Ruthenium-catalyzed homogeneous hydrogenolysis of esters to alcohols
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3 Scope of Ruthenium-Catalyzed Hydrogenolysis; Selection of the Solvents

1 Introduction

Catalytic reduction of carbonyl compounds is one of the many useful and widely applied synthetic reactions available. Hydrogenation of the carbonyl group in ketones and aldehydes to form their respective alcohols, using NaBH₄ or LiAlH₄ as reducing agents, has been well established. Besides these stoichiometric reagents, a wide variety of (transfer) hydrogenation catalysts are available. In general, excellent conversions of carbonyl compounds into alcohols can be accomplished. In contrast to the relative easy with which aldehydes and ketones are hydrogenated is the conversion of esters. Esters are only slowly reduced using stoichiometric amounts of NaBH₄ while acids are not reduced at all,¹² furthermore, esters are rather inert towards the direct reaction with molecular hydrogen to form the corresponding alcohols. The general reaction to form alcohols is depicted in scheme 1.

\[
\begin{align*}
\text{R}^1\text{C}=\text{O} & \text{R}^2 \xrightarrow{\text{Hydrogen source}} \text{R}^1\text{OH} + \text{HO-CR}^2 \\
\text{Scheme 1: Hydrogenolysis of esters to alcohols}
\end{align*}
\]

As was seen in chapter 1, the difficulty of hydrogenolysis of esters to alcohols is due to the endothermicity of the reaction under standard conditions. For the hydrogenolysis of esters, the reaction enthalpy for the reduction to the alcohol is relatively small, whereas the change in entropy is negative. The ‘cross-over’ temperature (\(\Delta H^\circ/\Delta S^\circ\)) has been estimated at \(200 \text{ – } 400 \text{ K}\) and relatively low temperatures and pressures are required to ensure good conversions.

In chapter 2, an efficient catalyst for the hydrogenolysis of dimethyl oxalate (1) to ethylene glycol (3) was reported (scheme 2).³
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{O} & \quad \text{Me} \\
\rightarrow & \quad \text{Ru-catalyst} & \quad \text{O} & \quad \text{OH} & \quad \text{Me} \\
\text{MeO} & \quad \text{O} & \quad \text{H} & \quad \text{OH} & \quad \text{MeOH} \\
(1) & \quad (2) & \quad (3) 
\end{align*}
\]

Scheme 2: Hydrogenolysis of dimethyl oxalate (1) to ethylene glycol (3)

The catalyst for this conversion was generated in situ starting from Ru(acac)₃ and the appropriate triphosphine ligand triphos (CH₃C(CH₂PPh₂)₃), and can be applied using relatively mild conditions (temperatures up to 120 °C and pressures lower than 80 bar). The in situ generated catalyst was the first homogeneous catalyst that provided a reproducible full conversion with a reasonable reaction rate for the hydrogenolysis of dimethyl oxalate (1) to ethylene glycol (3).

In the previous chapters, it became clear that catalysts currently available and documented are limited in their scope, i.e. the number of different substrates that can be converted. For example, the catalytic system reported by Matteoli et al.⁵ can only be used effectively in the hydrogenolysis of dimethyl oxalate (1); application of this catalyst for the conversion of other substrates invariably leads to zero or low conversions. The same is true for the catalyst of Grey et al.,⁴ which could only be applied in the hydrogenolysis of fluorinated esters. One may of course activate the substrate, but this would result in a good catalyst system for only a limited type of substrates. Activation of the substrate may be achieved by the introduction of suitable functional groups within the ester, such as fluorinated alkyl moieties as was applied by Grey.⁴ Another way of achieving the same goal is using a second ester function as activation for the first ester function; this was successfully demonstrated in hydrogenolysis by both Grey⁴ and Matteoli⁵ and later by some of us.³ The preferred catalyst, however, should be able to perform catalytic hydrogenolysis for a wider range of substrates.

As will be shown in this chapter, the scope of the catalyst developed in the previous chapter is not limited to the hydrogenolysis of 1 and similar esters solely. It can be applied for a variety of substrates, ranging from ketones and aldehydes to nitriles and esters. As will become clear at the end of this chapter, the solvent in which the conversion of the substrate is performed, largely
influences the outcome of the catalytic process. Furthermore, it will be shown that, depending on the additive chosen, the products of the hydrogenolysis may differ.

2 Results and Discussion

2.1 Scope of the catalyst; substrates

2.1.1 Hydrogenolysis of simple aliphatic di-esters

A range of simple aliphatic carboxylic acid di-esters were subjected to hydrogenolysis, table 3, gives the di-esters that were screened. In all cases, the catalyst system based on Ru(acac)$_3$ and the tripodal ligand triphos was applied. Entry 1 recalls dimethyl oxalate (1), this substrate was used in a number of occasions, and provides excellent comparison to established methods of ester hydrogenolysis.$^{3,4,5}$ As was shown in the previous chapter, depending on the catalytic system chosen this ester can readily be reduced to the corresponding α-hydroxy ester or diol. Using the ligand CH$_3$C(CH$_2$PPh$_2$)$_3$ in the presence of zinc, full conversion of the ester was observed and ethylene glycol (1) was obtained in quantitative yields. With a turnover frequency of 54 mol mol$^{-1}$h$^{-1}$ (based on the conversion after 16 hours), this catalyst was shown to be the most active in homogeneous catalyzed hydrogenolysis of the activated ester dimethyl oxalate.

Upon increasing the distance between the ester functions by the introduction of a -CH$_2$- group, as in dimethyl maleate (entry 2), catalytic activity is reduced to zero and no traces of alcohols were observed. Even when changing the solvent to the polar medium 1,1,1,3,3,3-hexafluoro-2-propanol (the choice of this solvent will become clear in section 2.2 of this chapter), no hydrogenolysis to the alcohol was observed and the ester was fully recovered after a reaction time of 16 hours. It could be argued that the activating effect of the second ester function present diminishes upon increasing the distance between both ester functions, similar as was found for o-, m-, and p-dimethyl phthalate.$^6$

In this case however, another explanation exists for the inability to hydrogenolyze this ester: the acidity of the -CH$_2$- protons and the structural similarity of the resulting dimethyl malonate compared with acetyl acetonate; the deprotonated substrate itself can act as a ligand and stabilizes the ruthenium catalyst.$^7$
Table 3: Hydrogenolysis of simple aliphatic esters

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>T.O.N. (T.O.F.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl oxalate</td>
<td>CH₃OH</td>
<td>Ethylene glycol</td>
<td>100</td>
<td>857 (54)</td>
</tr>
<tr>
<td>Dimethyl maleate</td>
<td>(CF₃)₂CHOH</td>
<td>1,4-butanediol</td>
<td>100</td>
<td>2019 (126)</td>
</tr>
</tbody>
</table>

General conditions: Ru(acac)₃ 10 μmol, 1.5 eq. triphos, in 15 ml solvent pH₂ = 80 bar, T=120 °C.

Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol); Turnover Frequency = amount of ester converted (mmol) per hour / amount of catalyst (mmol). T.O.N. and T.O.F. were determined as an average after the standard reaction time of 16 hours.

In entry 3, the chemoselectivity of the catalyst in hydrogenolysis of unsaturated di-esters was investigated by introducing a carbon-carbon double bond between the two ester functions, as in dimethyl maleate (4). In this case, not only both ester functions are reduced to the corresponding alcohols, but also the carbon-carbon double bond is effectively hydrogenated using the catalyst precursor Ru(acac)₃-triphos in 1,1,1,3,3,3-hexafluoro-2-propanol with NEt₃ present in the reaction mixture (scheme 3). The hydrogenation of the carbon-carbon double bond was not surprising since the hydrogenation of alkenes to alkanes using ruthenium catalysts is well documented and generally has a low activation barrier. Normally, catalytic hydrogenation of olefins proceeds much faster than carbonyl compounds. For example, a competition experiment in the hydrogenation of the aldehyde heptanal and the olefin 1-octene with RuCl₂(PPh₃)₃ as the catalyst precursor reveals that the olefin was saturated 250 times faster.

It was therefore assumed that hydrogenolysis of dimethyl maleate proceeds via intermediate formation of dimethyl succinate (5). The dimethyl succinate, however, was not isolated from
the reaction, nor was it monitored during the proceedings of reaction. Full conversion of dimethyl maleate was achieved over a period of 16 hours, and only 1,4-butanediol and methanol were observed as products.

\[
\text{OMe} \quad \text{Ru(acac)}_3 / \text{CH}_3(\text{CH}_2\text{PPh}_2)_3 / (\text{CF}_3)_2\text{CHOH} / \text{NEt}_3 / \text{H}_2 \\
\rightarrow \\
\text{OMe} \quad \text{Ru(acac)}_3 / \text{CH}_3(\text{CH}_2\text{PPh}_2)_3 / (\text{CF}_3)_2\text{CHOH} / \text{NEt}_3 / \text{H}_2 \rightarrow \\
+ 2 \text{MeOH}
\]

Scheme 3: Hydrogenolysis of dimethyl maleate

2.1.2 Hydrogenolysis of fatty acids, fatty acid esters and lactones

Confident in the hydrogenolysis of activated esters, the attention was focused on the hydrogenolysis of fatty acids and fatty acid methyl esters to the corresponding fatty alcohols (fatty alcohols are aliphatic alcohols of general formula CH\_3(CH\_2)_n OH in which n ranges from 5 to 21). Fatty acid methyl esters are mostly used as chemical intermediates to produce a number of oleochemicals such as soap, fatty alcohol, alkanolamides, alpha sulfo-methyl esters, sucrose esters and other detergents. Recently, methyl esters are also used in the production of environmentally friendly biodiesels and in the formulation of lubricants.

Most examples of fatty acid ester hydrogenolysis can be found in patent literature.\textsuperscript{10} The hydrogenolysis of fatty acid esters is a process dating back to the early 1930’s and is often performed with copper containing heterogeneous catalysts (Adkins catalyst), requiring drastic conditions, reaction temperatures are in the range of 250-300 °C and pressures of 200-300 bar are reported.\textsuperscript{11} Decarboxylation occurs as a side reaction, increasing with increasing temperature.\textsuperscript{12} Usually, starting materials for the production of fatty alcohols are natural fats and oils, which are first transesterified with methanol to the methyl esters that are subsequently reduced to the corresponding alcohols.
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

Several industrially relevant esters and acids have been submitted to hydrogenolysis using the catalyst derived from Ru(acac)$_3$-triphos. In table 4 the selected substrates are listed.

### Table 4: Hydrogenolysis of fatty acids and fatty acid esters (†)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>T.O.N. (T.O.F.) (mol mol$^{-1}$h$^{-1}$)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = H, Undecanoic Acid</td>
<td>CH$_3$OH</td>
<td>1-Undecanol</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(CF$_3$)$_2$CHOH</td>
<td></td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Esters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl palmitate</td>
<td>(CF$_3$)$_2$CHOH</td>
<td>Cetyl alcohol</td>
<td>94%</td>
<td>596 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sebacic methyl ester</td>
<td>(CF$_3$)$_2$CHOH</td>
<td>1,10-Decanediol</td>
<td>100%</td>
<td>800 (53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undecenoic methyl ester</td>
<td>(CF$_3$)$_2$CHOH</td>
<td>1-Undecanol</td>
<td>100%</td>
<td>700 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl oleate</td>
<td>(CF$_3$)$_2$CHOH</td>
<td>1-Octadecanol</td>
<td>100%</td>
<td>900 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lactones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undecanoic-γ-lactone</td>
<td>(CF$_3$)$_2$CHOH</td>
<td>1,4-Undecanediol</td>
<td>80%</td>
<td>250 (17)</td>
</tr>
</tbody>
</table>

† General conditions: Ru(acac)$_3$ 25 - 8 μmol, 1.5 eq. triphos, substrate 20 - 30 mmol, 15 ml solvent $p$H$_2$ = 80 bar $T$=120 ºC.
‡ T.O.N. = Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol);
  T.O.F. = Turnover Frequency = amount of ester converted (mmol) per hour / amount of catalyst (mmol).
  T.O.N. and T.O.F. were determined as an average after the standard reaction time of 16 hours.

In all cases, hydrogenation is performed in the polar alcohol 1,1,1,3,3,3-hexafluoro-2-propanol without any difficulty, excellent conversions to the corresponding alcohols were observed without traces of any side products. In the case that there is an additional unsaturated function present in the substrate, as is the case for undecanoic methyl ester (entry 4) or methyl oleate...
Ruthenium-Catalyzed Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

(entry 5), the double bond is effectively hydrogenated. The carbon-carbon double bond is presumably hydrogenated prior to hydrogenolysis of the ester function. Attempts to hydrogenate the parent carboxylic acids failed, no catalyst activity was observed. A priori, in situ esterification with the alcoholic solvent prior to hydrogenolysis was expected, but this was not observed. The inactivity of the catalyst precursor probably lies in the occurrence of a reaction between the acid and the ruthenium starting material, followed by decarbonylation of the acid leading to an inactive low valent ruthenium carbonyl species.³

Besides simple aliphatic acid esters, also lactones can be effectively converted to the corresponding diol. It was reported previously that a catalyst system consisting of Ru(acac)₃ / P(n-C₈H₁₇)₃ / NH₄PF₆ was able to hydrogenate γ-butyrolactone to 1,4-butadiol effectively.¹⁴ Reported reaction conditions (T = 200 °C, P = 50 bar), however, are more demanding than required for the catalyst Ru(acac)₃·triphos (T = 120 °C, P = 80 bar). Reaction rates (expressed as T.O.F.) are identical to those previously reported by Hara et al.¹⁴

2.1.3 Hydrogenolysis of benzoic acid esters

It is difficult to find examples of the hydrogenolysis of esters where the carbonyl is attached to an aromatic backbone such as benzoic acid esters. Because of its difficulty in hydrogenolysis, these types of esters represent a suitable model substrate to evaluate the true ability of the new catalyst.

The results in the hydrogenolysis of aromatic esters are summarized in table 5.

For comparison with aliphatic esters, entry 1 recalls the result obtained for the hydrogenolysis of dimethyl maleate. Like dimethyl maleate, dimethyl phthalate (7) is an activated ester, with the difference that the “backbone” consists of an aromatic ring, instead of a carbon-carbon double bond.
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

Table 5: Hydrogenolysis of dimethyl maleate and selected aromatic esters†

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Product</th>
<th>Conv. (%)</th>
<th>T.O.N. (mol mol⁻¹ h⁻¹)</th>
<th>T.O.F. (mol mol⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dimethyl maleate (4)</td>
<td>(CF₃)₂CHOH</td>
<td>1,4-Butanediol (6)</td>
<td>100</td>
<td>2019</td>
<td>126</td>
</tr>
<tr>
<td>2 Dimethyl phthalate (7)</td>
<td>(CH₃)₂CHOH</td>
<td>3H-Isobenzofuran-l-one (8); 1,2-Di(hydroxymethyl)benzene (9)</td>
<td>100</td>
<td>56 (3.5)</td>
<td>103 (5.6)</td>
</tr>
<tr>
<td>3 Methyl benzoate</td>
<td>CH₃OH</td>
<td>Benzyl alcohol (11)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 Benzyl benzoate (10)</td>
<td>(CF₃)₂CHOH</td>
<td>Benzyl alcohol (11)</td>
<td>97</td>
<td>2071 (129)</td>
<td></td>
</tr>
<tr>
<td>5 Hexafluoro-2-propyl benzoate</td>
<td>(CF₃)₂CHOH</td>
<td>Benzyl benzoate (10)</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

† General conditions: Ru(acac)₃ 10 μmol, 1.5 eq. triphos in 15 ml solvent pH₂ = 80 bar, T=120 °C.

‡ T.O.N. = Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol); T.O.F. = Turnover Frequency = amount of ester converted (mmol) per hour / amount of catalyst (mmol). T.O.N. and T.O.F. were determined as an average after the standard reaction time of 16 hours.

The reduction of the ester dimethyl phthalate (7) was observed to proceed in two steps. In the first step, one of the ester functions is reduced to the alcohol. Upon intramolecular transesterification, this mono-ester forms the lactone 3H-isobenzofuran-1-one (8).

As was seen in the section concerning fatty acid ester, the catalyst is also capable of hydrogenation of lactones, and 3H-isobenzofuran-1-one should not form any problem. Indeed, 8 is reduced in a subsequent step forming the product 1,2-di(hydroxymethyl)benzene in excellent yields (scheme 4).
Surprisingly enough, the mono-ester methyl benzoate could not be hydrogenolyzed to benzyl alcohol and methanol, neither in methanol nor in the highly polar solvent 1,1,1,3,3,3-hexafluoro-2-propanol any hydrogenolysis activity was observed and only the starting ester was recovered after 16 hours. The reason for this inactivity is not clear and is still under debate.

Benzyl benzoate (10) is an extremely interesting and challenging substrate for the investigation of catalyst activity. This ester, being both a non-activated and an aromatic ester, is an excellent benchmark substrate. Furthermore, it receives considerable attention from industry. Benzyl benzoate (10), together with benzoic acid, is formed on an industrial scale as a side-product in the air-oxidation of toluene to benzaldehyde and benzyl alcohol.\(^{15}\)

Large amounts of benzyl benzoate are converted by reduction into benzyl alcohol. For this conversion, a heterogeneous catalyst is employed with the same drawbacks as was mentioned before (high temperatures, high pressures and low selectivity).
Using our catalyst obtained from Ru(acac)$_3$ and triphos, conversion of this ester into two equivalents of benzyl alcohol was achieved in good yields and conversions, without formation of any side-products, using relatively mild conditions. This catalyst was previously shown to be the most active in the hydrogenolysis of the activated ester dimethyl oxalate, it is also the first ever reported catalyst able to convert aromatic esters to their corresponding alcohols in an easy and reproducible manner at excellent rates and selectivities.

2.1.4 Miscellaneous substrates

The catalyst presented is not only limited to hydrogenolysis of esters. As was seen in a number of the previous examples, the catalyst can be applied in the successful hydrogenation of carbon-carbon double bonds as well. Also, other functional groups, like aldehydes and ketones, were evaluated in hydrogenolysis.

Benzaldehyde was hydrogenated fully using the catalyst derived from Ru(acac)$_3$ and triphos under standard conditions and 1,1,1,3,3,3-hexafluoro-2-propanol as solvent in very short times (turnover frequencies exceeding 1500 mol mol$^{-1}$ h$^{-1}$). Furthermore, catalyst activity seems not to be influenced by the reaction medium, the aldehyde was even hydrogenated in benzyl alcohol with excellent catalyst turnover frequencies (1200 mol mol$^{-1}$ h$^{-1}$). Possibly, the aldehyde can even be hydrogenated in the pure substrate.

Other types of substrates that were briefly screened were ketones (acetone, which was fast and fully converted to $\text{iso}$-propanol); amides (benzyl benzamide, which showed no conversion at all) and nitriles.

Acetonitrile is hydrogenated in a very fast reaction to give a mixture of amines. It was shown that with the catalyst Ru(acac)$_3$ - triphos a mixture of primary and secondary amines could be obtained.$^{16}$

2.2 Selection of the solvent

As was briefly mentioned in the previous section (2.1), the solvent plays a decisive role in the ruthenium-catalyzed hydrogenolysis of esters. Depending on the solvent chosen, different
reaction rates or even products were observed. To determine the best suitable solvent for the catalytic hydrogenolysis of esters to alcohols, several solvents, ranging from polar to a-polar and being protic or non-protic, have been evaluated as a medium. To facilitate comparison of activity in different solvents, a benchmark substrate had to be chosen. Benzyl benzoate was selected as the substrate because it is a non-activated and aromatic substrate.

2.2.1 Primary Alcohols

Dimethyl oxalate was effectively hydrogenolyzed in simple alcohols such as methanol (37% conversion, see chapter 2). For benzyl benzoate, methanol appeared to be an unsuitable solvent. After a reaction period of 16 hours, no consumption of hydrogen gas had occurred and no hydrogenolysis had taken place, instead, methyl benzoate was formed as a product of transesterification of the substrate with the solvent (see table 6).

![Scheme 6: Transesterification prior to hydrogenolysis](image)

Table 6: Catalyst activity towards the hydrogenolysis of benzyl benzoate (10) in simple alcohols

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Product</th>
<th>T.O.N. (mol mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Methanol#</td>
<td>50</td>
<td>Methyl benzoate</td>
<td>1090</td>
</tr>
<tr>
<td>2 Ethanol#</td>
<td>23</td>
<td>Ethyl benzoate</td>
<td>673</td>
</tr>
<tr>
<td>3 2-Propanol</td>
<td>86</td>
<td>Benzyl alcohol</td>
<td>105</td>
</tr>
<tr>
<td>4 2,4-Pentanediol</td>
<td>14</td>
<td>None</td>
<td>n.d.</td>
</tr>
<tr>
<td>5 t-Butanol</td>
<td>0</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

| General conditions: Ru(acac)₃ 10 μmol, 1.5 eq. triphos, substrate 30 mmol, in 15 ml solvent pH₂ = 80 bar, T=120 °C. |
| T.O.N. = Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol); T.O.N. were determined as an average after the standard reaction time of 16 hours. |
| Transesterification of the starting material was observed, no product as result of hydrogenolysis. |

Further examination revealed that transesterification of benzyl benzoate to methyl benzoate starts immediately. Even after extended reaction times, only benzyl benzoate, the starting ester,
benzyl alcohol, formed as result of the transesterification, and methyl benzoate were present (scheme 6). The inactivity of the catalyst towards hydrogenolysis of methyl benzoate was observed previously in section 2.1.3. Also attempts at elevated temperatures (160 °C instead of 120 °C) failed, the catalyst appeared inactive and only transesterification occurred. Other primary alcohols such as ethanol lead to the same observation; ethyl benzoate was recovered after the reaction and no hydrogenolysis had taken place (table 6, entry 2).

2.2.2 Secondary and tertiary alcohols

Since transesterification seemed to play an important role in the attempted hydrogenolysis of benzyl benzoate, we turned our attention to secondary alcohols. Compared to primary alcohols, more bulky alcohols, such as secondary and tertiary alcohols, are less prone to transesterification, thus preventing the formation of inactive side-products.17 Indeed hydrogenolysis, under standard conditions in 2-propanol as the reaction medium, proved successful and full conversion of benzyl benzoate to benzyl alcohol was observed (table 6, entry 3). In contrast, when using 2,4-pentanediol only moderate conversion was achieved after 16 hours (14%). 2,4-Pentanediol was thought to be a useful solvent because of its formation during catalysis from the reduction of the acetyl acetone ligands. Further increasing the steric bulk of the solvent by applying t-butanol, decreased catalyst activity to almost zero, little or no hydrogenolysis was observed.

Transfer hydrogenation

Mixtures like 2-propanol / NEt₃ and formic acid / NEt₃ are well known reaction media for transfer hydrogenation reactions of unsaturated substrates. In transfer hydrogenation reactions, the hydrogen required for the reaction is transferred from a donor molecule to the unsaturated substrate, maintaining the overall unsaturation of the overall system (scheme 7).18 Numerous examples using this principle can be found in literature for the asymmetric hydrogenation of ketones to alcohols.19
The catalytic system of Ru(acac)$_3$ - triphos and NEt$_3$ in 2-propanol might in principle also be working according to this transfer hydrogenation mechanism. Hence, in order to exclude the possibility of transfer hydrogenation, the hydrogenolysis experiment was performed without hydrogen pressure in 2-propanol / NEt$_3$. During the reaction under these conditions, neither conversion of benzyl benzoate nor formation of acetone (from 2-propanol) was observed, only the starting ester was isolated afterwards. Furthermore, a similar check involving formic acid / NEt$_3$ as the hydrogen donor has not lead to hydrogenolysis either.

2.2.3 Highly polar primary and secondary alcohols

Grey et al. have reported the activation of an ester by introduction of activating groups close to the carbonyl function. In view of the observed transesterification of benzyl benzoate in primary alcohols, the idea was born to turn the undesired reaction into an advantage. Solvents were selected that have good susceptibility for transesterification and can act as well as an electron-withdrawing substituent in its benzoate ester, like 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol. Although secondary alcohols, like 2-propanol, are in general less active in transesterification, the acidity and polarity of the 1,1,1,3,3,3-hexafluoro-2-propanol may still lead to esterification with benzyl benzoate (10) (scheme 8).
Therefore, these alcohols were thought to be appropriate in hydrogenolysis by in situ formation of the product 2,2,2-trifluoroethyl benzoate and 1,1,1,3,3,3-hexafluoro-2-propyl benzoate as more activated esters that could subsequently undergo faster hydrogenolysis (scheme 6, $R^-$-CH(CF$_3$)$_2$). In addition, an increase in reaction rate may be anticipated in such solvents based on the concept of ionic hydrogenation, as has been proposed for tungsten complexes by Berke and Voges et al. In ionic hydrogenation, a proton and a hydride are sequentially transferred to the substrate. Similar proton-transfer reactions involving ruthenium hydride complexes in combination with very polar alcohols, as were observed by Ayllon et al. and Shubina et al. support this hypothesis. These kinds of interactions are proposed to be involved in the base promoted heterolytic splitting of dihydrogen.

Table 7 shows the polar alcoholic solvents that were evaluated in the ruthenium-catalyzed homogeneous hydrogenolysis of benzyl benzoate (10).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>T.O.N. (mol·mol$^{-1}$)</th>
<th>T.O.F. (mol·mol$^{-1}$·h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2-propanol</td>
<td>86</td>
<td>105</td>
<td>7</td>
</tr>
<tr>
<td>2 2,2,2-trifluoroethanol</td>
<td>99</td>
<td>896</td>
<td>70</td>
</tr>
<tr>
<td>3 Phenol</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 1,1,1,3,3,3-hexafluoro-2-propanol</td>
<td>70</td>
<td>2570</td>
<td>142</td>
</tr>
</tbody>
</table>

†General conditions: Ru(acac)$_3$ 10 µmol, 1.5 eq. triphosin 15 ml solvent pH$_2$ = 80 bar, T=120 °C.
‡T.O.N. = Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol); T.O.F. = Turnover Frequency = amount of ester converted (mmol) per hour / amount of catalyst (mmol). T.O.N. and T.O.F. were determined as an average after the standard reaction time of 16 hours.

Indeed when using fluorinated solvents, a marked increase in catalyst activity was observed. In the case of 2,2,2-trifluoroethanol, the ester was fully reduced with a turn over frequency of approximately 70 catalyst cycles per hour. When changing to the more polar alcohol 1,1,1,3,3,3-hexafluoro-2-propanol, which would lead to the introduction of a more electron withdrawing substituent in the benzyl ester, a further increase in activity was observed and excellent T.O.N. (over 2500 mol·mol$^{-1}$) and T.O.F. (exceeding 142 mol·mol$^{-1}$·h$^{-1}$) were achieved (entry 4).

Upon submitting the previously prepared ester 1,1,1,3,3,3-hexafluoro-2-propyl benzoate to the hydrogenolysis conditions used for benzyl benzoate, hydrogenolysis of the ester was observed.
Nevertheless, reaction rates appeared to be lower and furthermore, formation of benzyl benzoate was observed. Benzyl benzoate is the result of transesterification of the formed benzyl alcohol with the starting material. The lower rate of hydrogenolysis of this fluorinated ester compared to the hydrogenolysis of benzyl benzoate is contradicting the assumed activating effect and formation of the ester 1,1,1,3,3,3-hexafluoro-2-propyl benzoate as an intermediate in the hydrogenolysis of benzyl benzoate. In addition, if transesterification would be important, it should be possible to perform the reaction with catalytic amounts of 1,1,1,3,3,3-hexafluoro-2-propanol. Yet, when applying sub-stoichiometric amounts of 1,1,1,3,3,3-hexafluoro-2-propanol mixed in an inert solvent such as hexane, no activity was observed for the conversion of benzyl benzoate to benzyl alcohol. These observations lead to the notion that the overall polarity and acidity of the reaction medium is more important than the ability of the solvent to act as a reactant in transesterification. To verify this hypothesis, phenol was applied as solvent, because it has comparable acidity to 1,1,1,3,3,3-hexafluoro-2-propanol. Application of phenol as solvent was hampered by its high melting point and the limited solubility of the reactants, and successful hydrogenolysis failed.

![Graph](image)

**Figure 1: Catalyst activity versus solvent acidity**

The solvents in table 7 were analyzed in terms of acidity\(^{24}\) resulting in figure 1. As can be seen from figure 1, which shows catalyst activity as a function of solvent acidity, a linear relation
exists between the logarithm of the activity with increasing solvent acidity and proton donating ability.

This observation, *i.e.* lower catalyst activity with decreasing solvent polarity, also accounts for the observation that reaction rates (in terms of turnover frequency) decrease during hydrogenolysis, because the concentration of benzyl alcohol increases. Similar to the experiment where mixtures of 1,1,1,3,3,3-hexafluoro-2-propanol and 2-propanol were employed, here the concentration of benzyl alcohol was varied. In fact, increasing the benzyl alcohol concentration mimics the different stages in catalysis. Increasing amounts of benzyl alcohol (added to the starting solution before catalysis) slowed the reaction rate remarkably until no catalysis was observed in pure benzyl alcohol (table 8). The presence of benzyl alcohol in the reaction mixture, prior to hydrogenolysis, may prevent the formation of the catalytic species at all. η^1^-coordination of arenes to ruthenium compounds has been reported, although this seems in this case less likely in view of the other ligand, CH₃C(CH₂PPh₂)₃, present.²⁵

<table>
<thead>
<tr>
<th>Solvent (wt% BzOH in FIPA)</th>
<th>T.O.F. (mol⁻¹ mol⁻¹ h⁻¹)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

General conditions: Ru(acac)₃ 10 µmol, substrate 30 mmol, in 15 ml solvent pH₂ = 80 bar, T=120 °C.

Increased concentrations of benzyl alcohol may cause a decrease of the overall polarity of the reaction medium, besides that, benzyl alcohol may compete with the fluorinated alcohols in activation of the ruthenium hydride species (see chapter 4).

Activation of hydride complexes using proton donors is well known from Shubina,²⁶ Berke²⁷ and Chaudret.²⁸ Recently the equilibria of proton transfer from 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol and [(MeC(CH₂PPh₂)₃]Ru(CO)H₂] has been investigated and reported.²⁹
We have established that, besides activation of the ruthenium hydride, activation of the ester by the solvent is important. Activation of the substrate by the proton donating solvent was established for 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 9: Effect of the solvent on the carbonyl function of the ester

<table>
<thead>
<tr>
<th>Solvent</th>
<th>IR Wavenumber (cm(^{-1}))</th>
<th>(^{13})C Resonance (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Benzyl benzoate</td>
<td>1717</td>
<td>167.54</td>
</tr>
<tr>
<td>2 Benzyl benzoate in 2-propanol</td>
<td>1721</td>
<td>167.45</td>
</tr>
<tr>
<td>3 Benzyl benzoate in 2,2,2-trifluoroethanol</td>
<td>1702</td>
<td>167.83</td>
</tr>
<tr>
<td>4 Benzyl benzoate in 1,1,1,3,3,3-hexafluoro-2-propanol</td>
<td>1699</td>
<td>170.89</td>
</tr>
<tr>
<td>5 Benzyl benzoate in methanol</td>
<td>1720</td>
<td>167.50</td>
</tr>
<tr>
<td>6 Benzyl benzoate in tetrahydrofuran</td>
<td>1721</td>
<td>167.49</td>
</tr>
<tr>
<td>7 Benzyl benzoate/1,1,1,3,3,3-hexafluoro-2-propanol in THF</td>
<td>1721</td>
<td>167.53</td>
</tr>
</tbody>
</table>

We found that mixing solvents with benzyl benzoate can lead to significant weakening of the carbonyl carbon-oxygen bond as was observed by infrared spectroscopy: \(\nu(\text{C=O})\) shifts from 1720 cm\(^{-1}\) for benzyl benzoate (either pure or in 2-propanol or other alcohols) to 1699 cm\(^{-1}\) for benzyl benzoate dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (or 2,2,2-trifluoroethanol) (table 9). Additional support for this hypothesis was found by measurement of the \(^{13}\)C spectrum of several mixtures of benzyl benzoate in different solvents (50% v/v). The resonance for the carbonyl carbon atom showed a shift of approximately 3 ppm towards lower field in 1,1,1,3,3,3-hexafluoro-2-propanol compared to 2-propanol indicating a deshielding of the carbon atom. Activation of the carbonyl function is facilitated by the formation of hydrogen bonds between solvent and substrate and is more pronounced for stronger proton donating solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol and 2,2,2-trifluoroethanol. Table 9 gives these observations for different solvents. It can also be seen that the effect of these polar solvents diminishes when adding less polar solvents as THF (entry 7).
Solvent monitoring by deuteration

Hydrogenolysis of benzyl benzoate in 1,1,1,3,3,3-hexafluoro-2-propanol was also performed with dideuterium instead of dihydrogen. By doing so, one can monitor whether or not deuterium is being incorporated in the solvent. The experiment was performed starting from Ru(acac)$_3$ and triphos in an identical manner as for previous hydrogenolysis experiments. With this experiment we aimed to preclude the occurrence of a transfer hydrogenation mechanism involving the solvent and the corresponding hexafluoroacetone, which could in principle also be operating (Scheme 10).

![Scheme](image)

**Scheme 10: Hydrogenation by hydrogen transfer**

The crude reaction mixture taken from the autoclave was analyzed by $^1$H, $^2$H, $^{13}$C and $^{19}$F NMR to determine the deuterium content in both solvent and product. $^1$H NMR revealed full conversion of the ester to the corresponding benzyl alcohol. Based on the values of the integrals, the expected 50% enrichment of the alcohol with D-label was confirmed. $^2$H NMR confirmed the presence of the deuterium at the benzylic position. The integral associated with methine proton of the solvent showed no difference to the expected value and in the $^2$H NMR no deuterium signal was observed at the appropriate shift. The $^2$H-NMR experiment revealed three resonances that could be ascribed to the –OD of both 1,1,1,3,3,3-hexafluoro-2-propanol and to the –OD of benzyl alcohol, and a signal that could be attributed to the benzylic deuterium of the benzyl alcohol formed in the reaction. $^{13}$C NMR showed the expected signals. $^1$H-coupled $^{19}$F NMR showed the doublet at 76.99 ppm ($^3$J$_{HF}$ = 3.76 Hz). The conclusion of this experiment is therefore, that none of the solvent methine C-H has been converted to C-D, precluding a catalytic cycle involving hexafluoroacetone.
2.2.4 Decarbonylation of alcohols

One of the problems that may be encountered during catalytic hydrogenolysis of esters is the decarbonylation of the alcohol in the presence of a ruthenium catalyst. Chen et al. described the decarbonylation of primary alcohols, in the attempted synthesis of TpRuH(PPh₃)(CH₃CN) by treatment of TpRuCl(PPh₃)(CH₃CN) with NaBH₄. It was found that a species TpRu(CH₃)(CO)(PPh₃) (Tp=hydridotris(pyrazolyl)borate) could be isolated resulting from the decarbonylation of ethanol. The decarbonylation of alcohols was also previously reported by Van der Sluis et al. in the formation of RuH₂(PPh₃)₃ that led to the formation of RuH₂(PPh₃)₃(CO) at mild conditions using ethanol, 1-propanol or benzyl alcohol. In our catalytic system, the presence of increasing amounts of benzyl alcohol may lead to increasing decarbonylation, although no ruthenium carbonyl complexes have been observed.

2.2.5 Non protic polar solvents

It has thus far been established that solvent polarity is one of the important variables for successful hydrogenolysis of non-activated aromatic esters. To verify, and to evaluate whether protic polar solvents are required, several non-protic polar solvents were used.

In order to prevent transesterification, yet maintain solvent polarity, sulfolane was employed as solvent. Sulfolane, although a non-protic solvent, has characteristics comparable to common alcohols. In this solvent, no hydrogenolysis could be observed, and all of the starting material was recovered after the experiment.

Ionic liquids

Recently, ionic liquids received a lot of attention as possible green solvents in catalysis. Ionic liquids are organic salts with melting points lower than 100 degrees, often even lower than room temperature. They can be used to dissolve a wide range of organic and inorganic materials and have the property of being highly polar while noncoordinating. For hydrogenolysis, the ionic liquid [bmim][BF₄] was chosen as solvent ([bmim] = 1-butyl-3-methylimidazolium). This ionic liquid was applied in numerous other reactions before, among which hydrogenation reactions, and is now easily available via commercial sources.
Indeed hydrogenolysis of benzyl benzoate is observed although higher temperatures (160 °C) are required to obtain reasonable conversions (38%). One of the drawbacks of ionic liquids is the low solubility of hydrogen gas in ionic liquids, which may now form a rate-limiting problem. Since carbon dioxide is fully miscible with gases such as dihydrogen and it is highly soluble in ionic liquids, while at the same time the ionic liquid itself does not dissolve in the carbon dioxide, super critical CO₂ was employed to facilitate the introduction and dissolution of dihydrogen in the ionic liquid. However, by using super critical CO₂ as the co-solvent, no hydrogenolysis was observed. No hydrogenation of carbon dioxide was observed either, although this reaction is known to occur in scCO₂ in the presence of a ruthenium catalysts.

2.3 Additives used in hydrogenolysis

The preceding sections dealt with the hydrogenation of a variety of substrates in several solvents. In most cases, the presence of an additive in hydrogenolysis was required. Some examples were already mentioned briefly previously in this chapter.

2.3.1 Additives in the hydrogenolysis of dimethyl oxalate

In the first attempts of hydrogenolysis, dimethyl oxalate was used as the substrate. In this reaction, zinc was added as an additive. The role of zinc is twofold; it acts as a reducing agent in the formation of the ruthenium(II) catalyst, furthermore, the Lewis acidity enhances the reaction rate by activating the ester.

The ruthenium(III) in Ru(acac)₃ is reduced in situ by the zinc powder to a ruthenium(II) species in situ under the formation of Zn²⁺. Bennett et al. later reported that activated zinc dust or zinc amalgam is necessary in the formation of cis-[Ru(acac)₂(η²-C₈H₁₄)]₂ and [Ru(acac)₂(η⁴-nbd)] by reduction from Ru(acac)₃. They found a positive effect by the addition of water to dissolve the Zn²⁺. In the case of ester hydrogenolysis, however, the presence of water diminishes catalyst activity.

An additional effect resulting from the presence of zinc was attributed to the Lewis acidity of the metal, giving rise to the activation of the carbonyl function of the ester, rendering it more
prone towards hydrogenolysis. Activation by Lewis acids is known to facilitate the hydrogenation of ketones (figure 2).\(^1\)

\[
\text{M}^+\text{O} \overset{\text{catalyst}}{\rightleftharpoons} \text{HRu}
\]

**Figure 2: Activation of the carbonyl group by a Lewis acid\(^1\)**

2.3.2 Additives in the hydrogenolysis of dimethyl phthalate

In the first attempts to reduce aromatic esters, reaction conditions were copied from the hydrogenolysis of dimethyl oxalate to ethylene glycol.

Whereas the additive zinc proved to be valuable to the hydrogenolysis of dimethyl oxalate (1) to ethylene glycol (3), the addition of zinc to the reaction of dimethyl phthalate (7) in methanol leads to a lower activity compared to the reaction to which no additives were added, furthermore, conversion is stopped in the intermediate lactone (8) (scheme 11). When using an organic base in the catalysis, catalyst activity is markedly increased; 87% of the starting material is converted and 82% of the mono-hydrogenated ester could be obtained after 16 hours reaction time. When using an acid instead of a base, activity is comparable to the addition of NEt\(_3\). However, when changing both solvent and additive as in entry 5, total conversion of the starting ester is observed, and not only one of the ester functions is hydrogenated, but full hydrogenolysis to (2-hydroxymethyl-phenyl)-methanol is achieved within 16 hours.
Table 10: Additives used in the hydrogenolysis of dimethyl phthalate (7)\(^{†}\)

<table>
<thead>
<tr>
<th>Additive</th>
<th>Conversion (%)</th>
<th>Yield PHT (%)</th>
<th>Yield BHB (%)</th>
<th>T.O.F. (*) (mol mol(^{-1}) h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 None</td>
<td>31</td>
<td>30</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>2 Zn</td>
<td>25</td>
<td>18</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>3 NEt(_3)</td>
<td>87</td>
<td>82</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>4 HBF(_4)</td>
<td>91</td>
<td>79</td>
<td>0</td>
<td>3.4</td>
</tr>
<tr>
<td>5 IPA + HBF(_4)</td>
<td>100</td>
<td>18</td>
<td>78</td>
<td>5.6</td>
</tr>
</tbody>
</table>

\(^{†}\)General conditions: Ru(acac)\(_3\) \(10\mu\text{mol}\), substrate \(30\ \mu\text{mol}\), in \(15\ \mu\text{l}\) solvent \(pH_2 = 80\) bar, \(T=120\ ^\circ\text{C}\).

\(^{∗}\)T.O.N.=Turnover number = amount of ester converted (mmol) / amount of catalyst (mmol);

\(^{†}\)T.O.F. = Turnover Frequency = amount of ester converted (mmol) per hour / amount of catalyst (mmol).

In this particular case, the 2-propanol in the reaction is used in the formation of the ruthenium hydride, which is presumably involved in catalysis. Application of secondary alcohols in the synthesis of ruthenium(II) complexes was described by Nolan et al.\(^{39}\) for the preparation of ruthenium(II) dihydride phosphine complexes. The HBF\(_4\) present might be necessary in the hydrogenolysis for its importance in heterolytic splitting of the dihydrogen molecule (scheme 12).\(^{40}\) Furthermore, the formation of the intermediate lactone from methyl 2-hydroxymethylbenzoate is catalyzed by the presence of the acid. This is similar to the H\(_2\) activation by polar alcohols discussed in section 2.2.3 (scheme 9).

\[
\begin{align*}
\text{L} & \quad \text{M} \quad \text{L} \quad \text{L} + \text{H}_2 & \quad \longrightarrow & \quad \text{L} & \quad \text{M} \quad \text{L} \quad \text{L} ^{\dagger} \\
\text{L} & \quad \text{M} \quad \text{L} \quad \text{H} & \quad \longrightarrow & \quad \text{L} & \quad \text{M} \quad \text{L} \quad \text{H} & \quad \text{H} ^{+} \\
\text{L} & \quad \text{M} \quad \text{L} \quad \text{H} & \quad \longrightarrow & \quad \text{L} & \quad \text{M} \quad \text{L} \quad \text{H} & \quad \text{H} ^{+} \\
\end{align*}
\]

Scheme 12: Equilibrium between hydride and dihydrogen metal complexes

2.3.3 Additives in the hydrogenolysis of benzyl benzoate

When activated zinc is used in the hydrogenolysis of benzyl benzoate (10), no hydrogenolysis was observed at all. However, zinc is a heterogeneous additive in a homogeneous reaction, therefore the additive was changed to the soluble ZnCl\(_2\). When adding ZnCl\(_2\) to the reaction
mixture, however, again transesterification was observed, and 2-propyl benzoate was recovered as the sole product (entry 4). When adding the HBF₄ acid, partial hydrogenolysis was observed but the major product was an undefined polymeric material.

Instead of adding an acid, bases were tried in the hydrogenolysis of benzyl benzoate (10), NEt₃ as well as KO'Bu were added. Excellent hydrogenolysis was observed in this case, and a turnover number of 105 molmol⁻¹ could be achieved using the previously introduced catalyst system. The success of addition of a base was found in the heterolytic splitting of dihydrogen assisted by a transition metal. This type of hydrogen activation was thought to play an important role in the hydrogenation of a variety of substrates.

\[
\text{Scheme 13: Base assisted heterolytic splitting of dihydrogen}^{41}
\]

2.3.4 Additives and ligands combined

As was seen in chapter 2, excellent catalytic activity was observed using tridentate coordinating ligands. Preferably, facially coordinating ligands were used. Furthermore, it was shown that best catalytic activity was observed in polar alcohols such as 1,1,1,3,3,3-hexafluoro-2-propanol in the presence of a base such as NEt₃. The role of the NEt₃ was ascribed to the necessity of a base in heterolytic hydrogen splitting, a reaction important in hydrogenation. In chapter 1, the concept of intramolecular heterolytic splitting of dihydrogen was introduced, in which the base is provided by a coordinated ligand. It was attempted to combine the need for a tripodal ligand with the requirement of a base by the preparation of a mixed P,N-tripod ligand (chart 1). Tridentate P,N-donor ligands were applied in homogeneous transfer hydrogenation reactions of ketones as was reported earlier and proved to be very successful.⁴²
Furthermore, to increase the electron density of the ruthenium center and render it more nucleophilic for the attack on the carbonyl carbon atom of the ester, more basic groups were introduced onto the tripodal backbone of the ligand as in CH₃(CH₂PMe₂)₃.

Table 11: Facially coordinating ligands used in hydrogenolysis (†)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MeC(CH₂PPh₂)₃ 13a</td>
<td>(CH₃)₂CHOH</td>
<td>99</td>
</tr>
<tr>
<td>2 MeC(CH₂PPh₂)₃ 13a</td>
<td>(CF₃)₂CHOH</td>
<td>99</td>
</tr>
<tr>
<td>3 MeC(CH₂PMe₂)₃ 13c</td>
<td>(CH₃)₂CHOH</td>
<td>0</td>
</tr>
<tr>
<td>4 MeC(CH₂PMe₂)₃ 13c</td>
<td>(CF₃)₂CHOH</td>
<td>0</td>
</tr>
<tr>
<td>5 MeC(CH₂PPh₂)₂(CH₂NEt₂) 13b</td>
<td>(CF₃)₂CHOH</td>
<td>0</td>
</tr>
<tr>
<td>6 Ph₂PC₃H₆PPh₂ / PPh₃ 14</td>
<td>(CF₃)₂CHOH</td>
<td>4</td>
</tr>
</tbody>
</table>

†) General conditions: Ru(acac)₃ 10 µmol, substrate 30 mmol, in 15 ml solvent pH₂ = 80 bar, T=120 °C.

In table 11 the results for the different ligands are summarized. Apart from the facially coordinating derivatives of the triphos ligand MeC(CH₂PPh₂)₃ (13a), also the combination of a didentate dppp ligand, Ph₂PC₃H₆PPh₂ (14), together with an additional equivalent of PPh₃ was employed in catalysis, to verify the necessity of a tripodal system and check the possibility of exchanging the tripod ligand by equal amounts of simpler ligands (entry 6). Introducing more basic ligands such as MeC(CH₂PMe₂)₃ or MeC(CH₂PPh₂)₂(CH₂NEt₂) did not have the desired effect, and no increase in activity could be observed. The chosen ligands, however, can cause problems in handling prior to catalysis. MeC(CH₂PMe₂)₃ is highly sensitive towards oxygen and required careful handling in an oxygen free environment to prevent oxidation to the non-reactive phosphine oxide. The MeC(CH₂PPh₂)₂(CH₂NEt₂) on the other hand might suffer from protonation by the solvent.
3 Conclusions

An active catalyst for the hydrogenolysis of a wide variety of substrates is available. The catalyst is generated in situ starting from Ru(acac)$_3$ and the tripodal ligand triphos as was mentioned in a previous chapter. The catalyst is not limited to the hydrogenolysis of activated substrates, but non-activated substrates are readily hydrogenated as well. The catalyst is able not only to hydrogenolyze ester functionalities, but also other functional groups can be reduced using molecular hydrogen. To our knowledge, this catalyst is the only homogeneous ruthenium catalyst able to hydrogenate non-activated esters. In several cases, it appeared important to select the appropriate solvent and additive, which greatly influences the outcome of the reaction in terms of the products.

Besides the hydrogenated product, the transesterified product is obtained in case the wrong conditions are chosen. Overall best performance in catalysis was observed using 1,1,1,3,3,3-hexafluoro-2-propanol as solvent and NEt$_3$ as additive. The hydrogen involved for the conversion is obtained directly from the hydrogen gas; transfer hydrogenation involving the solvent 1,1,1,3,3,3-hexafluoro-2-propanol does not play a role. The solvent mainly serves to activate the substrate and the catalyst complex. Under standard conditions (120 °C, 80 bar hydrogen) full conversion of the ester has been obtained after short reaction times. The reaction, however, slows down considerably due to the formation of increasing amounts of the product alcohol.

Knowing that solvent polarity is extremely important, a possible substitute for the solvent 1,1,1,3,3,3-hexafluoro-2-propanol seems to be found in the use of the ionic liquid [bmim][BF$_4$] although additional optimization still has to be performed in order to obtain conversions comparable to those in the polar alcohol.

4 Experimental section

4.1 Equipment

Gas Chromatography

Diluted THF or acetone solutions (internal standards, p-xylene or mesitylene, were added for comparison) were analyzed using a Varian 3300 gas chromatograph equipped with a
Ruthenium-Catalyzed Homogeneous Hydrogenolysis of Esters to Alcohols

DB-5 capillary column (length = 30 m, internal diameter $\varnothing = 0.32$ mm, film thickness $1 \mu$m) and a FID detector. Injection and detection temperatures were set at 250 °C. After injection, the temperature of the GC was kept at 70 °C during 2 minutes. After two minutes, the GC was warmed to 230 °C with a gradient of 20 °C per minute. The GC was kept at 230 °C for an additional 5 minutes before cooling down to 70 °C.

Nuclear magnetic resonance spectroscopy

The characterization of the compounds was based mainly on NMR techniques. $^1$H, $^{19}$F and $^{31}$P NMR spectra were recorded on a Varian Mercury 300 spectrometer. $^1$H NMR spectra were referenced to tetramethylsilane (TMS), $^{19}$F-NMR spectra to CFCI$_3$ and $^{31}$P-NMR spectra to 85% H$_3$PO$_4$. All samples were measured at room temperature with deuterated chloroform (99.8 atom % D, Cambridge Isotope Laboratories, Inc.) as the solvent. Conversions were determined using the resonances of the benzyl protons of benzyl benzoate (10) (5.5 ppm relative to TMS, CDCl$_3$) and benzyl alcohol (4.5 ppm relative to TMS, CDCl$_3$).

Infrared Spectroscopy

Infrared measurements were performed in solution (2 ml benzyl benzoate in 2 ml solvent) using NaCl windows with a Bio-Rad FTS-7 infrared spectrometer.

Autoclave System*

All experiments were performed using a homebuilt stainless steel autoclave designed for reactions under pressures up to 130 bar (for a full description, see page 38 of chapter 2). The total volume of the autoclave (beaker, valves and tubing) was approximately 200 ml. The contents in the autoclave were stirred using a magnetic stirring bar. The autoclave was heated

* Since high gas pressures were involved, safety precautions had to be taken at all stages of studies involving high pressure equipment.
externally by an electrical heating device and controlled by measurement of the temperature within the reaction mixture. A Viton® O-ring was used as a seal between the top and the beaker of the autoclave to ensure leak-proof working.

4.2 Chemicals

All manipulations were carried out using standard Schlenk techniques in a dried nitrogen atmosphere. Common solvents were obtained from Acros Organics, and stored on the appropriate drying agent. 1,1,1,3,3,3-Hexafluoro-2-propanol was obtained from ABCR. The alcoholic solvents were dried on sodium and distilled prior to use. Drying agents were obtained from Acros Organics; Sikkon Blue™ was obtained from Fluka. The ionic liquid [bmim][BF_4] was received as a gift from prof. K. Seddon at the Queen's University of Belfast and was used as received. All other solvents were distilled prior to use and stored in a dried nitrogen atmosphere. Hydrogen gas (purity 5.0, 99.999%) was obtained in 10m³ cylinders from Hoek Loos B.V. Holland, and used without additional purification or drying. Ru(acac)_3 was purchased from Acros Organics and used without further purification. RuCl_3·xH_2O was obtained from Johnson and Matthey and used as received.

The tripodal ligand 1,1,1-tris(diphenylphosphinomethyl)ethane was obtained from Acros Organics, recrystallized from a boiling hexanes solution and subsequently stored in a protective nitrogen atmosphere. The ligands MeC(CH_2PMe_2)_3, MeC(CH_2PPh_2)_2(CH_2NEt_2) were prepared according to literature procedures, purified by fractional distillation and stored in an inert nitrogen atmosphere.

1,1,3,3,3-hexafluoro-2-propyl benzoate (12)

The fluorinated ester 1,1,3,3,3-hexafluoro-2-propyl benzoate was prepared following a modified literature procedure. 20 ml benzyll chloride (0.17 mol) and 20 ml 1,1,1,3,3,3-hexafluoro-2-propanol (0.19 mol) were mixed in an Erlenmeyer and stirred overnight at 20°C. During the reaction, a white fluffy powder precipitated while acidic vapors evolved from the flask. The supernatant was decanted, and the ester was subsequently washed with a small amount of water to remove unreacted acid.
After washing with a small amount of ethanol, the final product was purified by sublimation, yielding 36 gram (80% yield).

$^{1}H$ NMR (CDCl$_3$, 300.135 MHz): $\delta$/ppm 8.15 (d, $^{3}J_{HH}$=8.1 Hz 2H); 7.66 (t, $^{3}J_{HH}$=7.6 Hz 1H); 7.50 (t, $^{3}J_{HH}$=7.6 Hz, 2H); 6.10 (septet, $^{3}J_{HF}$=6.6 Hz, 1H).

$^{19}F$ NMR (CDCl$_3$, 282.407 MHz): $\delta$/ppm 16.76.

$^{13}$C NMR (CDCl$_3$, 75.476 MHz): $\delta$/ppm 163.33 ppm C=O; 134.69 (ar), 131.27 (ar), 128.82 (ar) 120.74 (q, $^{1}J_{CF}$=277 Hz), 67.01 (septet $^{2}J_{CF}$=34.8 Hz).

**Purification of the esters**

Pure esters were obtained by washing 10 ml of the ester overnight with a 2 M NaHCO$_3$ solution (200 ml). The mixture was extracted with CH$_2$Cl$_2$ after which the collected fractions were dried using MgSO$_4$. After filtration, the mixture was concentrated in vacuo, and the ester was dried overnight on Sikkon Blue™ (CaSO$_4$). After removal of the CaSO$_4$, the ester was fractionally distilled under reduced pressures.

### 4.3 General hydrogenolysis experiment

Unless stated otherwise, all reactions were performed using a reaction temperature of 120 °C and an initial (valve) pressure of 80 bar over a period of 16 hours. The pressure drop observed after 16 hours was approximately 10 bar upon full conversion of the ester. In all cases, hydrogenolysis proceeded very clean, and no other products than the alcohols were observed using NMR and GC analysis.

Reaction mixtures were prepared using standard Schlenk techniques. The catalytic mixture was prepared by weighing 10 $\mu$mol Ru(acac)$_3$ and 15 $\mu$mol 1,1,1-tris(diphenylphosphinomethyl)-ethane (and if necessary the solid substrate or additive) in a Schlenk vessel of 25 ml. The Schlenk vessel (closed by a septum) was then repeatedly flushed with nitrogen to remove oxygen from the flask. 15 ml solvent was introduced using a syringe. Additional heating was sometimes required to obtain a homogeneous solution. After cooling the solution to room temperature, the substrate (30 mmol; although the amount may differ over several experiments, for example
in the case of fatty acid esters, smaller quantities were used due to the difficulty in handling caused by the viscosity of the liquids) and the additive (3mmol) were added by a syringe. The autoclave was flushed three times with dry nitrogen, after which the catalyst mixture was introduced into the autoclave by a cannula under exclusion of oxygen. The autoclave was then pressurized to 80 bar (valve pressure at room temperature) and the heater was set to 120 °C. After 16 hours, the autoclave was cooled to room temperature and the pressure was released to normal atmospheric pressure. The contents of the autoclave were concentrated, and analysis of the crude reaction mixture was performed.

Hydrogenolysis in ionic liquid with super critical CO₂

The hydrogenolysis of benzyl benzoate in the ionic liquid [bmim][BF₄] and supercritical CO₂ was performed in a manner identical to the general hydrogenolysis experiments. For safety reasons, this experiment was performed in an autoclave of 50 ml volume. Because of problems associated with the Viton® O-ring in combination with the scCO₂, closing of this autoclave was achieved by a copper O-ring forced between the beaker and the top of the autoclave. In this experiment, next to the hydrogen pressure, the autoclave was pressurized to 150 bar with CO₂ and heated to 100 °C. After 16 hours, the autoclave was allowed to reach room temperature and was subsequently vented through a cold trap to prevent loss of substrate and product. After analysis, no hydrogenolysis of the ester was observed, however, corrosion of the autoclave was noted, presumably caused by the chloride content in the ionic liquid.

4.4 Deuteration experiment

65.5 mg Ru(acac)₃ (164.4 μmol) and 170.3 mg triphos (272.6 μmol) were dissolved in 15 ml of 1,1,1,3,3,3-hexafluoro-2-propanol (142.5 mmol). To the mixture 6.4384 grams of benzyl benzoate (30.3 mmol) and 0.357 grams of NEt₃ (3.5 mmol) were added. The mixture was transferred to the autoclave using the before described procedure and the mixture was flushed three times with 17 bar of dihydrogen. After releasing the pressure to 1 bar, the autoclave was pressurized with 80 bar of deuterium and the autoclave was heated to 120 °C. The reaction mixture was stirred overnight (20 hours) and a pressure drop of 15 bar was observed. The
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The autoclave was allowed to cool to room temperature after which the pressure was released and the contents of the autoclave were transferred to a round bottomed flask. The crude mixture was analyzed by NMR spectroscopy.

$^1$H NMR (300.13 MHz, CDCl$_3$): $\delta$/ppm 7.47 (m, ar, 10H), 4.71 (s, -CH$_2$-2H), 4.36 (sept, $\text{J}_{HF}$ = 6 Hz, CF$_3$CHCF$_3$, 5H).

$^2$H NMR (46.07 MHz): $\delta$/ppm 3.95 (b, -OH), 2.93 (s, PhCD$_2$OX).

$^{13}$C NMR (125.68 MHz, CDCl$_3$): $\delta$/ppm 139.4, 129.07, 128.96, 128.60, 127.80, 123.07 (q, $\text{J}_{CF}$ = 282.79 Hz); 69.40 (sept, $\text{J}_{CF}$ = 33.55 Hz), 65.17 (m, $\text{J}_{CD}$ = 22.50 Hz).

$^{19}$F NMR (282.407 MHz CDCl$_3$): $\delta$/ppm 76.99 (d, $\text{J}_{HF}$ = 3.76 Hz).

5 References


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