)\text{Fe}(\text{C}_5\text{H}_5)\text{CHMeNMe}_2\)\(^{1}\)\(^{\text{Fe}}\)\(^{\text{PPr}_2-1,2}\).

### Table 2: Examples of homogeneous catalyzed transfer-hydrogenation reactions\(^{16}\)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(<a href="%5Ctext%7BPP%7D_3">\text{RuH}(\eta^2-H_2)</a>]^* (a)</td>
<td>Unsaturated Ketones</td>
<td>28,29</td>
</tr>
<tr>
<td>(<a href="%5Ctext%7BPP%7D_3">\text{RuH}(\eta^2-H_2)</a>]^*</td>
<td>Ketones, alkenes</td>
<td>28</td>
</tr>
<tr>
<td>(\text{RuH}_2(\eta^2-H_2)_2(\text{PPH}_3)_3)</td>
<td>Ketones</td>
<td>30</td>
</tr>
<tr>
<td>(\text{RuH}<a href="%5Ceta%5E2-H_2">\text{HB}(3,5-\text{Me}_2\text{Pz})_3</a>_2) (b)</td>
<td>Ketones</td>
<td>23</td>
</tr>
<tr>
<td>((\eta^2-H_2)(\text{dppb})\text{Ru}(\mu-\text{Cl})_3\text{RuCl(dppb)}) (c)</td>
<td>Acetophenone</td>
<td>24</td>
</tr>
</tbody>
</table>

\(a\) \(\text{PP}_3=P(\text{CH}_2\text{CH}_2\text{PPH}_2)_3\). \(b\) \(\text{HB}(3,5-\text{Me}_2\text{Pz})_3=\text{hydridotris}(3,5-\text{dimethyl})-\text{pyrazolylborate}\).

\(c\) \(\text{dppb}=\text{Ph}_2\text{P(\text{CH}_2)_4}\text{PPH}_2\).
2 Hydrogenation of carbonyl compounds

As can be seen from the tables in the previous paragraph, the field of hydrogenation is extremely wide. Our main interest is directed towards the reduction of carbonyl derivatives and in particular the hydrogenolysis of esters to their corresponding alcohols. The remainder of this chapter will therefore give a brief overview on the reduction of a variety of carbonyl containing derivatives and will then further focus in on this interesting subject.

2.1 Hydrogenation of Aldehydes and Ketones

Transfer hydrogenations are very well examined and documented and, in general, high yields of the hydrogenated products are obtained after the reaction. Transfer hydrogenation is thought to occur via two different pathways, depending on the catalyst used.\textsuperscript{35} For non-transition metal catalysts, direct transfer of hydrogen via a cyclic mechanism is proposed (scheme 5, a). Transition metals are thought to form a metal hydride that transfers the hydrogen to the carbonyl function (scheme 5, b). These hydridic species have indeed been isolated in some cases for hydrogen transfer reactions.\textsuperscript{35}

\[
\text{Scheme 5: Modes of hydrogen transfer}^{35}
\]

Especially the group of Noyori has extensively studied the transfer hydrogenation of ketones and a lot of information regarding this conversion has been published.\textsuperscript{36}
Kinetic and mechanistic studies on the RuCl$_2$(PPh$_3$)$_3$ catalyzed transfer hydrogenation of ketones were performed within the group of Bäckvall. These studies have yielded a generally accepted mechanistic Scheme in which the active catalysts was thought to be RuH$_3$(PPh$_3$)$_3$, formed in the presence of a base via the intermediate RuHCl(PPh$_3$)$_3$ starting from RuCl$_2$(PPh$_3$)$_3$ (scheme 6). The added base was only required in the formation of the active catalyst and did not play any role in the splitting of dihydrogen.

2.2 Hydrogenation of Carboxylic acids

Direct hydrogenation of carboxylic acids to the corresponding alcohols is a relatively difficult and inefficient reaction and is usually performed by esterification of the acid prior to hydrogenation. One of the problems encountered in the hydrogenation of carboxylic acids is esterification of the starting acid with the product alcohol. As a result not all of the acid is converted, and next to the produced alcohol, esters remain. A suitable catalyst was found in the complex Ru$_4$H$_4$(CO)$_{12-x}$L$_x$ (L=PBu$_3$, PPh$_3$) that was successfully used to hydrogenate mono-, and dicarboxylic acids to their corresponding alcohols. Hydrogenation of carboxylic acids was also investigated by He et al. who studied the use of homogeneous bimetallic complexes of
the groups 8 to 10 with 6 or 7 metals. Whereas Ru(acac)$_3$ was able to convert C$_{14}$H$_{29}$COOH for only 2 percent at 160 °C, 93% conversion was achieved with both Ru(acac)$_3$ and Re$_2$(CO)$_{10}$ present in the reaction mixture (Re$_2$(CO)$_{10}$ itself gave only 1 % at 170 °C).

2.3 Hydrogenolysis of Esters

2.3.1 General considerations

Hydrogenation, in general, is an exothermic reaction and the equilibrium usually lies far towards the hydrogenated product under most operating temperatures. However, not all these transformations are as straightforward as they seem; some substrates are more readily hydrogenated than others. For example, the ease of hydrogenation of carbonyl containing derivatives can be ordered according to the following list: acid chlorides > aldehydes, ketones > anhydrides > esters > carboxylic acids > amides.\textsuperscript{41}

In contrast to the hydrogenation of ketones and aldehydes, the reduction of esters is more troublesome. Esters are a stable class of compounds and, with a few exceptions, are reduced with difficulty and survive most catalytic hydrogenations; as a result, esters frequently make excellent solvents because of their relative inertness towards reactions with molecular hydrogen. The products of ester reduction may be acids (a), hydrocarbons (a, b and c), ethers (d) or alcohols (b and e) depending on the mode of attack, which seems to be determined largely by the substrate itself.\textsuperscript{42} Formally, the reduction of esters to alcohols should be referred to as hydrogenolysis, because the molecule is cleaved during or subsequent to the reaction with hydrogen. Therefore, in the remainder of the text, the term hydrogenolysis will be used when the reduction of esters is discussed.
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

\[
\begin{align*}
R^1-O-C-R^2 + H_2 & \longrightarrow R^1H + HO-C-R^2 \\
R^1-O-C-R^2 + 2H_2 & \longrightarrow R^1OH + R^2CH_3 + H_2O \\
R^1-O-C-R^2 + 3H_2 & \longrightarrow R^1H + R^2CH_3 + 2H_2O \\
R^1-O-C-R^2 + 2H_2 & \longrightarrow R^1-O-CH_2R^2 + H_2O \\
R^1-O-C-R^2 + 2H_2 & \longrightarrow R^1OH + R^2CH_2OH
\end{align*}
\]

Scheme 7: Products formed in the hydrogenolysis of esters

The difficulty of ester hydrogenolysis can be explained by considering the thermodynamics associated with the reaction with molecular hydrogen to form alcohols. Examination shows that the change in enthalpy during the reaction is fairly small. Furthermore, the entropic change under standard conditions is negative.

![Diagram of ester hydrogenolysis]

Table 4a: Energy change associated with hydrogenolysis of esters to alcohols

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>(\Delta H^\circ) (kJ mol(^{-1}))</th>
<th>(\Delta S^\circ) (J mol(^{-1}) K(^{-1}))</th>
<th>(\Delta G^{298}) (kJ mol(^{-1}))</th>
<th>(\Delta G^{400}) (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>-CH(_3)</td>
<td>-47.5</td>
<td>-67.1</td>
<td>-27.5</td>
</tr>
<tr>
<td>2</td>
<td>-CH(_3)</td>
<td>-CH(_3)</td>
<td>-24.7</td>
<td>-63.3</td>
<td>-5.8</td>
</tr>
<tr>
<td>3</td>
<td>-CH(_3)</td>
<td>-CH(_2)CH(_3)</td>
<td>-76.1</td>
<td>-197.7</td>
<td>-17.2</td>
</tr>
<tr>
<td>4</td>
<td>-C(<em>6)H(</em>{11})</td>
<td>-CH(_3)</td>
<td>-86.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-C(_6)H(_5)</td>
<td>-CH(_3)</td>
<td>-13.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For relevant hydrogenolysis reactions, \(\Delta H^\circ/\Delta S^\circ\) has been estimated at 200-400K, so the equilibrium towards the product at these temperatures is favorable. Hydrogenolysis should in principle be possible at ambient temperature, however, the reaction has a high activation barrier and kinetic restraints prevent the reaction from proceeding. At higher temperatures, the
entropic change of the reaction becomes more unfavorable, so a temperature should be chosen at which the change in free energy, $\Delta G^{\text{rxn}}$, remains negative, yet the activation barrier can be overcome. Some examples are given in table 4a.\(^{43, 44, 45}\) For comparison, table 4b gives similar information for the hydrogenation of some examples of aldehydes and ketones.

![Chemical structure diagram](attachment:image.png)

**Table 4b: Energy change associated with hydrogenolysis of aldehydes and ketones to alcohols**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>$\Delta H^o$ (kJ mol(^{-1}))</th>
<th>$\Delta S^o$ (J mol(^{-1}) K(^{-1}))</th>
<th>$\Delta G^{298}$ (kJ mol(^{-1}))</th>
<th>$\Delta G^{400}$ (kJ mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 -CH(_3)</td>
<td>-CH(_3)</td>
<td>-69.7</td>
<td>-149.4</td>
<td>-25.2</td>
<td>-10.0</td>
</tr>
<tr>
<td>2 -CH(_3)</td>
<td>-H</td>
<td>-85.5</td>
<td>-130.2</td>
<td>-46.7</td>
<td>-33.4</td>
</tr>
<tr>
<td>3 -C(_6)H(_5)</td>
<td>-H</td>
<td>-73.7</td>
<td>-135.2</td>
<td>-33.4</td>
<td>-19.6</td>
</tr>
</tbody>
</table>

2.3.2 Stoichiometric methods
In case of aldehydes, primary alcohols and in the case of ketones secondary alcohols can be obtained in high yields using NaBH\(_4\) or LiAlH\(_4\) as reducing agent. In contrast to the hydrogenation of aldehydes and ketones, the hydrogenolysis of esters and carboxylic acids to the corresponding alcohols is rather difficult. Esters are slowly reduced to the corresponding alcohols using NaBH\(_4\),\(^{46}\) whereas acids can not be reduced at all. All carbonyl groups, however, are reduced using stoichiometric amounts of LiAlH\(_4\).\(^{47}\) With Zn(BH\(_4\))\(_2\) a milder reduction method is employed and it is even possible to discriminate between aliphatic and aromatic esters, the first are easily hydrogenated, while the second are not reactive.\(^{48}\) Other possibilities involve indirect methods as hydrosilylation of the ester followed by hydrolysis of the formed silyl ether leading to the primary alcohol.\(^{49}\)

2.3.3 Heterogeneous hydrogenolysis of esters
Industrially there is a great need for successful hydrogenolysis of esters using mild conditions. Current industrial applications of the hydrogenolysis of esters require harsh conditions\(^{50}\) and often depend on the use of environmentally hazardous materials such as copperchromite,\(^{51}\) a catalyst that exists since the discovery by Adkins in 1931.\(^{52}\) A more recent example is the

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catalyst used by the Mitsubishi corporation, this metal supported catalyst is based on zirconium and chromium and is requires operating temperatures of 345 °C. The catalyst is used in the production of benzaldehyde (3) and benzyl alcohol (2) by contacting the ester benzyl benzoate (1) with molecular hydrogen (scheme 8).

\[
\text{Scheme 8: Formation of benzyl alcohol and benzaldehyde by reduction of benzyl benzoate}
\]

The development of this catalyst was born from a problem associated with the formation of benzyl alcohol by hydrogenation of benzoic acid over a copper and chromium containing catalyst. During production, large amounts of benzyl benzoate (by esterification of the produced alcohol with the starting material) and toluene (as a result of over-reduction) were obtained as useless by-products. Besides this catalyst, other catalysts have appeared and been applied in the reduction of esters or carboxylic acids. All these catalyst are based on the application of supported metal oxides.

\[
\text{Scheme 9: Sources of benzyl benzoate and derivatives thereof}
\]

Despite their development, often these catalysts show low selectivity towards the formation of the alcohol, and a wide variety of side-products are obtained after the hydrogenolysis of the ester. Side products may consist of acids, ethers but also alkanes were isolated after the reaction. As an example, scheme 10 shows the formation of several of the products that can be obtained from the catalyzed hydrogenolysis of dicarboxylic acid esters.
Homogeneously catalyzed hydrogenolysis of carboxylic acid esters

Numerous examples of homogeneous hydrogenation of carbonyl derivatives like aldehydes or ketones\textsuperscript{57} as well as olefinic derivatives\textsuperscript{58} can be found in literature. Even hydrogenation of carbon-carbon bonds is readily achieved using noble metal catalysts.\textsuperscript{59} The hydrogenolysis of esters, however, is a fairly new development, and only a few publications have appeared over the years describing catalysts able to hydrogenolyze esters to their corresponding alcohols successfully.\textsuperscript{60,61} The reported catalysts can be grouped as anionic, neutral or \textit{in situ} generated ruthenium catalysts.

\textbf{Scheme 11:} General hydrogenolysis reaction

Neutral Ruthenium Complexes

Until recently, ruthenium-catalyzed hydrogenolysis of esters was limited to activated esters. Activation of the substrate may be achieved by the introduction of suitable functional groups within the ester, such as a second ester function. The electron withdrawing character of the substituent results in activation of the first ester function. An example in which this principle has been employed is the ruthenium-catalyzed hydrogenolysis of dimethyl oxalate (4) to methyl glycolate (5) and ethylene glycol (6, scheme 12).
Matteoli et al. have extensively studied the conversion of similar activated esters using the ruthenium cluster compound H₄Ru₄(CO)₈(PBu₃)₄.⁶²,⁶³ The cluster compound had proved to be successful in the hydrogenation of carboxylic acids to the corresponding alcohols,³⁹ and was applied in the hydrogenolysis of carboxylic acid esters.⁶¹ The catalyst showed activity for a variety of esters, however, activity showed limited, and a lot of different by products are formed stemming from esterification, transesterification and decarboxylation.

For example, application of the cluster H₄Ru₄(CO)₈(PBu₃)₄ in the hydrogenolysis of diethyl malonate leads to the formation of ethyl-3-hydroxypropanoate, ethyl propanoate by dehydration followed by hydrogenation, ethyl acetate was formed by hydrolysis followed by decarboxylation and a variety of other products resulting from transesterification of ethyl acetate, ethylpropanoate and ethyl 3-hydroxypropanoate.
The attempted hydrogenolysis of dimethyl succinate (7) to 1,4-butane diol lead to the formation of γ-butyrolactone (8) as a result of internal transesterification of the formed alcohol function with the remaining ester function in the molecule. The formed γ-butyrolactone in turn is not converted further to the 1,4-butane diol. A similar observation was made when hydrogenolyzing dimethyl o-phthalate (9), this substrate leads to the formation of the lactone 3H-isobenzofuran-1-one (10), the transesterified product methyl benzoate (11) and methanol. It is remarkable to note that in a similar reaction the substrates dimethyl m-phthalate (12) and dimethyl p-phthalate (13) do not react. Even when the temperature is raised to 200 °C these esters are not converted to the corresponding alcohols. According to these observations it was claimed that the ease at which aromatic and aliphatic di-esters are hydrogenolyzed is related to the distance between the two functional groups; increase in the number of bonds between the ester functions leads to a decrease in activity.

Although \( \text{H}_4\text{Ru}_4(\text{CO})_8(\text{PBu}_3)_4 \) appears to be a good catalytic precursor, it was not at all sure that the true catalytic species is still a cluster with the same nuclearity. In the crude from the reduction of dimethyl oxalate in the presence of this catalytic precursor, only \( \text{H}_4\text{Ru}_4(\text{CO})_9(\text{PBu}_3)_3 \) and \( \text{H}_4\text{Ru}_4(\text{CO})_{10}(\text{PBu}_3)_2 \) were detected of the Ru_4 cluster derivatives. Since no free metal and no free phosphine are present in the crude, a decomposition reaction must take place with formation of simpler ruthenium species containing more than one phosphine molecule per ruthenium atom.

With the complex \( \text{Ru}(\text{CO})_2(\text{CH}_3\text{COO})_2(\text{PBu}_3)_2 \), the hydrogenolysis of dimethyl oxalate was studied in more detail, specifically the activating effect of the second ester function was studied by monitoring the product composition of the reaction at different temperatures over a variety of reaction times. It was found that the hydrogenolysis of dimethyl oxalate (4) proceeds in two subsequent steps by intermediate formation of methyl glycolate (5).

The first reaction readily takes place at a temperature of 120 °C and a hydrogen pressure of 130 bar. The subsequent reaction, though, is more difficult and requires more drastic conditions with respect to temperature. In order to facilitate the conversion to ethylene glycol (6), a temperature of 180 °C and prolonged reaction times were required (figure 2).
Besides the formation of methyl glycolate and ethylene glycol, several other products were observed in trace amounts that resulted from transesterification of the product alcohol (6) with the methyl glycolate (5). The mixture of (5) and (6) lead to the formation of the transesterified product (15), on the other hand etherification of two equivalents of the diol (6) resulted in the formation of (14) under catalytic conditions (scheme 14).

Scheme 14: The conversion of dimethyl oxalate to ethylene glycol and the formation of by-products

2.3.6 Anionic Ruthenium Complexes

Other systems reported for the hydrogenolysis of esters to alcohols are the ruthenium catalysts prepared by Grey et al. Special attention was directed towards the use of anionic complexes as K+[H2Ru(Ph3P)2Ph2PC6H4]-.C10H8.(C2H5)2O and K2+[H4Ru2(Ph3P)3(Ph2P)].2C6H14O3 in
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

The hydrogenation of polar substrates. These catalysts were believed to be the first homogeneous ruthenium systems able to hydrogenate aliphatic esters. This anionic ruthenium hydride complex was prepared by the reduction of [HRuCl(PPh$_3$)$_2$]$_2$ with potassium naphthalide leading to K$_2$[H$_2$Ru(Ph$_3$P)(Ph$_2$P)]$_2$.2diglyme. The anionic catalyst system already proved to be valuable in the hydrogenation of a variety of ketones, aldehydes, and nitriles and good to high yields of the corresponding alcohols and amines were achieved. However, in the case of esters, the scope of this catalytic system showed to be extremely limited. Preliminary experiments with these catalysts showed that the compound K$^+$(H$_2$Ru(Ph$_3$P)$_2$Ph$_2$PC$_6$H$_4$)$_2$.C$_{10}$H$_8$.(C$_2$H$_5$)$_2$O when applied in the hydrogenolysis of simple formate esters lead to decarbonylation of the methyl-, (16) and ethyl formate esters (17) instead of hydrogenating them (scheme 15).

![Scheme 15: Decarbonylation of formate esters](image)

The ability to decarbonylate the esters was attributed to the basicity of the catalyst compound, based on the findings that alkyl formates can be easily catalytically decomposed in the presence of basic alkoxides. Use of the other anionic complex, K$_2$(H$_4$Ru$_2$(Ph$_3$P)$_3$(Ph$_2$P)].2C$_6$H$_{14}$O$_3$, as the catalyst exhibited the same problem of decarbonylation although to a lesser extent.

Experiments to determine the catalytic activities of the anionic ruthenium catalysts were continued with activated esters. As was seen from the examples of Matteoli et al., activated esters are esters containing electron-withdrawing substituents adjacent to the ester functionality, rendering the carbonyl carbon to be more susceptible to a nucleophilic attack of the catalyst. Matteoli et al. used a second ester function as the electron withdrawing substituent to activate the ester for hydrogenolysis. Grey et al., however, attempted to activate
an ester by the introduction of electron withdrawing groups such as trifluoromethyl substituents, like in the ester methyl trifluoroacetate (18). The idea of using fluorinated substituents was born from the observation that the anionic ruthenium catalysts used in the hydrogenation of aldehydes lead to higher activities when fluorinated substrates were used; hexafluoroacetone was much faster hydrogenated to 1,1,1,3,3,3-hexafluoro-2-propanol than normal acetone was hydrogenated to 2-propanol. The best catalyst for the hydrogenolysis of these activated substrates again proved to be K$_2^+$[H$_4$Ru$_2$(Ph$_3$P)$_3$(Ph$_2$P)]$^+$·2C$_6$H$_{14}$O$_3$, with this catalyst, methyl trifluoroacetate was converted to an extent of 88% at 6.2 bar hydrogen pressure and 90 °C whereas the catalyst K$^+$[H$_2$Ru(Ph$_3$P)$_2$Ph$_2$PC$_6$H$_4$]$^+$.C$_{10}$H$_8$.C$_2$H$_5$.O stopped at 10% conversion (scheme 16).

\[
\begin{array}{cccc}
\text{F}_3\text{C} & \text{O} & \xrightarrow{\text{H}_2^\Delta \text{Catalyst}} & \text{F}_3\text{C} & \text{OH} + \text{MeOH} \\
\text{(18)} & & & \text{(19)} \\
\end{array}
\]

Scheme 16: Hydrogenolysis of the activated ester (Grey)

Hydrogenolysis proceeds faster when the substrate is dissolved in toluene, although the neat ester can also be hydrogenolyzed. This catalytic system was also applied in the hydrogenolysis of dimethyl oxalate as an activated di-ester. This ester was hydrogenated to methyl glycolate in 10% to 70% conversion. The electron-withdrawing effect of the formed α-hydroxy group is less pronounced, and further hydrogenolysis of methyl glycolate to ethylene glycol does not occur.

Finally, it has been attempted to convert simple aliphatic esters without activating substituents into alcohols using homogeneous anionic ruthenium complexes. Methyl acetate was used as a non activated substrate, leading to the formation of ethyl acetate, ethanol and methanol under fairly mild conditions (T=90 °C, P=6.2 bar). The hydrogenolysis requires a non-coordinating solvent. Use of coordinating solvents or additives largely suppresses the reaction. Furthermore a Lewis acid is necessary to activate the ester. Ethyl acetate and methyl propionate are also hydrogenated although with some difficulty. Aromatic esters are inactive.
### Table 5: Hydrogenolysis of substrates with electron-withdrawing substituents

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conversion (%)</th>
<th>T.O.F.&lt;sup&gt;b&lt;/sup&gt; (mol mol&lt;sup&gt;-1&lt;/sup&gt;h&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOAc</td>
<td>2</td>
<td>22</td>
<td>1.7</td>
<td>EtOH, EtOAc, MeOH</td>
</tr>
<tr>
<td>MeOAc</td>
<td>2</td>
<td>5</td>
<td>0.4</td>
<td>EtOH, EtOAc, MeOH</td>
</tr>
<tr>
<td>MeOAc</td>
<td>2</td>
<td>0</td>
<td>0.0</td>
<td>No hydrogenolysis</td>
</tr>
<tr>
<td>ErOAc</td>
<td>2</td>
<td>8</td>
<td>0.6</td>
<td>EtOH</td>
</tr>
<tr>
<td>EtCO₂Me</td>
<td>2</td>
<td>5</td>
<td>0.4</td>
<td>nPrOH, EtCO₂nPr, MeOH</td>
</tr>
<tr>
<td>CF₃CO₂Me</td>
<td>1</td>
<td>10</td>
<td>1.6</td>
<td>CF₃CH₂OH, MeOH</td>
</tr>
<tr>
<td>CF₃CO₂Me</td>
<td>2</td>
<td>88</td>
<td>6.9</td>
<td>CF₃CH₂OH, MeOH</td>
</tr>
<tr>
<td>CF₃CO₂CH₂CF₃</td>
<td>1</td>
<td>100</td>
<td>26.0</td>
<td>CF₃CH₂OH</td>
</tr>
<tr>
<td>CF₃CO₂CH₂CF₃</td>
<td>2</td>
<td>100</td>
<td>39.0</td>
<td>CF₃CH₂OH</td>
</tr>
<tr>
<td>(CO₂Me)₂</td>
<td>1</td>
<td>10</td>
<td>1.6</td>
<td>HOCH₂CO₂Me, MeOH</td>
</tr>
<tr>
<td>(CO₂Me)₂</td>
<td>2</td>
<td>70</td>
<td>5.5</td>
<td>HOCH₂CO₂Me, MeOH</td>
</tr>
</tbody>
</table>

<sup>a</sup>Catalyst 1: K⁺[H₃Ru(Ph₃P)₂Ph₂PC₆H₄]⁺·C₁₀H₈·Et₂O, catalyst 2: K₂⁺[H₄Ru₂(Ph₃P)(Ph₂P)]²⁻·2C₆H₁₄O₃; <sup>b</sup>Per mol ruthenium. Corrected for 2 in the case of catalyst 2. <sup>a</sup>Conditions: toluene (3ml); ester (5.7 mmol); 90 °C; 20h; catalyst 1 = 0.035 mmol; catalyst 2 = 0.017 mmol; hydrogen = 6.2 bar. <sup>b</sup>Actual ester conversion to hydrogenolysis products.

#### 2.3.7 In situ generated catalysts

One of the pioneers in the homogeneous catalytic hydrogenolysis of esters are Wada et al.\(^67\) Their research involved the homogeneous hydrogenation of succinic anhydride (20) to γ-butyrolactone (10) and the successive hydrogenation to 1,4-butanediol (21).\(^68\)

![Scheme 17: Hydrogenation of succinic anhydride via γ-butyrolactone](image)

The catalyst used in this reaction is formed in situ from Ru(acac)₃ and tri-n-octylphosphine in the presence of NH₄PF₆ in tetraglyme. Whereas triaryl-, or tri(branched alkyl) phosphines proved to be ineffective, high activity was observed using tri(linear alkyl) phosphines. The catalyst system was applied to the hydrogenation of cyclic esters to 1,4 α,ω-diols under fairly mild conditions of 50 bar hydrogen pressure and a temperature of 200 °C. Marko previously...
reported a similar ligand dependence for the rhodium catalyzed hydrogenation of ketones to the corresponding alcohols.\textsuperscript{69} Catalyst activity increased upon increasing basicity of the coordinating phosphine ligand, and an optimum was found for the basic ligand PEt\textsubscript{3}. Further increase of the electron donating power of the ligand by the introduction of larger or branched alkyl substituents, however, resulted in lower activities, explained by the increased steric hindrance caused by the ligand. 

Hydrogenation of cyclic esters was achieved readily, whereas linear esters were much harder to hydrogenate. Furthermore the catalyst deactivated with small amounts of succinic acid present.

Recently we discovered a new and effective catalyst precursor for the homogeneous hydrogenolysis of esters to alcohols based upon the findings of Hara \textit{et al.}\textsuperscript{68} This system comprises of an \textit{in situ} generated catalyst from Ru(acac)\textsubscript{3} and a tripodal phosphorus ligand triphos in an alcoholic solvent (acac = acetylacetonate; triphos = H\textsubscript{3}CC(CH\textsubscript{2}PPh\textsubscript{2})\textsubscript{3}),\textsuperscript{70,71} and will receive further attention in the following chapters.

\section*{3 Objective and justification}

Catalytic processes constitute the basis of many successful industrial processes and find widespread application in the manufacture of base chemicals. Despite the substantial and successful use of catalysts in the production of fine chemicals, there is yet a need for new developments in this area. The Innovation Oriented Research Project (I.O.P.) aims to set up new and effective means for the development of catalyst to enable more efficient ways for the production of chemicals, because current methods can become outdated and in the long term less economical.

The project described in the next chapters concerns the conversion of esters to their corresponding alcohols.

Alcohols find widespread application in different fields of chemistry, either as solvents (mainly C\textsubscript{1}-C\textsubscript{6} alcohols) or as starting material for subsequent conversions. Especially in fine chemical industries, alcohols form a large and significant part of the feedstock for further synthesis of drugs, perfumes or the manufacture of additives for food applications such as fragrances.
Alcohols are usually obtained by direct reaction of synthesis gas (to give methanol), by synthesis from olefins by the oxo-reaction (C₃-C₂₀ alcohols) or from the Ziegler process.²

In a number of cases, industries may have higher oxygenates at their disposal, sometimes, these may be abundant or even waste material, e.g. oxygenates stemming from over-oxidation of hydrocarbons. These oxygenates, e.g. carboxylic acids, esters, amides can be used as a feedstock for the production of alcohols by reduction.

The goal of this I.O.P. project was the development of an industrially applicable catalyst to facilitate this conversion, leading to a process for the homogeneous hydrogenolysis of esters to alcohols.

4 Outline

In this thesis, the search for a suitable homogeneous catalyst for the hydrogenolysis of esters to alcohols is described. Chapter 1 provides a general introduction to the subject of hydrogenation and hydrogenolysis catalyzed by transition metal complexes. The emphasis of this chapter concerns the hydrogenolysis of carbonyl compounds, especially esters. Next, in chapter 2, the selection of suitable starting complexes, which can function as catalyst precursors, as well as the selection of ligands will be addressed. Since many hydrogenations are effectively catalyzed by ruthenium compounds in homogeneous solution, the focus will be on ruthenium complexes. Most of the catalysts that are involved in the hydrogenolysis of esters are limited regarding the type of substrates that can be converted to the desired products. Therefore, in chapter 3, the catalyst developed in the previous chapter is subjected to a number of selected substrates to determine its capabilities and scope. Furthermore, in chapter 3, the crucial role of the solvent in which the reaction is performed will be addressed. Chapter 4 deals with extension of our fundamental knowledge of the catalyst system and describes attempts to isolate and synthesize novel catalyst precursor complexes. These new complexes are subsequently evaluated in a number of benchmark reactions. Finally, in chapter 5, the kinetics of selected reactions are described, which, together with a number of observations and literature precedents, have been used to give a proposal for the mechanism of ruthenium-catalyzed hydrogenolysis of esters.
5 References


Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols


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Hydrogenation and hydrogenolysis; an introduction
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b) Matteoli, U.; Menchi, G.; Bianchi, M.; Piacenti, F.; Ianelli, S.; Nardelli, M.
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