A thesis presented by

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University of St Andrews

Supported ionic liquid phase catalysis in continuous supercritical flow

In application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

September 2012
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I, Rubén Duque, hereby certify that this thesis, which is approximately 46,500 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in March 2009 and as a candidate for the degree of Doctor of Philosophy in January 2010; the higher study for which this is a record was carried out in the University of St Andrews between 2009 and 2012.

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Finally, I would like to thank the European Community for the financial support through an Initial Training network № 215193-2 (NANOHOST), and the University of St Andrews which hosted me for three years and a half and sponsored me for the last six months of the PhD.
The separation of the expensive catalysts from the solvent and reaction products remains one of the major disadvantages of homogeneous catalytic reactions, which are otherwise advantageous because of their high activity, tuneable selectivity and ease of study.

Ideally, the homogeneous reactions would be carried out in continuous flow mode with the catalyst remaining in the reactor at all times, whilst the substrates and products flow over the catalyst.

The system we have been studying is one where the catalyst is dissolved in a thin film of an ionic liquid, and this is supported within the pores of a microporous silica. This supported ionic liquid phase (SILP) catalyst is then placed in a tubular flow reactor, similar to that used for heterogeneous reactions. The raw materials are then injected into the rig, pass through the reactor and the products and the raw materials that have not reacted are collected at the other end of the rig. Supercritical CO$_2$ is used to transport the raw materials and products along the catalyst bed, allowing a continuous flow mode with low leaching for both the catalyst and the ionic liquid.

We have applied this procedure first to alkene metathesis catalysed by a ruthenium complex that has been especially designed to dissolve in 1-butyl-3-methylimidazolium triflamide (BMIM NTf$_2$), which was used as ionic liquid. Activity is observed for the ring closing metathesis of diethyl 2,2-diallylmalonate, but the catalyst is not stable, only allowing about 300 turnovers. This instability is attributed to the formation of Ru=CH$_2$ moieties, which dimerise to an inactive species. More success is achieved with internal alkenes such as 2-octene and especially methyl oleate. Self metathesis of methyl oleate continues for $>10,000$ turnovers over 10 h, with only small decreases in activity. The cross metathesis of methyl oleate with dimethyl maleate has also been studied. Cross metathesis dominates in the early stages of the reaction but the cross metathesis products diminish with time. Surprisingly, the catalyst does not deactivate since self metathesis of methyl oleate continues. The phase behaviour of the reaction was monitored and gave us an insight into the reasons for this change in selectivity.

Methoxycarbonylation reactions in continuous flow proved to be a much more difficult process than the previous metathesis reactions. Higher catalyst loading was needed to reduce
the reaction times. The first continuous flow reactions showed conversion predominantly, if not exclusive, of 1-octene isomerised products. The presence of ionic liquid (IL) in the SILP system was essential, otherwise the catalyst leached out of the reactor very quickly. Batch reactions showed that none of the studied parameters (absence of presence of either BMIM NTf\(_2\), OMIM NTf\(_2\), silica or CO\(_2\)) had any influence on the reaction, but when observing the results it was noticed that the reactions that gave the best results were performed in a close range of pressures between 55 and 70 bar, indicating that the reaction might be pressure dependent. Further continuous flow reactions in that range of pressures gave the best conversions to methoxycarbonylation products. Unfortunately, at these pressures and without CO\(_2\) the reaction took place in a liquid phase and thus substantial IL and catalyst leaching was observed, causing a decrease in conversion and making the reaction not feasible under continuous flow conditions. Nevertheless, the catalyst system composed of Pd, 1,2-bis(di-tert-butylphosphinomethyl)benzene (DTBPMB) ligand and acid showed an excellent linear selectivity, usually higher than 90%, both in batch and continuous flow reactions.

Hydrogenation reactions of dimethyl itaconate (DMI) and dibutyl itaconate (DBI) using Rh-MeDuPhos showed excellent activity and enantioselectivity in a batch mode. In a continuous flow mode IL leaching caused a decrease of the enantioselectivity. The best results were obtained when CO\(_2\) was not present. On the other hand, the absence of CO\(_2\) implied that the reaction was performed in a liquid phase and therefore abundant IL leaching was observed along with a decrease in the enantioselectivity.

A study of the reaction behaviour when using CO\(_2\) in its different phases (liquid, gas and supercritical) was carried out. Under supercritical conditions IL leaching was avoided but conversion was not observed. When using CO\(_2\) in its liquid phase some conversion was observed and full conversion occurred in its gas phase, but abundant IL leaching caused a decrease in the enantioselectivity.

Better results were obtained by immobilising a Rh-MeDuPhos catalyst onto alumina via heteropoly acids. The effect of pressure, H\(_2\) flow and substrate flow were studied and the stability of the reaction in the long term was examined under optimal conditions. More than 12,900 TONs were achieved after 4 days of continuous reaction, with conversions higher than 90% during the 3 first days and e.e. higher than 99% during the 2 first days.
### ABBREVIATIONS

#### Unities

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>°C</td>
<td>Celsius degree</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>cP</td>
<td>centipoises</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
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<td>h</td>
<td>hour</td>
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</tr>
<tr>
<td>m</td>
<td>metre</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mmol</td>
<td>milimol</td>
</tr>
<tr>
<td>mS</td>
<td>milisiemens</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>N</td>
<td>newton</td>
</tr>
<tr>
<td>Pa</td>
<td>pascal</td>
</tr>
<tr>
<td>ppm</td>
<td>part per million</td>
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<tr>
<td>V</td>
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<tr>
<td>wt</td>
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#### Techniques

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<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>ICP-MS</td>
<td>inductively coupled plasma mass spectrometry</td>
</tr>
<tr>
<td>ICP-OES</td>
<td>inductively coupled plasma optical emission spectroscopy</td>
</tr>
<tr>
<td>MW</td>
<td>microwaves</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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## Chemicals and other terms

<table>
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<tr>
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<th>Full Form</th>
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<tr>
<td>BF₄</td>
<td>tetrafluoroborate</td>
</tr>
<tr>
<td>BMIM</td>
<td>1-butyl-3-methylimidazolium</td>
</tr>
<tr>
<td>BMMIM</td>
<td>1-butyl-2,3-methylimidazolium</td>
</tr>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEF</td>
<td>diethyl fumarate</td>
</tr>
<tr>
<td>DEM</td>
<td>diethyl maleate</td>
</tr>
<tr>
<td>DMM</td>
<td>dimethyl maleate</td>
</tr>
<tr>
<td>EMIM</td>
<td>1-ethyl-3-methylimidazolium</td>
</tr>
<tr>
<td>HMIM</td>
<td>1-hexyl-3-methylimidazolium</td>
</tr>
<tr>
<td>ILs</td>
<td>ionic liquids</td>
</tr>
<tr>
<td>MMIM</td>
<td>1-methyl-3-methylimidazolium</td>
</tr>
<tr>
<td>MO</td>
<td>methyl oleate</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NTf₂</td>
<td>bis(trifluoromethanesulfonyl)amide</td>
</tr>
<tr>
<td>OMIM</td>
<td>1-octyl-3-methylimidazolium</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>PF₆</td>
<td>hexafluorophosphate</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>RTILs</td>
<td>room temperature ionic liquids</td>
</tr>
<tr>
<td>scCO₂</td>
<td>supercritical carbon dioxide</td>
</tr>
<tr>
<td>SCF</td>
<td>supercritical fluid</td>
</tr>
<tr>
<td>SILP</td>
<td>supported ionic liquid phase</td>
</tr>
</tbody>
</table>
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Chapter 1

General introduction
As the title of this thesis declares, the two main topics are ionic liquids (ILs) which we used to make supported ionic liquid phase catalysts (SILP catalysts) and supercritical carbon dioxide (scCO₂). In this general introduction I aim to give the reader an insight into the history, properties and applications of both of them separately and also into the combination of both together, namely biphasic IL/SCF systems and SILP catalysts/SCF systems.

1.1 IONIC LIQUIDS

Ionic liquids are salts that are liquid at low temperature and represent a class of solvents with non-molecular ionic character.

1.1.1 History of ionic liquids

The history of ionic liquids began in 1914 when the first report of a room temperature molten salt was reported by Walden.¹ He reported the physical properties of ethylammonium nitrate, [EtNH₃]+[NO₃]⁻, with a melting point of 12 ºC. It was formed by the reaction of ethylamine with concentrated nitric acid. However, it has not found many uses due to its high reactivity.

In 1948 Hurley and Weir were looking for a cheaper and easier way to electroplate aluminium, and developed the first ionic liquids with chloroaluminate anions when they mixed and heated powdered pyridinium halides with aluminium chloride to produce a colourless liquid.²

In the late 1970s Osteryoung et al.³, ⁴ and Hussey et al.⁵, ⁶ in the 1980s, carried out extensive research into room temperature chloroaluminate melts. These melts can be regarded as the first generation of ionic liquids. Nevertheless, they have little use due to their hygroscopic nature and because they have to be prepared and used under an inert atmosphere. At that time research and development was focused on the electrochemical applications of these ionic liquids.⁸

In the early 1980s Hussey, Seddon and co-workers⁹ began to use chloroaluminate melts as non-aqueous polar solvents for the study of transition metal complexes, and in the mid 1980s, low melting point ionic liquids were proposed as solvents for organic synthesis by Fry and Pienta¹⁰ and Boon et al.¹¹
In the 1990s, molten salts with melting points below 100ºC became well known as unique media for chemical reactions, and the term “room temperature ionic liquids” (RTILs) was assigned to them. Then in 1990 the first publications appeared with an ionic liquid used for homogeneous catalysis by Chauvin et al.\textsuperscript{12} and Carlin et al.\textsuperscript{13} Based on the work of Wilkes and Zaworotko,\textsuperscript{14} it became clear that ionic liquids were not restricted to chloroaluminate melts and they prepared the first water-stable representative in 1992, with 1-ethyl-3-methylimidazolium as cation and tetrafluoroborate as anion. These ionic liquids, which could be prepared and safely stored without an inert atmosphere, unlike the previous chloroaluminate melts, became known as the second generation of ILs.

Although these ILs are still used nowadays, their use is limited to those applications where water free conditions can be realised at acceptable costs.\textsuperscript{15} This is because of their relatively high sensitivity towards hydrolysis, not as pronounced as those of the previous chloroaluminate melts but still problematic. Endres et al.\textsuperscript{16} found that the undried ionic liquid [BMIM][PF\textsubscript{6}] attacked the gold substrate when hydrolysed because of the formation of HF, and the aggressiveness increases with an increase in the water content.

In 1996 the synthesis of IL with CF\textsubscript{3} containing anions and other fluorinated alkyl groups was published by Bonhôte et al.\textsuperscript{17} These ILs are water stable, but despite this and other very suitable properties, the high price of the Li[(CF\textsubscript{3}SO\textsubscript{2})\textsubscript{2}N] starting material may be a major problem for their application on a larger scale.

Our work has been based on carbonylation, alkene metathesis and hydrogenation reactions. The first example in the literature of each one of these reactions using ILs was published by Knifton\textsuperscript{18} in 1985 for the carbonylation reaction, where he claimed the toluene carbonylation using an aluminium halide alkyl pyridinium halide “melt” catalyst, by Chauvin and Olivier-Bourbigou\textsuperscript{19} in 1995 in which good results in the self metathesis of 2-pentene were obtained and in 1996 by Suarez et al.\textsuperscript{20} where they demonstrated cyclohexene hydrogenation in ILs.

At the present time the number of RTILs synthesized exceeds 500. Among them 1,3-dialkylimidazolium salts have been receiving an increasing amount of attention in the last few years, becoming the most vigorously developing field in IL research. There is virtually no limit to the number of salts with low melting points, but Earle and Seddon\textsuperscript{21} have estimated
this number to be of the order of 1 billion and research into their properties and uses is intensifying.

As an example Figure 1 shows the number of publications containing the words “ionic liquids” and “molten salts” in the title in the last 30 years. As seen, the average number of papers in the last decade is continuously increasing, reflecting the growing interest in ionic liquids.

![Graph showing the number of publications containing the words “ionic liquids” and “molten salts” in the title determined by SciFinder Scholar as a function of time.](image)

**Figure 1:** Publications containing the words “ionic liquids” and “molten salts” in the title determined by SciFinder Scholar as a function of time

This interest in ILs has led to their commercial availability in recent years, and as an example, Table 1 shows some of the 145 commercially available ILs based on the imidazolium cation readily available nowadays from Aldrich (as August 2012).22
Table 1: Different commercial ILs based on the imidazolium cation

<table>
<thead>
<tr>
<th>Ionic liquid</th>
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<tr>
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<tr>
<td>1-Butyl-3-methylimidazolium trifluoromethanesulfonate</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>1-Propyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>1,2-Dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>1,2-Dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl)methide</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium dicyanamide</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium hexafluorophosphate</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium nitrate</td>
<td><img src="image9" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium tetrachloroaluminate</td>
<td><img src="image10" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium thiocyanate</td>
<td><img src="image11" alt="Structure" /></td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium tosylate</td>
<td><img src="image12" alt="Structure" /></td>
</tr>
</tbody>
</table>
1.1.2 Physical properties of ionic liquids

As their name suggests, ILs are liquids made of ions, but, in contrast with other ionic compounds present in nature, they have a melting point below 100°C, and it is this unusual property what makes ILs exceptional compounds. Other naturally occurring ionic compounds can be seen in Table 2, with their applications and melting points.

Table 2: Several ionic compounds with their melting point

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride (salt)</td>
<td>801</td>
</tr>
<tr>
<td>Calcium carbonate (calcium source)</td>
<td>825</td>
</tr>
<tr>
<td>Potassium bromide (sedative)</td>
<td>734</td>
</tr>
<tr>
<td>Sodium fluoride (cleaning agent)</td>
<td>993</td>
</tr>
<tr>
<td>Lithium chloride (desiccant)</td>
<td>605</td>
</tr>
<tr>
<td>Potassium iodide (nutritional supplement)</td>
<td>680</td>
</tr>
</tbody>
</table>

As seen in Table 2, ionic compounds in nature have high melting points and so are solids at room temperature and cannot be used as solvents. ILs on the other hand have both qualities, ionic behaviour and the liquid state, which make them exceptional as solvents. In fact, some of them break the general rule “like dissolve like” and can dissolve both polar and non polar compounds. As an example, the tetrachloroaluminate based ILs can dissolve non polar benzene by up to 50% by volume.23

The reason why ILs are liquids at room temperature has been explained as arising from the fact that they do not pack well into a crystal lattice, unlike the typical inorganic salts (Figure 2), due to the combination of bulky and unsymmetrical organic cations with the flexible inorganic and charge-delocalized anionic counterparts (Figure 3).
Their efficiency as good solvents can be seen by the variety of substances they can dissolve. These include organic, inorganic and organometallic compounds and materials such as salts, fats, proteins, amino acids, surfactants, sugars, polysaccharides, crude oil, inks, plastics, and even DNA and cellulose.\textsuperscript{24, 25}

ILs are usually composed of poorly coordinating ions which make them highly polar but non coordinating solvents. They tend also to be immiscible with non polar organic solvents, providing an opportunity for operating in two phase’s systems.

One of the major problems of traditional organic solvents is that they evaporate into the atmosphere and usually their vapours are flammable and toxic. This does not happen with the ILs which usually have an extremely low vapour pressure that can be assumed as negligible. As an example, Kabo et al.\textsuperscript{26} gave the vapour pressure of [BMIM][PF$_6$] at 298.15 K as $10^{-11}$ Pa. This property characterizes ILs as green solvents since they do not evaporate into the atmosphere. Unlike traditional organic solvents, they are not explosive and can be used repeatedly avoiding hazardous exposure and air pollution problems.

In addition ILs present three major advantages compared to organic solvents:

- They are able to solvate both polar and non-polar species allowing them to dissolve a wide range of organic, inorganic an organometallic compounds.
- They are generally stable towards thermal decomposition, some being stable up to 450 $^\circ$C.
- Some are not miscible with many organic solvents allowing the extraction of organic products from two phase systems.
• Others (e.g. octadecyl trioctylphosphonium iodide) can be miscible with heptane and immiscible with polar substances \(^{27,28}\).

On the other hand, their main disadvantage is their high viscosities at room temperature making them difficult to handle as their viscosities can be more than a hundred times higher than those of organic solvents, ranging between about 10 cP to 500 cP at room temperature and decreasing with an increase in temperature. \(^{29}\)

The density of the ILs is often higher than that of water, ranging between 1 and 1.6 g/cm\(^2\). It usually decreases with increasing temperature.

Some physical and chemical properties of ILs can be altered by changing the length of the alkyl chain in the cation and the anion. Bonhôte \textit{et al.}\(^{17}\) claimed that an increase in the N-alkyl chain length in N-alkylmethimidazolium cations leads to an increase in the viscosity. Huddleston \textit{et al.}\(^{30}\) concluded that the density of ILs depends upon the alkyl chain length, increasing with a decrease in the alkyl chain length on the cation or an increase in the molecular weight of the anion. Aki \textit{et al.}\(^{31}\) noticed also that the hydrophobicity of an IL increases with an increase in the alkyl chain length, and Wasserscheid reported that an increase in the anion size leads to a decrease in the melting point. \(^{8}\)

There have been few measurements of the surface tension of ILs. The values (48.8 N m\(^{-1}\) for [BMIM][PF\(_6\)] as example) are lower than that of water (72.7 N m\(^{-1}\) at 20 °C) but higher than those of alkanes (16.0 N m\(^{-1}\) for pentane to 25.6 N m\(^{-1}\) for dodecane at 20 °C). \(^{32}\) The surface tension values for ILs decrease with an increase in the alkyl chain length towards the values of the alkanes.

In summary we can deduce another property of the ILs, and this is such as they can be tuned to meet specific requirements just by changing either the anion, or the length of the alkyl chain in the cation, or both. For example, the solubility of water in ILs can be changed from total miscibility to almost total immiscibility just by changing the anion from Cl\(^-\) to PF\(_6\)^-. In Figure 4 we can see some cations where different alkyl chains can be attached and in Table 3 some of the different anions.
Wasserscheid has suggested that the good thermal stability of ionic liquids, up to 450°C, is limited by the strength of their N-C and N-H bonds. According to Endres et al.\textsuperscript{16} such high temperatures are only tolerated for a short period of time, leading to decomposition with a long time exposure. This good thermal stability, in addition to the extremely low vapour pressure, allows removal of the water content in the IL by heating under vacuum, making water contents below 1 ppm easily achievable.

ILs also have high conductivities (≈10 mS cm\textsuperscript{-1}) and a significantly large electrochemical window; the electrochemical potential range over which the electrolyte is neither reduced nor oxidized at an electrode. While water has a value of about 1.2 V, some IL values are over 6 V. This widening of the electrochemical window has allowed the electrodeposition of metals and semiconductors at room temperature, and for example, Al, Mg, Si, Ge, and rare earth elements can be obtained from RTILs.
The refractive indexes of ILs are similar to those of organic solvents. Some values can be seen in Table 4 as well as some other values of general properties.

<table>
<thead>
<tr>
<th>IL</th>
<th>Molecular weight (g)</th>
<th>Density (g ml(^{-1}))</th>
<th>Viscosity (cP)</th>
<th>Melting point (°C)</th>
<th>Surface tension (N m(^{-1}))</th>
<th>Refractive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMIM BF(_4)</td>
<td>226.02</td>
<td>1.12</td>
<td>219</td>
<td>-81</td>
<td>46.6</td>
<td>-</td>
</tr>
<tr>
<td>HMIM BF(_4)</td>
<td>254.08</td>
<td>1.14</td>
<td>314</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMIM PF(_6)</td>
<td>284.18</td>
<td>1.36</td>
<td>450</td>
<td>10</td>
<td>48.8</td>
<td>1.409</td>
</tr>
<tr>
<td>HMIM PF(_6)</td>
<td>312.24</td>
<td>1.29</td>
<td>585</td>
<td>-61</td>
<td>43.4</td>
<td>-</td>
</tr>
<tr>
<td>MMIM N(\text{TF}_2)</td>
<td>377.28</td>
<td>1.56</td>
<td>44</td>
<td>22</td>
<td>-</td>
<td>1.4220</td>
</tr>
<tr>
<td>EMIM N(\text{TF}_2)</td>
<td>391.31</td>
<td>1.52</td>
<td>28</td>
<td>4</td>
<td>-</td>
<td>1.4231</td>
</tr>
<tr>
<td>BMIM N(\text{TF}_2)</td>
<td>419.36</td>
<td>1.43</td>
<td>69</td>
<td>-25</td>
<td>37.5</td>
<td>1.4271</td>
</tr>
</tbody>
</table>

The solubility of gases in ILs is usually low and decreases with an increase in the temperature or a decrease in the pressure. Anthony et al.\(^{34}\) studied the solubility of different gases in BMIM PF\(_6\) using a gravimetric technique due to the non volatility of the ILs. In this work they demonstrated that CO\(_2\) has the highest solubility and strongest interactions with the IL followed by ethylene and ethane. Argon and oxygen, on the other hand, had very low solubilities and weak interactions. All the gases obeyed the Henry’s law regime up to 13 bar except CO\(_2\), which is more soluble in ILs than in other solvents. This high solubility in ILs has been attributed to the large quadrupole moment of CO\(_2\).

Imidazolium based ILs are frequently hygroscopic; however, the solubility of water in the ILs increases with a decrease in the alkyl chain length and decreases with an increase in substitution in the imidazolium ring, as seen in Table 5.
Table 5: Maximum water content in different ILs \(^{35-37}\)

<table>
<thead>
<tr>
<th>IL</th>
<th>Water max content (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMIM PF(_6)</td>
<td>2640</td>
</tr>
<tr>
<td>BMMIM PF(_6)</td>
<td>2540</td>
</tr>
<tr>
<td>PMIM NTf(_2)</td>
<td>3810</td>
</tr>
<tr>
<td>BMIM NTf(_2)</td>
<td>3300</td>
</tr>
<tr>
<td>DMIM NTf(_2)</td>
<td>1450</td>
</tr>
<tr>
<td>BMMIM NTf(_2)</td>
<td>6380</td>
</tr>
<tr>
<td>BM(_4)IM NTf(_2)</td>
<td>33090</td>
</tr>
<tr>
<td>BMIM BF(_4)</td>
<td>19500</td>
</tr>
<tr>
<td>BMMIM BF(_4)</td>
<td>13720</td>
</tr>
</tbody>
</table>

As seen in Table 5, with the same cation the solubility of water in ILs depends upon the anion, increasing in the order: PF\(_6\) < NTf\(_2\) < BF\(_4\). The solubility of organic solvents such as benzene, toluene and xylene in ILs increase with an increase in the alkyl chain length and with the more bulky anions in the order BF\(_4\) < PF\(_6\) < NTf\(_2\).\(^{38}\)

1.1.3 Applications of ionic liquids

Due to their properties ILs have many applications in several processes. As a result of their low volatility and non flammability, in the last decades there has been a great increase in their study due to the need for environmentally friendly green solvents. Nowadays, they are not just used as solvents, but also as catalysts or catalyst activators, electrolytes for batteries, photochemistry and electrosynthesis and even as advanced heat transfer fluids and lubricants.\(^{39}\)

The dissolving power of ILs is extended even to cellulose, which previously was only known to be soluble in an explosive organic solvent. Cellulose is produced in nature at the rate of 10\(^{11}\) tons per year, making it the most abundant natural organic chemical and hence, the most important source of bio-renewable chemicals.\(^{40}\)
Another application of the ILs is their use in batteries because of their high conductivity and wide electrochemical window. Solvents for the electrolytes in Li batteries are aprotic due to the requirements of wide electrochemical windows up to the cathodic limit of the Li/Li\(^+\) potential, but the aprotic organic solvents are usually volatile and flammable, making ILs which are neither volatile nor flammable and have a wide electrochemical window ideal for this purpose.\(^{16}\) Also as a result of their electrochemical window and low vapour pressure they are very efficient for the electrodeposition of metals, allowing deposition above 100°C and making possible the electroplating of water sensitive metals such as aluminium or titanium. Previously this was impossible because of the use of water baths.\(^{40}\)

ILs are widely used in industry and here we relate as an example some of the processes used by different companies around the world.

The major application and maybe the most successful example of an industrial process using ILs is the BASIL\(^{\text{TM}}\) (Biphasic Acid Scavenging utilising Ionic Liquids) process created by BASF. In this process 1-methylimidazole is used to scavenge the acid formed during the synthesis of alkoxyphenylphosphines from the chloride analogues and then recycled and introduced again into the system (Figure 5).

![Figure 5: The BASIL\(^{\text{TM}}\) process](image)

The original process used triethylamine to scavenge the acid and produced triethylammonium chloride with 50% yield and 8 kg m\(^{-3}\) h\(^{-1}\) space/time yield as a dense insoluble paste, making the mixture difficult to handle. With the substitution of the triethylamine for methylimidazole, the salt by-product can be easily separated as a discrete liquid phase and besides, the yield is increased to 98% and the space/time yield increased to 690.000 kg m\(^{-3}\) h\(^{-1}\).\(^{41,42}\) This process can also be extrapolated to any kind of acid scavenging (Table 6).
### Table 6: Reactions suitable for the BASIL™ process

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acylation</td>
<td>$\text{R}^\text{I} \text{O} + \text{R}^\text{II} \text{Cl} \rightarrow \text{R}^\text{I} \text{O} \text{R}^\text{II} + \text{HCl}$</td>
</tr>
<tr>
<td>Elimination</td>
<td>$\text{R} \text{Cl} \rightarrow \text{R} \text{H} + \text{HCl}$</td>
</tr>
<tr>
<td>Phosphorylation</td>
<td>$\text{R}^\text{I} \text{O} + \text{R}^\text{II} \text{P} \text{Cl} \rightarrow \text{R}^\text{I} \text{PO} \text{R}^\text{II} + \text{HCl}$</td>
</tr>
<tr>
<td>Sulfurylation</td>
<td>$\text{R}^\text{I} \text{O} + \text{R}^\text{II} \text{SO} \text{Cl} \rightarrow \text{R}^\text{I} \text{SO} \text{R}^\text{II} + \text{HCl}$</td>
</tr>
<tr>
<td>Silylation</td>
<td>$\text{R}^\text{I} \text{O} + \text{R}^\text{II} \text{Si} \text{Cl} \rightarrow \text{R}^\text{I} \text{Si} \text{OR}^\text{II} + \text{HCl}$</td>
</tr>
<tr>
<td>Deprotonation</td>
<td>$\text{Ph}^+\text{P}^\text{III} \text{Ph}^\text{II} \text{H} + \text{Ph}^+\text{P}^\text{III} \text{Ph}^\text{II} \text{Cl} \rightarrow \text{Ph}^+\text{P}^\text{III} \text{Ph}^\text{II} \text{R} + \text{HCl}$</td>
</tr>
</tbody>
</table>

BASF also used ILs to perform the chlorination of butan-1,4-diol with HCl as chlorinating agent instead of poisonous phosgene. This reaction without the IL gives three side products apart from the desired dichlorinated one (Figure 6). When the IL is used only the 1,4-dichlorobutane is obtained with 98% selectivity.

![Figure 6: Chlorination of butan-1,4-diol without IL](image)

Another application found in BASF for the ILs is their use as entrainers in order to break azeotropic systems, especially the ones where water is one of the components. The IL traps the water in these cases allowing distillation of the other product in pure form. Afterwards the IL is recycled in a falling film evaporator. The costs of separation and recycling of the IL are significantly reduced in this way because of the non requirement of a second distillation column for the IL due to its high vapour pressure.
The first commercialised application of ILs belongs to the Eastman Chemical Company in Texas, which from 1996 to 2004 had been doing the SnI₂ catalysed isomerisation of 3,4-epoxybutane to 2,5-dihydrofuran, a useful and versatile chemical intermediate, in \([\text{[P(C}_{18}\text{H}_{37})(\text{C}_{8}\text{H}_{17})_{3}]\text{SnI}_{3}]\). The main use of the ionic liquid was to allow the separation of polar side products by extraction of the ionic liquid and catalyst, present as \([\text{[P(C}_{18}\text{H}_{37})(\text{C}_{8}\text{H}_{17})_{3}]\text{SnI}_{3}]\) into heptane, leaving the polar products undissolved. At present the plant is not operative due to a decline in the market for furan products.\(^{45}\)

IFP (Institut Français du Pétrole), was the first company to operate an IL pilot plant. They implemented the use of ILs in a modification of a previous process called Dimersol to develop a new process patented as Difasol. By this process they obtain the dimerisation of alkenes such as propene and butene to their more valuable branched dimer homologues, hexene and octene.\(^{42}\) As a result of implementing the IL in the process, in which the dimer product phase separates from the IL containing the catalyst, they obtain:

- A much better use and recyclability of the catalyst and hence reduced catalyst disposal and cost.
- A better dimer selectivity.
- A higher yield into dimers even with a low concentration of alkene feed.
- A possible extension of the Dimersol process to higher less reactive alkenes.
- Smaller reactor requirement.

Degusa is another company which is developing ILs. One of their applications is the hydrosilylation of alkenes with polydimethylsiloxanes (Figure 7).

These surface active products are useful in a broad range of industrial applications. Polyethers and ethers with different ethylene and propylene oxide content have also been also studied.\(^{46}\) Degusa also uses the ILs as additives and dispersants in paints in order to get improved finish, appearance and drying properties. In addition water based pigments can be used now in all types of paints, coatings, lacquers and inks, thus reducing the use of volatile
organic compounds. They are also investigating the use of ILs in lithium batteries and solar cells.

Air Products and Chemicals, Inc., an American based company, patented a new technology to store at low pressure and deliver reactive hazardous gases such as phosphine (PH₃), arsine (AsH₃) and boron trifluoride (BF₃) using ILs. They stored Lewis acid gases, such as BF₃ in Lewis base ILs like [C₅MIM][BF₄]. Lewis base gases such as PH₃ or AsH₃ can be stored in Lewis acid ILs like [C₅MIM][Cu₂Cl₃] or [C₅MIM][Cu₂Br₃]. The gases can be easily withdrawn afterwards from the containers by applying vacuum or by entrainment in a flowing stream of gas.

Iolitec (Ionic Liquid Technologies) is a recent new company (created in 2003) that, as its acronym suggests, works on the synthesis of ILs and their thermodynamic, electrochemical and biotechnological applications. They are developing ILs for use as the active species in sensors, as thermofluids for heat transport and heat storage, as electrolytes for the electrochemical deposition of metals and as high tech additives for cleaning processes and lubricants. ILs are also used as electrolytes in dye-sensitised solar cells, an alternative to the silicon-based solar cells. In this field, Iolitec has become Europe’s leading supplier of ILs for their use in these solar cells. Nowadays one of Iolitec’s research projects is centred in the development of ILs for their use in energy storage devices such as lithium ion batteries, supercaps and fuel cells.

ILs have been used too in the nuclear industry as separation media for nuclear fuel and as electrolytes for the recovery of uranium and lanthanides.

The South African company, SASOL, investigated the use of ILs in metathesis and alkene trimerisation reactions. They focused on the self metathesis of 1-octene where 7-tetradecene and the volatile ethylene are produced (Figure 8).

\[ 2 \text{1-octene} \rightarrow \text{7-tetradecene} + \text{ethylene} \]

**Figure 8: 1-octene metathesis**

To do so, they used the Grubbs catalysts 1st and 2nd generation and the Grubbs-Hoveyda version (Figure 9).
Results with the Grubbs catalyst were not very good, but they observed higher yields and selectivities towards 7-tetradecene while using the 2\textsuperscript{nd} generation one and even better when using the Grubbs-Hoveyda catalyst. They also realised that with the shortening of the alkyl chain length in the imidazolium cation of the IL better results were obtained.

The use of ILs as solvents in catalysis presents some advantages due to their characteristics:

- Very low vapour pressure
- Good as separation media using phase separation, distillation or extraction.
- High heat transfer.
- Possibility of working in a liquid phase in a wide range of temperatures.
- Use of electrochemical processes.
- They are able to work at reduce pressure.
- Possible use of microwaves to accelerate the reactions.
- Possibility of catalyst immobilization.

However, they also present some problems:

- High price of the commercial ILs.
- High viscosity.
- Low gas solubility.
- Difficult purification.

The possibility of immobilising the catalyst in the IL provides the advantages of both homogeneous and heterogeneous catalysis, acting like a solid by immobilizing the catalyst and as a liquid by allowing the catalyst to move freely. Reactants and products can, in addition, be immiscible with the IL allowing an easy separation.
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Catalyst immobilization can be carried out in two different ways:

- Using an ionic precursor like \([\text{Rh(nbd)}(\text{PPh}_3)_2]^+\text{[PF}_6^-\text{]}\)\(^{55}\) or an ionic ligand like \((\text{TPPMSNa})\)\(^{56}\) (ionic bond).
- Grafting the catalyst in the cation\(^{57}\) or anion\(^{58}\) of the IL (covalent bond).

Furthermore the IL/catalyst can be immobilized within a solid support, e.g. silica, making a supported ionic liquid phase catalyst (SILP catalyst). This is the catalyst type we will use in our own experiments.

SILP systems are based on the early work of Davis et al. on supported aqueous phase catalysts.\(^{59}\) Replacing water by an IL overcomes the main limitation of aqueous phase catalysts namely the depletion of the aqueous layer. By supporting the IL in a solid phase, lower leaching levels and higher activity than in biphasic systems can be achieved. SILP systems require significantly reduced amounts of IL which is desirable from both an economic and a toxicological point of view. Thus, a small amount of IL impregnating the support gives rise to a thin layer of IL over a great surface area improving considerably the mass transfer because of the increased surface area.

As examples, Mehnert et al. showed how SILP systems had enhanced activity with comparable selectivity to the biphasic analogues in the batch hydroformylation reaction of 1-hexene\(^{60}\) and in the batch hydrogenation of 1-hexene, cyclohexene and 2,3-dimethyl-2-butene.\(^{61}\) Furthermore, in the hydrogenation reactions the catalyst could be reused for 18 batch runs without any significant loss of activity and the catalyst leaching was below the detection limit. The more polar aldehydes formed in the hydroformylation reactions caused significant leaching of both IL and catalyst.

Wolfson et al. also compared the activity between biphasic IL-organic solvent and SILP system in batch hydrogenation reactions.\(^{62}\) In different examples the SILP system provided more activity and selectivity than the biphasic system. In both systems, the catalyst phase could be recycled without loss of activity. Breitenlechner et al. showed how SILP catalysts combined the enhanced catalytic activity with an improved selectivity over biphasic and homogeneous systems for batch hydroamination reactions.\(^{63}\)
Furthermore, Heck, aldol, epoxidation, hydrogenation, cyclopropanation, Mukaiyama aldol condensation and oxidative kinetic resolution batch reactions have also been successfully performed with SILP systems.

The examples described in the previous paragraphs were all carried out as batch reactions. For practical applications in industry, however, the ideal process would involve a continuous flow system where substrates are continuously fed into the reactor, where they react in the presence of the catalyst and the products are collected at the other end. The catalyst remains in the reactor at all times. Such systems were previously exclusively applied for heterogeneous catalytic reactions. Nowadays the use of SILP systems allows the desired homogeneous catalysts to be used in continuous flow.

Riisager et al. published the first SILP catalysed continuous flow mode hydroformylation of propene in the gas phase and 1-octene in the liquid phase. The system presented no catalyst leaching and the only problem they found was the poor solubility of CO/H₂ gas in the IL that induced mass transfer limitations.

The same group reported the first continuous flow methanol carbonylation, commonly known as the Monsanto process, using a SILP catalyst. The outcome of the experiments, made at conditions similar to the typical industrial process, showed how, in order to obtain the same productivity as observed in batch reactions, the SILP process design required a smaller reactor size than the one used in the industry, and with 100 times less of the IL-catalyst solution. These promising results led to the filing of a world patent.

They also reported for the first time the continuous flow, gas phase asymmetric hydrogenation of methyl acetoacetate. Enantiomeric excess between 65% and 82% were obtained in the more than 100 h continuous reaction at a low substrate flow rate of 3 g/day.

SILP catalysts were also used in the continuous flow ring opening of epoxides, hydrogenation and hydroamination reactions.

As indicated above, the introduction of IL into the system increases the activity and often selectivity of the reaction due to the homogenisation of the heterogeneous catalyst. Nevertheless, even with optimised systems, there are some problems for gas phase and liquid phase reactions. For reactions where the flowing medium is a liquid, catalyst leaching
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presents a problem due to the partial solubility of the IL in the organic phase. In addition, if
gaseous reagents are used with liquid substrates, there can be problems of gas depletion. The
gas initially dissolved within the liquid is readily available for reaction, but, once it has been
used up, the high aspect ratio of the pores ensures that diffusion of further gas to the
reacting site is very slow. For gas phase reactions, the number of substrates is limited because
of the low volatility of most attractive ones, or the throughput is low because the partial
pressure of the substrate is very low. All these problems can be circumvented with the use of
scCO$_2$ as the transport medium.
1.2 **SUPERCRITICAL FLUIDS**

A supercritical fluid (SCF) is the state of a compound, mixture or element that is above its critical temperature (T<sub>c</sub>) and critical pressure (p<sub>c</sub>), but below the pressure required to condense it into a solid (Figure 10).

![Phase diagram of CO<sub>2</sub> showing the supercritical region. Modified from ref 81](image)

**Figure 10**: Phase diagram of CO<sub>2</sub> showing the supercritical region. Modified from ref 81

### 1.2.1 History of supercritical fluids

The history of supercritical fluids starts in 1680 with the research of Denys Papin. He designed a high pressure vessel and used it to prove that the boiling of water could be suppressed by the action of pressure. Then, more than a century after, in 1822, the experimental physicist Baron Charles Cagniard de LaTour speculated that this suppression of boiling must have a limit and proved the existence of the critical point, calling this new state of matter “l’état particulier”.<sup>82</sup> Almost 50 years later Thomas Andrews introduced the term “critical point” and described the supercritical state in his study of CO<sub>2</sub>.<sup>83,85</sup> The studies in SCF increased rapidly and in 1879 Sajotschewsky published the critical points for eight more compounds.<sup>86</sup> The same year, Hannay and Hogarth made the first solubility studies on SCF, observing too that the critical point of a liquid increased if a solid was dissolved within it, and that a very finely divided solid could be produced by rapidly reducing the pressure of a
supercritical solution. This is nowadays the basis for the rapid expansion of a supercritical solution (RESS) process.

In 1896, Paul Villard, who was working on phase behaviour noticed that, under a SCF some substances melted before they dissolved, even though the temperature was not being raised. However this observation was no exploited until 1994, when Weidner et al. developed the method to obtain particles from a gas saturated solution (PGSS) based on the same principle. In the early 1920s the use of SCF in extraction and purification started to emerge. In the 1940s different applications in the petrochemical industry were introduced, and in the 1950s new solutions were proposed using SCFs in processes for coal, mineral oil and wool manufacturing.

Another name in the history of SCFs is Kurt Zosel, who developed the use of scCO$_2$ for natural product extraction. This technique found an application in the extraction of caffeine from green coffee beans, nowadays producing more than 100,000 tons of decaffeinated coffee worldwide.

1.2.2 Properties of supercritical fluids

When a fluid is in its supercritical region the phase boundary between liquid and gaseous phases disappears and the two distinct phases converge into a single supercritical phase. As an example we can see in (Figure 11) the change in the phases from the liquid/gas region, when we approach the supercritical region and when we are in it.

![Figure 11: Phases appearance while approaching the supercritical region.](image)

An orange rhodium complex was added to enhance the contrast.
A fluid in its supercritical region behaves like a gas due to the fact that it fills all the volume of the container, but not a vapour, because a vapour is a gas whose temperature is less than the critical temperature. Nonetheless the properties of a fluid in the supercritical region are generally described as a combination of those of a liquid and a gas, with the exception of some properties that are not intermediate between the ones of liquids and gases but higher near the critical point than they are in liquids or gases on their own. Compressibility and heat capacity are two examples of such behaviour. Around the critical point there is another region known as the “compressible region” (Figure 12) where the compressibility is considerably greater than would be predicted from the ideal gas law.

![CO2 phase diagram with an expansion around the critical point showing the compressible region (blue)](image)

As seen in the expansion of the critical point area, the compressible region not only lies on the supercritical region, but also in the liquid and gas regions, showing that even liquids, which are supposed to be incompressible, have a considerable compression near the critical point.

The values of critical temperature, pressure and density of some organic and inorganic substances are shown in Table 7 and Table 8 respectively.
Table 7: Critical points of some organic substances

<table>
<thead>
<tr>
<th>Supercritical fluid</th>
<th>Critical temperature (°C)</th>
<th>Critical pressure (bar)</th>
<th>Critical density (g ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>31.1</td>
<td>73.8</td>
<td>0.466</td>
</tr>
<tr>
<td>Dimethyl ether</td>
<td>126.9</td>
<td>54</td>
<td>0.242</td>
</tr>
<tr>
<td>Methane</td>
<td>-82.6</td>
<td>46.0</td>
<td>0.163</td>
</tr>
<tr>
<td>Ethane</td>
<td>32.2</td>
<td>48.7</td>
<td>0.207</td>
</tr>
<tr>
<td>Propane</td>
<td>96.7</td>
<td>42.5</td>
<td>0.220</td>
</tr>
<tr>
<td>Ethylene</td>
<td>9.2</td>
<td>50.4</td>
<td>0.214</td>
</tr>
<tr>
<td>Propylene</td>
<td>91.8</td>
<td>46.0</td>
<td>0.228</td>
</tr>
<tr>
<td>Methanol</td>
<td>239.5</td>
<td>80.8</td>
<td>0.273</td>
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<tr>
<td>Ethanol</td>
<td>240.7</td>
<td>61.4</td>
<td>0.276</td>
</tr>
<tr>
<td>Benzene</td>
<td>289.5</td>
<td>30.3</td>
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</tr>
<tr>
<td>Acetone</td>
<td>235</td>
<td>47.0</td>
<td>0.278</td>
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</tbody>
</table>

Table 8: Critical points of some inorganic substances

<table>
<thead>
<tr>
<th>Supercritical fluid</th>
<th>Critical temperature (°C)</th>
<th>Critical pressure (bar)</th>
<th>Critical density (g ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>374.0</td>
<td>220.6</td>
<td>0.322</td>
</tr>
<tr>
<td>Ammonia</td>
<td>132.4</td>
<td>113.2</td>
<td>0.235</td>
</tr>
<tr>
<td>Helium</td>
<td>-267.9</td>
<td>2.26</td>
<td>0.069</td>
</tr>
<tr>
<td>Argon</td>
<td>-122.5</td>
<td>48.6</td>
<td>0.531</td>
</tr>
<tr>
<td>Krypton</td>
<td>-63.7</td>
<td>54.9</td>
<td>0.912</td>
</tr>
<tr>
<td>Xenon</td>
<td>16.6</td>
<td>58.3</td>
<td>1.099</td>
</tr>
<tr>
<td>HCl</td>
<td>51.5</td>
<td>82.6</td>
<td>0.42</td>
</tr>
<tr>
<td>HBr</td>
<td>90.0</td>
<td>85.5</td>
<td>-</td>
</tr>
<tr>
<td>HI</td>
<td>150.7</td>
<td>83</td>
<td>-</td>
</tr>
</tbody>
</table>
The properties of SCFs are usually intermediate between those of gases and liquids (Table 9), and may vary considerably with little changes in temperature or pressure, especially near the critical point. As an example we can see in Figure 13 the variation of the CO\textsubscript{2} density with temperature and pressure.

As seen in Table 9 the higher viscosity values correspond with the lower diffusivity values and vice versa. Diffusivity values are higher in the supercritical phase than in the liquid phase. That means that species will diffuse faster through a SCF than through a liquid, implying that SCF will be more efficient at penetrating through microporous materials thus increasing the rate of mass transport. Diffusivity values vary if other parameters change too, as shown by Liong et al.\textsuperscript{98} (Figure 14). Diffusivity values decrease with an increase in pressure, density or viscosity of CO\textsubscript{2}, whilst they remain more or less stable with an increase in temperature at a constant density.
They also noticed that the decrease of diffusivity with increasing pressure is less pronounced at higher pressures due to the fact that the density and viscosity are less sensitive at higher pressure.

One interesting property of supercritical fluids is that, above the critical point, they cannot be liquefied by compression alone. As a result of this it is possible to change the density and other thermodynamic properties of the supercritical fluid from a gas-like phase to a liquid-like phase without any phase separation. A fluid in its supercritical state can therefore have appreciable density, sufficient enough to exhibit liquid-like solvent properties, whilst maintaining the gas-like characteristics of mass transport and diffusion into solids.

The majority of studies on SCFs have focused on four fluids: CO$_2$, ethane, ethylene and water, with CO$_2$ being by far the most widely studied. It has several advantages over the others, including being non-toxic, non-flammable and available in high purity. Its critical
point (73.8 bar, 31.1 °C) are also relatively accessible. These characteristics make this green solvent the most widely used.

The case of supercritical water is curious because of its behaviour as a polar liquid in the vicinity of the critical point. There, the dielectric constant is reduced making organic species more soluble but with a decrease in the solubility of salts. Due to this fact it has been investigated as a medium for the oxidation of organic compounds.

### 1.2.3 Applications of supercritical fluids

The use of the SCFs as solvents instead of organic compounds can offer several advantages such as improved reaction rates, selectivity control and process safety when using scCO$_2$ due to its non flammable, non explosive and non toxic properties.

Supercritical fluids have been mainly used as solvents in, for example, Diels-Alder reactions, inter and intramolecular Heck reactions, Suzuki coupling reactions, alkylation reactions, photochemical reactions, cyclopropanation reactions, hydroformylation reactions, olefin metathesis, etc. ScCO$_2$ has also been used as a solvent with a silica immobilised catalyst in metathesis reactions. A heterogeneous catalytic process is developed, thus avoiding catalyst leaching but the reactivity is lower than when using a homogeneous catalyst. This application has also be extended to continuous flow processes for hydrogenation, Friedel-Crafts alkylation, etherification and hydroformylation reactions.

A good example of reaction rate improvement was shown by Kainz et al. for the asymmetric hydrogenation of imines where they showed how the reaction time can be decreased from 24 h to 1.5 h when changing the solvent from CH$_2$Cl$_2$ to scCO$_2$ (Figure 15).
Figure 15: Improved conversion in an imine asymmetric hydrogenation reaction by using scCO$_2$\textsuperscript{105}

An example of selectivity control can be seen in the hydroboration reaction of vinylanisole published by Carter \textit{et al.}\textsuperscript{106} Here, by changing the solvent from THF to scCO$_2$, the regioselectivity changed from a combination of the four products (branched and linear alkylboronate esters, alkenylboronate ester and 4-ethylanisole) to complete selectivity to the branched alkylboronate ester (Figure 16).

Figure 16: Improved selectivity in a hydroboration reaction by using scCO$_2$\textsuperscript{107}

Supercritical CO$_2$ can also be used as a protective group. It is known that ruthenium catalysts deactivate in the presence of N-H groups. Therefore, the reactions involving substrates containing this group may need a protection and a deprotection step, increasing the reaction time and the number of steps with a consequent decrease in yield. When scCO$_2$ is used as solvent, it reacts reversibly with the amine forming carbamic acid and acting like a temporary protecting group. Fürstner \textit{et al.}\textsuperscript{108} applied this to a ring closing metathesis reaction. The substrate was dissolved in scCO$_2$ protecting the amine as a carbamic acid, the reaction was performed and then the carbamic acid from the product was converted back spontaneously to the free amine when the pressure was released (Figure 17).
Besides acting as a protecting group, scCO₂ can also act as a C1 building block for the polymerisation of different compounds as seen by Super et al. earlier in 1997 when they described the copolymerization of 1,2-epoxycyclohexane and CO₂ using CO₂ as both reactant and solvent (Figure 18).

Due to their good solvent properties, SCFs are also used in extraction, precipitation and crystallization techniques. Amongst the biggest industrial applications of SCF extraction is the extraction of caffeine from green coffee beans to make decaffeinated coffee, and the extraction of bitterness and anti-microbial elements from hops used to make beer. More than 100,000 tons of decaffeinated coffee (Figure 19) and around 33,000 tons of hops are extracted annually without any loss of flavour.
Figure 19: Coffee extraction vessel (>60 m³)\textsuperscript{114}
1.3 CATALYSIS IN BIPHASIC IL/SCF SYSTEMS

Catalysis can be divided into three main classes. Homogeneous, where the catalyst is dissolved in the same phase as the substrates and products, heterogeneous, where the catalyst is separate from the reagents and products and biological, in which enzymes are employed. From an economical approach, a major interest lies in homogeneous catalysis since higher activities can be obtained and product selectivities can be engineered while using very small amounts of the precious and expensive catalysts. Nevertheless, the main problem with homogeneous catalysts arises from the separation and recyclability of these catalysts after reaction. One approach to circumventing this problem involves the use of IL as solvents, either in a biphasic or in a SILP system.

In the IL/organic biphasic systems the products in the organic phase can be easily separated from the catalyst, which usually remains in the IL phase. Although this method can be optimised by the choice of IL and organic solvent, activities are often reduced due to mass transfer limitations and some catalyst leaching may occur as a result of the mutual solubility of the two phases.

As indicated above, supercritical CO\textsubscript{2} has remarkable properties such as rapid diffusion, low viscosity and practically no surface tension. As a result it offers certain advantages when combined with ILs in a biphasic system, including:

- A wider substrate selection than is possible for biphasic IL/gas reactions.
- Lower solubility of the ionic liquid and the catalyst in scCO\textsubscript{2} compared with biphasic IL/organic phases.
- Fast diffusion of all species to the catalytic centres.

Although CO\textsubscript{2} is extremely soluble in ILs, the reverse is not the case with no apparent IL solubilisation in the CO\textsubscript{2} phase. This means that leaching should be low. In addition, scCO\textsubscript{2} can reduce the viscosity of the IL and enhances the solubility of gases such as hydrogen (Figure 20), oxygen and methane in ILs, hence reducing gas transport problems.

Potentially, these advantages allow for high reaction rates, high rates of transport of substrate over the catalyst and low leaching of both the catalyst and the ionic liquid. Supercritical CO\textsubscript{2} can therefore, as Blanchard \textit{et al.} first suggested, be used as co-solvent and extractant in IL.
biphasic systems. In addition, the favourable properties of CO₂ in terms of very low toxicology, few environmental hazards, process safety and low material costs makes it especially attractive for green and sustainable synthetic processes.

![Figure 20: Solubility of hydrogen in [EMIM][BTA] at a constant partial pressure p(H₂) = 30 bar as a function of the added CO₂ pressure as determined by high-pressure ¹H NMR spectroscopy.]

There are several examples in the literature of IL/SCF biphasic systems. Brown et al.\textsuperscript{123} reported the asymmetric hydrogenation of tiglic acid in [BMIM]PF₆ / H₂O followed by the extraction of the product with scCO₂ (Figure 21). The reaction provided conversions over 97\% with e.e. around 90\% and the catalyst could be reused for four further cycles with no apparent loss of activity. Although no catalyst leaching tests were reported, the ruthenium catalyst was far more soluble in the IL than in scCO₂ so the products were obtained pure and free from IL or catalyst but containing some water. Asymmetric hydrogenation of 4-isobutylatropic acid to give the well-known anti-inflammatory drug ibuprofen was also performed with this system (Figure 22). Poor enantioselectivity was observed but with methanol added at 100 bar H₂ 85\% e.e. was observed, which is higher than that reported for the same reaction in aqueous/organic biphasic media (64\% e.e.).

![Figure 21: Tiglic acid hydrogenation](image1.png)  
![Figure 22: Ibuprofen synthesis](image2.png)
More work on batch alkene hydrogenation in an IL with scCO₂ extraction was carried out by Liu et al.¹²⁴ and Solinas et al.¹²¹ The latter also showed how hydrogen solubility in IL increased with the addition of CO₂, another example of CO₂ enhancing the solubility of gases in ILs.

Ballivet-Tkatchenko et al.¹²⁵ reported methyl acrylate dimerisation in IL/scCO₂ biphasic systems showing equivalent results to those obtained in monophasic ones. Supercritical CO₂ can also be used as a C1 building block. As an example, Kawanami et al.¹²⁶ reported the synthesis of cyclic carbonates from epoxides and scCO₂ using IL as catalysts (Figure 23). With the use of CO₂ in the supercritical state quantitative conversion with 100% selectivity was achieved within five minutes and with turnover frequencies (TOF) 77 times larger than those previously reported.

![Figure 23: Carbonate synthesis from epoxides and CO₂](image)

The biphasic IL/scCO₂ system was first conducted in continuous flow by Sellin et al.¹²⁷ with the hydroformylation of 1-octene. The substrates dissolved in scCO₂ were passed through the IL layer in which the catalyst was dissolved at the bottom of the reactor. The products and unreacted substrates were removed by the scCO₂ phase flowing out of the top of the reactor (Figure 24). The experiment was run for over 30 hours with neither loss of activity nor catalyst leaching.

![Figure 24: Schematic of continuous flow homogeneous catalysis using a SCF–IL biphasic system](image)
Further studies by the same group\textsuperscript{128} showed activities comparable with those required for commercial systems, but with a lower linear selectivity than desired. Nevertheless, the linear selectivity was increased later with specially designed ligands.\textsuperscript{129, 130}

Bösmann \textit{et al.}\textsuperscript{131} reported the continuous flow hydrovinylation of styrene with a system more close to a fixed bed reactor. The ionic catalyst solution was confined in the reactor by two metal filters while the reaction phase composed of a continuous flow of styrene and CO\textsubscript{2} and a pulsed flow of ethylene. Although no leaching data were provided, the catalyst showed remarkable stability over 60 hours.

More examples of this biphasic system can be found for Friedel-Crafts\textsuperscript{132} and metathesis\textsuperscript{133} reactions and have also been reviewed.\textsuperscript{134-136}

Continuous flow biphasic IL/scCO\textsubscript{2} has also been applied in biocatalysis, in particular enzymatic reactions including transesterification,\textsuperscript{137} acylation\textsuperscript{138} and kinetic resolution of enantiomers\textsuperscript{139} have been reported.
1.4 SILP CATALYSTS AND SCF SYSTEMS

SILP catalysts with supercritical flow offer advantages over ionic liquids, biphasic IL/SCF and SILP with gaseous or liquid flow because of their low catalyst leaching, high rates of reaction, wide substrate scope and relatively accessible pressures.

Although catalyst leaching is almost negligible in biphasic IL/SCF systems, due to the insolubility of the IL and catalysts in the carrier CO₂ gas, mass transfer limitations are still present due to the large volume of IL used. The use of SILP catalysts circumvents this problem.

SILP catalysts are heterogeneous and therefore easy to separate from the mixture of substrates and products. Nevertheless, the catalytically active species are dissolved in the IL and so they act as true homogeneous catalysts with similar activities to those obtained in related liquid phase reactions. They therefore represent systems that provide the heterogenisation of a homogeneous catalyst keeping the advantages of both systems; namely easy separation and high activity. Furthermore the amount of IL used is much smaller than in biphasic systems lowering the costs and toxicity levels.

The SILP system is formed by a narrow film of IL/catalyst over a very large surface area decreasing the mass transfer problems due to a better contact with substrates and providing high catalyst activity (Figure 25). The IL can be supported either by adsorption or grafting. Supercritical CO₂ has been used to transport substrates and products into and out of the reactor as a means of overcoming the shortcomings of liquid or gas phase reactions described previously.
There are some examples in the literature using such systems in batch experiments. Wang et al.\textsuperscript{140} reported the synthesis of cyclic carbonates from epoxides, using a silica SILP catalyst and scCO\textsubscript{2} as solvent and reagent. Furthermore the SILP catalyst could be reused four times with only a slight loss of activity, constant selectivity and a leaching level of bromide ion that was only 8 ppm. The IL (\textit{n}-Bu\textsubscript{4}NBr) was immobilised by adsorption onto the silica in this case.

This synthesis of cyclic carbonates was also carried out with the IL grafted onto silica,\textsuperscript{141, 142} a polymer support\textsuperscript{143} and molecular sieves\textsuperscript{144} all using CO\textsubscript{2} as solvent and reagent, but not in its supercritical state.

Batch wise oxidations of alcohols to aldehydes with oxygen and a ruthenium catalyst were also performed with ILs grafted onto silica\textsuperscript{145} or a polymer.\textsuperscript{146} Supercritical CO\textsubscript{2} was used as the solvent in both cases, with the advantage that first, it assists in water removal avoiding aldehyde hydration and overoxidation, and second, it increases the solubility of oxygen in the SILP system whilst also increasing the safety of handling O\textsubscript{2} in the presence of organic compounds. As a result these systems showed higher activity than the most active ruthenium based aerobic catalysts reported previously.

In 2007, a SILP-scCO\textsubscript{2} system was first applied to a continuous flow process by Hintermair \textit{et al.}\textsuperscript{147} They reported the continuous flow hydroformylation of 1-octene using a SILP catalyst where a rhodium complex was dissolved in [OMIM][NTf\textsubscript{2}] supported onto silica by adsorption. The system is shown schematically in Figure 26.
This SILP catalyst filled a typical packed bed reactor where substrates and products flowed through dissolved in scCO₂. The effluent from the reactor was depressurised and pure products and unreacted substrates were recovered (Figure 27).
The outcome of these experiments showed higher rates than the comparable biphasic and commercial hydroformylation reactions. The substrate flow rate was found to be the main factor affecting the reaction giving higher conversions at lower flow rates. Furthermore the system was stable for over 40 hours with a very low catalyst leaching of 0.5 ppm. Later on, the same group published a full paper\textsuperscript{148} with analysis of all the conditions affecting the catalysis. They found that high IL loadings, high syngas/substrate ratios and low flow rates favoured high conversions whereas the opposite, namely low IL loadings, low syngas/substrate ratios and high flow rates favoured high TOF. They also studied the phase behaviour of the mixture. The phase transition from two phases (liquid + gas) to one phase (supercritical) occurred at 106 bar for the mixture, but they noted that the best reaction rate took place at 100 bar where the mixture is in an expanded liquid phase. This is due to the fact that in the supercritical phase substrate concentration in the IL and catalyst layer is reduced because of the better solubilising power of $\text{scCO}_2$ and, syngas availability, which has negative order for the hydroformylation reaction, is enhanced. The only commercialised catalytic reaction using pressurised $\text{CO}_2$ also operates in the expanded liquid phase.\textsuperscript{149}

Hintermair et al.\textsuperscript{150} also published the continuous enantioselective hydrogenation of dimethyl itaconate using a chiral Rhodium SILP catalyst under $\text{scCO}_2$ flow (Figure 28).

![Figure 28: Enantioselective hydrogenation of methyl itaconate\textsuperscript{150}](image)

The reaction was carried out over 65 hours. Full conversion to product was achieved continuously with no signs of catalyst leaching above the detection level of 1 ppm. During the first ten hours of reaction the enantioselectivity (e.e.) was $\text{>99\%}$, subsequently decreasing to the level of 70-75\%. That was explained as arising from partial decomposition of the active species of catalyst forming unselective rhodium hydrogenation catalysts. TOFs were over 2000 h$^{-1}$ which gave a turnover number (TON) of 115000 moles of substrate per
mole of rhodium after the reaction. A high space-time yield of 0.3 kg h\(^{-1}\) L\(^{-1}\) was achieved corresponding to 50 g of substrate converted by 3 mg of catalyst in 0.4 mL IL after 65 hours.

As a result of our research we have reported on the use of SILP catalysts with SCF flow for alkene metathesis reactions\(^{151}\) and the outcome will be discussed later in this thesis.

The first example in the literature of continuous flow biocatalysis using SILP catalysts with a scCO\(_2\) stream was published by Lozano et al.\(^{152}\) They grafted the ILs onto a polymeric monolithic material and then they immobilised the enzyme *Candida antarctica* lipase B (CALB) by simple adsorption of an aqueous solution of the enzyme. With this system they performed the transesterification reaction of vinyl propionate and citronellol (Figure 29).

![Figure 29: Vinyl propionate and citronellol transesterification reaction](image)

The activity of the reaction showed a dependence on the temperature, achieving a maximum at 80 °C and 10 Mpa. The productivity reached over 92% yield and a turnover number of 35.8 \(\times\) 10\(^4\) mol product / mol enzyme. Furthermore enzyme leaching was not observed. A comparative reaction using silica as the support for the IL had a productivity seven times lower than in the monolith.
1.5 AIMS OF THE THESIS

The aim of this thesis was the application of different catalytic process in a continuous flow mode. More precisely, the main aim was focussed on the transformation of renewable starting materials such as methyl oleate into more valuable compounds such as $\alpha,\omega$-diesters. Diesters are potential starting materials for the production of useful chemicals such as high molecular weight polyesters, polyamides, macrocyclic compounds, etc. For instance, the diester resulting from methyl oleate self-metathesis was used as starting material for the preparation of civetone, an ingredient in musk perfumes.\textsuperscript{153}

How to achieve this transformation was based on the idea of a metathesis-isomerisation-methoxycarbonylation cascade reaction (Scheme 1).

![Scheme 1: Metathesis-methoxycarbonylation cascade reaction of methyl oleate](image)

The starting point would be the cross-metathesis reaction of methyl oleate (1) and dimethyl maleate (2) to produce a mono- (3) and a di-ester (4). In a consecutive isomerisation-methoxycarbonylation reaction the mono-ester would be transformed into another di-ester. Thus the overall reaction would be the following (Scheme 2).
General introduction

This reaction presents a 100% atom economy and the two esters obtained would be of great interest for industrial applications. For example they could be reduced to form diols or diamines and then by polycondensation reactions they could be transformed into different useful polymers (Scheme 3).

These polymers could find applications as fibres, plastics, coatings, elastomers, adhesives, nyons and many more.\textsuperscript{154}

A second aim in this thesis was the performance of asymmetric catalytic reactions in a continuous flow mode. In particular asymmetric hydrogenation reactions of typical prochiral substrates were chosen as a model (Scheme 4).
1.6 NOTES AND REFERENCES


50. [http://www.iolitec.de/](http://www.iolitec.de/)


Chapter 1


91. E. B. Auerbach, Pat N°, BR277946, 1926.


Chapter 1

113. P. Alessi, F. Vecchione and I. Kikic, in 10th European meeting on supercritical fluids, Colmar (France), 2005.


Chapter 2

Metathesis reactions
Metathesis reactions are organic reactions of alkenes or alkynes which involve the scission and redistribution of their fragments. The simplest example is that where two alkenes react with each other interchanging the alkyl chains between them as seen in Scheme 5.

\[ \text{Scheme 5: Metathesis reaction} \]

The different types of metathesis reactions are summarised in Table 10.

**Table 10: Metathesis reaction types**

<table>
<thead>
<tr>
<th>Metathesis type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkene self-metathesis</td>
<td><img src="image" alt="Alkene self-metathesis" /></td>
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<tr>
<td>Alkene cross-metathesis</td>
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</tr>
<tr>
<td>Ring closing alkene metathesis</td>
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<tr>
<td>Alkyne self-metathesis</td>
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<td>Ring closing alkyne metathesis</td>
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<td>Acyclic diene metathesis</td>
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<tr>
<td>Allene metathesis</td>
<td><img src="image" alt="Allene metathesis" /></td>
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</tbody>
</table>
2.1 HISTORY

Like many chemical processes, alkene metathesis was found by accident as an outgrowth of the study of Ziegler polymerisations with alternative metal systems.\(^1\) Since then the research in this area has focused on the understanding of the mechanism and afterwards on the development of new catalysts.

The first proposed mechanism consisted of a pair-wise exchange of alkylidenes through a “quasicyclobutane” mechanism in which two alkenes coordinated to the metal and exchanged alkylidene groups through a symmetrical intermediate (Scheme 6). With a few assumptions, this mechanism could account for most of the basic metathesis transformations.\(^2\)

![Scheme 6: Initial proposed mechanism](image1)

A few years later, in 1971, Yves Chauvin proposed a new mechanism (Scheme 7) that turned out to be correct.\(^3\) He observed that the pair-wise mechanism such as the “quasicyclobutane” mechanism, predicted only the two alkenes resulting from pair-wise exchange of the two ends of the starting alkenes. However, the alkenes resulting from cross products were observed very early in the reaction. Chauvin proposed then a mechanism that involved the fragmentation of the alkene (a non-pairwise mechanism) through what has become known as the “carbene” mechanism.

![Scheme 7: Chauvin's proposed mechanism for the alkene metathesis](image2)
Metathesis reactions

With the mechanism already accepted the race to find good catalysts started. The first catalytic systems found were those of tungsten and molybdenum with either mixtures of their oxides with alumina, or mixtures of WCl₆ or MoCl₅ with organoaluminium compounds as co-catalysts. Later, it was discovered that pure metal carbenes could also act as initiators for catalysis. These have several benefits such as a tolerance for functional groups, freedom from side reactions, stereospecificity, control of polymer molecular weights, no need of Lewis acid co-catalysts and rational initiator design. The first of these initiators were the so-called Fischer metal carbenes. These made it possible to demonstrate the interchange of chains between the metal and alkenes⁴ (Scheme 8) and they verified that carbenes could initiate alkene metathesis and not just only propagate it.

![Scheme 8: Interchange between tungsten and alkene](image)

Richard Schrock, who was working with tantalum, reported the first isolable methylene complex in 1975 (Scheme 9).⁵

![Scheme 9: Preparation of the first tantalum methylene complex](image)

Isolation of these new complexes allowed their reactions to be studied in detail. It was found that these complexes showed no metathesis, but rearrangement of an intermediate tantalacyclobutane complex.⁶ Further studies showed that alkoxide ligands encouraged metathesis over rearrangement. As an example, Ta(CHCMe₃)(OCMe₃)₂Cl(PMe₃) was proved capable of metathesising cis-2-pentene.⁷ Schrock also showed tungsten complexes to be able to metathesise alkenes.⁸

At the time Schrock was studying the tantalum and tungsten catalysts, Tebbe was doing the equivalent with titanium. He reported the metathesis between isobutene and methylenecyclohexane back in 1979 (Scheme 10).⁹
Chapter 2

Sche

mee

10: Titanium catalysed metathesis

This titanium catalyst proved to be useful for terminal alkene metathesis and ring opening metathesis polymerisation.

One disadvantage of the tungsten catalysts was their sensitivity towards air and some functional groups. To overcome this problem, Schrock focused on molybdenum complexes as catalysts in the late 1980s in the hope that they would be more tolerant of functionalities than tungsten. He found molybdenum catalysts to be more active at lower temperatures due to the easier loss of the alkene in the molybdacyclobutane intermediate. They were also effective in ring closing metathesis (RCM) and ring opening metathesis polymerisation (ROMP) but still sensitive to air and water.

In California, Grubbs et al. were trying to synthesise ruthenium alkylidene complexes capable of metathesising alkenes and in 1992 the first was announced (Scheme 11), which afterwards came to be known as the Grubbs 1st generation catalysts. This type of catalyst was found to be stable to water, acid and many other functional groups. The precursors for the active species were 16-electron complexes instead of the 18-electron molybdenum complexes.

Scheme 11: First metathesis-active Ruthenium alkylidene complex synthesis
The mechanism of the metathesis reaction using this first generation Grubbs catalyst was studied and several conclusions were elucidated. For the first step, shown in Scheme 12 both the dissociative and the associative mechanisms were considered. The dissociative mechanism would involve first phosphine dissociation to yield a 14 electron intermediate followed by alkene coordination, while the associative mechanism would involve first the alkene coordination to yield an 18 electron intermediate followed by the phosphine dissociation.

Scheme 12: Dissociative (1) versus associative (2) mechanisms

The conclusion of a study with labelled phosphines\textsuperscript{12} indicated that the dissociative mechanism was operative and the overall mechanism was the one shown in Scheme 13.

Scheme 13: 1\textsuperscript{st} generation Grubbs catalyst metathesis mechanism

After the alkene is inserted, it couples with the alkylidene to yield the metallacyclobutane that can break down in two different ways. The first productive way yields new alkene and alkylidene compounds whereas the second unproductive way regenerates the starting materials.

The catalytic activity is dictated then by the rate of the different processes:

- Phosphine dissociation ($k_1$)
- Phosphine re-coordination ($k_{-1}$)
- Alkene insertion ($k_2$)

\[ \text{Initiation} \]
\[ \text{Propagation} \]
The optimal activity is obtained when phosphine dissociation is fast \((k_1 \text{ large})\) and when the 14 electron intermediate incorporates the alkene faster than it re-coordinates the phosphine \((k_{-1}/k_2 \text{ small})\).

The 1st generation catalysts proved to be more effective when the PPh\(_3\) groups were exchanged for the more electron donating PCy\(_3\) groups. Following this path, pioneering work by Nolan\(^{13}\) and Grubbs\(^{14}\) proved that N-heterocyclic carbene (NHC) ligands (Figure 30) were even better due to their larger steric bulk and excellent electron donating properties, which allowed them to stabilise the 16-electron species. These different Grubbs catalysts, later called the “Grubbs 2nd generation” catalysts were able to metathesise tri- and tetra-substituted alkenes and showed rates for the RCM and ROMP over 100 times greater than the ones with the Grubbs 1st generation catalysts.

![Figure 30: Different N-heterocyclic carbenes](image)

A small NHC such as that shown in Figure 30(a) can form 2nd generation catalysts such as \((\text{NHC})_2\text{Cl}_2\text{Ru} = \text{CHR}\) which provide high electron density around Ru but have otherwise limited use because bis(NHC)s are not capable of dissociation to initiate the reaction. On the other hand, more bulky NHC catalysts (Figure 30(b)(c)) form \((\text{NHC})(\text{PR}_3)_2\text{Cl}_2\text{Ru} = \text{CHR}\). These 2nd generation catalysts still have a phosphine to dissociate and have more electron density than the 1st generation ones. Furthermore the performance of the NHC of Figure 30(b) can be improved by hydrogenating the imidazolium ring transforming this ligand to a more electron donating one and improving the catalytic activity.\(^{15}\)

Measuring both the initiation and propagation constants \(k_1\) and \(k_{-1}/k_2\) showed that 1st generation catalysts had larger \(k_1\) constants (around two orders of magnitude) than the 2nd generation catalysts and therefore better initiation, but the 2nd generation catalysts had larger \(k_{-1}/k_2\) constant (around four orders of magnitude) than the 1st generation ones and therefore better coordination with unsaturated substrates. Thus, despite slower initiation, 2nd generation catalysts led to overall faster rates of catalysis.
Changes in both the halogen ligands and the alkylidene ligand also vary the catalytic activity. As well as with the phosphine ligands, when the initiation step is favoured the propagation step is disfavoured, and thus, changing Cl by Br or I led to improved initiation but worse propagation.

Another possibility to increase $k_1$ is to add a phosphine scavenger to the reaction mixture in order to improve the concentration of the 14 electron intermediate, but this does not work because it also increases the rate of the competing catalyst decomposition.

A variety of 2nd generation catalysts has been investigated. Amongst them are the Grubbs-Hoveyda 2nd generation catalysts that will be the catalyst used in our experiments. This catalyst (Figure 31, right) was reported by Hoveyda in 2000. It showed higher rates for the initiation step without decreasing the propagation rate giving therefore higher yields of metathesis.

The Grubbs-Hoveyda catalyst was developed as a means for catalyst recycling that is favoured due to its boomerang ligand which was originally believed to release from and return to the catalyst. Recent studies involving fluorescence (fluorescent aryl ether) or $^{19}$F NMR studies (fluorinated aryl ether) have, however, cast doubt on this interpretation. In our experiments we are using a version of the Grubbs-Hoveyda catalyst (Figure 32) which has an ionic tag attached with the purpose of immobilising the catalyst into the ionic liquid. This ionic tag is anchored to the benzylidene fragment through a 3 carbon spacer, and has shown high levels of recycling combined with very low levels of Ru contamination in the product.
In order to test the recyclability of the catalyst, the RCM of a tri-substituted diene was carried out in BMIM NTf₂ as solvent as shown in Scheme 14.

The conversion was found to be higher than 90% in the three first reaction cycles and decreased to 50% in the last (6th) cycle. The same reaction was carried out in a biphasic system BMIM PF₆/toluene (1 : 3), showing conversion higher than 90% over 8 cycles of reaction, proving the high recyclability of the catalyst.\(^\text{18}\)

The main disadvantage usually related to the use of homogeneous Ru complexes is the difficulty in removing the toxic ruthenium waste from the product due to catalyst leaching. In this previous example, ICP-MS analysis on the product showed extremely low ruthenium leaching levels ranging between 1.2 and 22 ppm.

Alkene cross-metathesis was also tested in this study, but although good conversion was observed for the first runs it decreased quickly afterwards showing poor recyclability levels.

As an outgrowth of all this huge investigation in catalysis, the Nobel Prize in Chemistry was awarded to Robert H. Grubbs, Richard R. Schrock and Yves Chauvin in 2005 in recognition of their contributions to the development of this widely used process.
2.2 RESULTS AND DISCUSSION

The experiments were carried out in a continuous flow system where the pure substrates (previously distilled and passed through an alumina column) and scCO$_2$ flowed through a SILP catalyst bed (the continuous flow system will be explained in detail in Section 6.4). The reactions conditions, unless otherwise stated, were temperature of 50 °C, 100 bar of pressure and substrate flow of 0.15 ml/min over 4.4 g of a SILP containing a catalyst loading of 0.02 wt% Ru metal/SiO$_2$ and an IL loading of 29 wt% BMIM NTf$_2$/SiO$_2$. Samples were collected each hour and the products analysed by GC-MS, $^1$H and $^{19}$F NMR and ICP-OES to check conversion and both IL and catalyst leaching. Similar systems have been used before for hydroformylation$^{19}$ and asymmetric hydrogenation$^{20}$ reactions. Most of the results of this chapter were published as a full paper in 2011.$^{21}$

2.2.1 Ring closing metathesis

Our initial experiments focused on the ring closing metathesis of the typical benchmark substrate diethyl diallylmalonate (Scheme 15). In this reaction the mass balance was close to 100% assuming the loss of ethylene (b.p. = -103.7 °C) which was vented to the atmosphere and was not observed in the GC-MS analysis.

In different runs with catalyst loadings between 0.02 and 0.18 wt% Ru/SiO$_2$ (Table 11) good activity was achieved during the first hour as seen in Figure 33.

![Scheme 15: Diethyl diallylmalonate ring closing metathesis](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min$^{-1}$)</th>
<th>Catalyst loading (wt% Ru/SiO$_2$)</th>
<th>TON after 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/100</td>
<td>0.1</td>
<td>0.183</td>
<td>242</td>
</tr>
<tr>
<td>2</td>
<td>r.t./100</td>
<td>0.2</td>
<td>0.047</td>
<td>549</td>
</tr>
<tr>
<td>3</td>
<td>50/100</td>
<td>0.2</td>
<td>0.021</td>
<td>550</td>
</tr>
<tr>
<td>4</td>
<td>r.t./100</td>
<td>0.2</td>
<td>0.023</td>
<td>542</td>
</tr>
</tbody>
</table>
Nevertheless after the first hour the catalyst activity decreased rapidly indicating its degradation. Diethyl diallylmalonate is a terminal alkene and during the catalyst cycle may produce Ru-methylidene intermediates that have been previously reported to dimerise producing inactive species such as that shown in Figure 34.22

![Figure 34: Grubbs catalyst inactive species](image)

Nonetheless, considering the low catalyst loading and the fast flow rate, high turnovers were obtained in a short time period. By reducing the catalyst loading and increasing the flow rate of the substrate (Table 11, Entries 3 and 4), it was possible to obtain 550 turnover numbers (TON = mol\(_{\text{product}}\)/mol\(_{\text{catalyst}}\)) in 6 h, but the conversions were found to be low and dropped significantly with time. Although more TONs were obtained than in repetitive batch reactions in a shorter time, the instability of the catalyst makes this system unacceptable for use with this type of substrate.
2.2.2 Alkenes self-metathesis

The self-metathesis of different alkenes was tested in continuous supercritical flow. Experiments were done with both terminal and internal alkenes each showing a different behaviour. The results are summarised below.

2.2.2.1 Terminal alkenes

As in the ring closing metathesis, terminal alkenes were expected to degrade the Ru catalyst via formation of methylidene species which dimerise to form inactive Ru catalysts. The terminal alkenes chosen were 1-pentene which yields 4-octene plus ethylene (Scheme 16) and 1-octene which yields 7-tetradecene plus ethylene (Scheme 17).

![Scheme 16: 1-pentene self-metathesis](image)

![Scheme 17: 1-octene self-metathesis](image)

In the self-metathesis of 1-pentene (Table 12, Entry 1), 25 g of substrate were pumped into the system over a period of 6.5 hours. Unfortunately, no products were recovered in the collection vessel. The collection vessel itself was not cooled and therefore one can assume that 1-pentene did not react and was evaporated when collected again due to its low boiling point of 30 ºC.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON after 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/60</td>
<td>0.1</td>
<td>0.021</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>50/100</td>
<td>0.2</td>
<td>0.022</td>
<td>28</td>
</tr>
</tbody>
</table>

Furthermore, the SILP catalyst changed colour during the reaction from green to brown indicating catalyst deactivation.
When 1-octene was used as substrate (Table 12, Entry 2) its higher boiling point (121 °C) prevented its evaporation from the collection vessel. However, analysis of the different samples along the 6 h of reaction showed some conversion only during the first hour and none afterwards. The conversion in the first hour was less than 1% which corresponds to 28 TONs. This result supports the idea of the formation of a methylidene species from terminal alkenes which deactivates the catalyst through its dimerisation.

2.2.2.2 Internal alkenes

In order to establish a comparison between internal and terminal alkenes, the internal analogues of 1-pentene and 1-octene namely 2-pentene and 2-octene were used in metathesis reactions. Self-metathesis of 2-pentene (Scheme 18) yields 3-hexene and 2-butene while self-metathesis of 2-octene (Scheme 19) yields 6-dodecene and 2-butene.

![Scheme 18: 2-pentene self-metathesis](image)

In the case of 2-pentene, the two metathesis products have low boiling point and therefore the products were collected in a vessel cooled with dry ice. In one run (Table 13, Entry 1) the collecting vessel was not cooled during the first 3 hours and nothing was recovered during this period (Figure 35).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON after (5) or 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/100</td>
<td>0.1</td>
<td>0.020</td>
<td>631</td>
</tr>
<tr>
<td>2</td>
<td>50/60</td>
<td>0.1</td>
<td>0.023</td>
<td>2929</td>
</tr>
<tr>
<td>3</td>
<td>50/100</td>
<td>0.1</td>
<td>0.024</td>
<td>(3371)</td>
</tr>
<tr>
<td>4</td>
<td>50/100</td>
<td>0.1</td>
<td>0.021</td>
<td>(2148)</td>
</tr>
</tbody>
</table>
In another run (Table 13, Entry 2) where the collection vessel was cooled from the beginning some conversion was observed throughout all the reaction, proving that only methylidene species resulting from terminal alkenes degrade the catalyst. The initial conversion of 50% in the first hour decreased to 25% after 6 h (Figure 36), reaching 2929 TONs. Although the catalyst does not degrade immediately in the presence of internal alkenes some deactivation occurred with time.

In this run the pressure was lower than the critical pressure of CO$_2$ (73.8 bar) and therefore the reaction was carried out in an expanded liquid phase instead of a supercritical phase.

When the reaction was carried out with 2-octene under supercritical conditions (Table 13, Entries 3 and 4) a similar pattern was observed as seen in Figure 36. Initial conversions were
around 45% and dropped to around 30% after 5 hours. High turnover frequencies (TOF = \( \frac{n_{\text{mol}_{\text{product}}} \cdot n_{\text{mol}_{\text{catalyst}}}^{-1}}{h^{-1}} \)) up to 800 h\(^{-1}\) were achieved and consequently a TON higher than 3300 was obtained after 5 hours of reaction. The collected samples were analysed by ICP-OES in order to check catalyst leaching, which was as low as 0.2-0.8 ppm of ruthenium. This minimal leaching proves the integrity of the catalyst immobilisation in a SILP system when coupled with scCO\(_2\) as a transport vector.

The effect of the IL chain length was checked in these 2-octene metathesis reactions. Both SILP systems with either 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide BMIM NTf\(_2\) or 1-octyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide OMIM NTf\(_2\) resulted in similar behaviour showing little difference between them.

Self-metathesis of our main starting material methyl oleate was also attempted. Oleochemical metathesis is a valuable reaction since it transforms low value feedstocks into useful chemicals for petrochemistry and polymerization. Self-metathesis of methyl oleate (Scheme 20) yields dimethyl octadec-9-enedioate and 9-octadecene as products. These products have high boiling points and thus there was no need to cool the collection vessel. Mass recovery was close to 100% and any mass loss was due to small leaks in the rig.

![Scheme 20: Methyl oleate self-metathesis](image)

Table 14: Methyl oleate self-metathesis conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min(^{-1}))</th>
<th>Catalyst loading (wt% Ru/SiO(_2))</th>
<th>TON after 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/100</td>
<td>0.05</td>
<td>0.020</td>
<td>1895</td>
</tr>
<tr>
<td>2</td>
<td>r.t./100</td>
<td>0.05</td>
<td>0.007</td>
<td>6676</td>
</tr>
<tr>
<td>3</td>
<td>50/100</td>
<td>0.05</td>
<td>0.006</td>
<td>4214</td>
</tr>
</tbody>
</table>
Self-metathesis of methyl oleate was carried out for 10 hours (Table 14, Entry 1). The conversion was at equilibrium (around 66%) for the first 6 hours and then decreased slightly to reach 44% in the 10th hour (Figure 37). TOF over 500 h⁻¹ were achieved for the major part of the reaction reaching a total TON of 4249 after the 10 hours. ICP-OES analysis of the collected samples showed a concentration of ruthenium leaching ranging between 10 and 15 ppm.

![Figure 37: Methyl oleate self-metathesis](image)

Even more impressive results were obtained when the reaction was carried out at room temperature and the catalyst loading was decreased by a factor of 3 to 0.07 wt% Ru/SiO₂ (77 ppm) (Table 14, Entry 2). The conversion started at 58% in the first hour and finished at 40% after 9 h (Figure 37). This corresponds to a decrease of around 10% in conversion, but that was balanced by the increase of TOF to values between 1440-1020 h⁻¹ reaching a remarkable TON of more than 10,000 after 9 hours of reaction. Ruthenium levels in the product were below the detection limit of ICP-OES (<0.3 ppm).

Much higher turnover numbers (up to 470,000) have been obtained in the cross-metathesis of methyl oleate with 2-butene by using very low catalyst loadings in batch reactors, but the catalyst, albeit in small amounts, remained in the reaction products.²³

Self-metathesis of methyl oleate was also tried at a low catalyst loading with a different variation of the Grubbs-Hoveyda catalyst (Figure 38) that was expected to be more stable over time (Table 14, Entry 3). However, the results showed that the conversion decreased with time, and at a higher rate compared with the usual catalyst as seen in Figure 37.
2.2.3 Alkenes cross-metathesis

After verifying the feasibility of the system for self-metathesis reactions, attempts were made to carry out cross metathesis reactions in continuous flow. Different combinations of alkenes were studied. First cross-metathesis was studied using the substrates that gave the best results in self-metathesis reactions namely methyl oleate and 2-octene.

2.2.3.1 Methyl oleate and 2-octene cross-metathesis

The cross-metathesis of methyl oleate and 2-octene (Scheme 21) yields a combination of 8 possible products, 4 from the cross-metathesis between methyl oleate and 2-octene and the other 4 from the self-metathesis of each substrate with itself.

![Scheme 21: Methyl oleate and 2-octene cross-metathesis](image-url)
As our objective is to favour cross-metathesis over self-metathesis, the reaction was performed using a ratio of methyl oleate/2-octene (1 : 4). The rest of the reaction conditions were the same as previous self-metathesis reactions namely 50 °C, 100 bar of pressure and 0.1 ml/min of substrate using 4.4 g of a SILP system containing 0.02 wt% Ru/SiO₂ and 29 wt% BMIM NTf₂/SiO₂.

The results were remarkable as seen in Figure 39. The mass recovery during the reaction was between 70-80%, which is good assuming that the low boiling point 2-butene resulting from the self-metathesis of 2-octene evaporated in the collection vessel and vented to the atmosphere. From the 8 possible products 7 were detected by GC-MS analysis of the collected samples excluding the aforementioned 2-butene.

![Graph showing conversion over time](image)

**Figure 39: Methyl oleate and 2-octene cross-metathesis**

The total conversion based on methyl oleate over the 6 h reaction was stable at 90% which is higher than the conversions previously obtained in the self-metathesis of each starting material separately. Note that the equilibrium position for self metathesis allows only 80 % conversion. Besides no hint of catalyst deactivation was observed. Even more remarkable is the selectivity of the reaction. Cross-metathesis, the desired reaction, was favoured against self-metathesis representing 67% of the total conversion. TOFs over 400 h⁻¹ were achieved throughout the reaction accumulating a total TON of 2245 after 6 h of which 1226 belonged to cross-metathesis products (Figure 40).
With this example the feasibility of the system was also extended to cross-metathesis reactions.

### 2.2.3.2 Methyl oleate and dimethyl maleate cross-metathesis

Because of our interest in α,ω-diesters, the cross metathesis of methyl oleate (MO) and dimethyl maleate (DMM) was investigated next (Scheme 22). This cross-metathesis reaction has been suggested before in the literature but has not apparently been carried out.\(^{24}\)

DMM is a symmetric molecule around the double bond and thus its cross-metathesis with MO yields only two products. Among the products one might also expect the ones produced by the self-metathesis of MO, and so, in order to minimise them, DMM was added in excess in the initial mixture to favour the cross-metathesis. The aim of this reaction then was to achieve as much selectivity as possible towards cross-metathesis. The calculations were made on the basis of the MO self- and cross-metathesis. DMM self metathesis yields itself or the
Metathesis reactions

$E$-isomer, dimethyl fumarate, so was not included in the calculations. All the products have high boiling points and therefore none were lost and the mass recovery was close to 100%.

A first standard run was made at 50 ºC, 100 bar of pressure and 0.15 ml/min of a mixture MO/DMM (1 : 4) over 4.4 g of a SILP with 0.02 wt% Ru/SiO$_2$ and 29 wt% BMIM NTf$_2$/SiO$_2$ (Figure 41).

![Figure 41: Methyl oleate and dimethyl maleate cross-metathesis](image)

After the first hour of reaction 71% conversion was achieved with a higher selectivity towards cross-metathesis (58% of conversion) than self-metathesis (42% of conversion), but consecutive samples showed a decrease of the total conversion indicating some catalyst deactivation. Most unexpected was the change in selectivity towards the self-metathesis products reaching 100% after 7 h of reaction. TOFs of around 500 h$^{-1}$ were achieved accumulating in a total TON of 3962 after 8 h of reaction of which 510 corresponded to the cross-metathesis products. IL leaching was low ($^{19}$F NMR evidence) and ICP-OES analysis of the samples showed ruthenium leaching of 8 ppm.

From this point we focused on attempting to increase the selectivity towards cross-metathesis and therefore all the different parameters of the reaction were analysed to check their effect on the selectivity.
2.2.3.1 Effect of catalyst

First a blank reaction without any catalyst was performed. A solution of MO and DMM was stirred for several days in the presence of a SILP catalyst composed of 1 g SiO$_2$ with 29 wt% BMIM NTf$_2$/SiO$_2$ and no conversion was observed as expected.

Another reaction was performed using the original Grubbs-Hoveyda 2$^{nd}$ generation catalyst (Figure 42) to check the effect of the ionic tag attached to the boomerang ligand in our catalyst 1.

![Figure 42: Grubbs-Hoveyda 2$^{nd}$ generation catalyst and our catalyst 1](image)

Conversion started at 75% and decreased to 50% after 6 h of reaction. A similar selectivity pattern as in the previous standard reaction was observed with cross-metathesis slightly higher initially but decreasing with time. However, green coloured samples were recovered indicating catalyst leaching. This was confirmed by the change in colour to purple when the catalyst in the samples was quenched by the addition of ethyl vinyl ether which leads to catalytically inactive Fisher type carbenes.$^{25}$

![Figure 43: Methyl oleate and dimethyl maleate cross-metathesis with Grubbs-Hoveyda 2$^{nd}$ generation catalyst](image)
2.2.3.2.2 Effect of ionic liquid

In Section 2.2.2.2 we discussed the effect of the variation in the IL alkyl chain length on the self-metathesis of 2-octene. Now the absence of IL in the SILP catalyst will be examined.

A similar system was previously reported by Van Berlo et al. They deposited the Grubbs-Hoveyda 2nd generation catalyst directly onto silica by the evaporation of a toluene solution. This was successfully used as a low leaching supported catalyst for the metathesis of a variety of alkenes and gave up to 4000 TON after 2 h in the ring-opening metathesis of cyclooctene under continuous flow, with ruthenium leaching as low as 7 ppb. Non-polar organic solvents were used as the transport vector but the system is not suitable for polar substrates as the catalyst may be washed away.

We then performed the cross-metathesis reaction of MO with 8 fold excess of DMM under the standard conditions of 50 °C, 100 bar of pressure and substrate flow of 0.15 ml/min with our Grubbs-Hoveyda 2nd generation like catalyst supported onto 4.4 g of silica with a loading of 0.02 wt% Ru/SiO₂. These supported catalysts are purely heterogeneous whilst the previous SILP catalysts are considered to be homogeneous catalysts.

Conversions started at 70% and decreased to 54% after 6 h of reaction (Figure 44) which is in the same range as previous reactions. However cross-metathesis selectivity did not improve and was even lower than in previous SILP systems.

![Figure 44: Methyl oleate and dimethyl maleate cross-metathesis with supported catalyst not containing IL](image-url)
2.2.3.2.3 Effect of dimethyl maleate excess

Two reactions were carried out in order to analyse the effect of excess DMM compared with a previous reaction which had a 4 fold excess (Table 15, Entry 1 and Figure 41). One had an equimolecular flow of DMM (Table 15, Entry 2 and Figure 45) while the other had an 8 fold excess (Table 15, Entry 3 and Figure 46).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dimethyl maleate excess</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>50/100</td>
<td>0.15</td>
<td>0.023</td>
<td>3133/510</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>50/100</td>
<td>0.15</td>
<td>0.022</td>
<td>3058/586</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>50/100</td>
<td>0.1</td>
<td>0.017</td>
<td>2448/336</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>50/100</td>
<td>0.1</td>
<td>0.019</td>
<td>2118/445</td>
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</tbody>
</table>

As seen in Figure 45 when DMM was fed in an equimolecular amount to that of MO, the reaction profile was similar to that obtained when the DMM was fed in a 4 fold excess. The selectivity towards cross-metathesis was lower than the self-metathesis during all the reaction including during the first hour where it was higher with a higher DMM excess. Nevertheless, feeding an equimolecular amount of DMM gave 19% cross-TON which is slightly higher than the 16% cross-TON obtained with 4 fold DMM excess.

Figure 45: Methyl oleate and dimethyl maleate cross-metathesis at ratio (1 : 1)
The selectivity towards cross-metathesis was not increased either when DMM was fed in an 8 fold excess of MO (Figure 46). A similar reaction profile was observed again presenting a catalyst deactivation with time and cross-metathesis selectivity decreasing to 0 after four hours. Besides, only 13% cross- TONs were achieved, which is a lower value than when using a 4 fold DMM excess.

![Figure 46: Methyl oleate and dimethyl maleate cross-metathesis at ratio (1 : 8)](image1)

The fact that when the reactions were stopped the catalyst was still active for self-metathesis of MO but not for cross-metathesis with DMM suggests that the catalyst had difficulties in forming carbenes with DMM. Thus a reaction was made feeding first only DMM for 2 hours and then a mixture MO/DMM (1 : 4) (Table 15, Entry 4 and Figure 47). The reaction profile again did not change compared with previous experiments.

![Figure 47: Methyl oleate and dimethyl maleate cross-metathesis feeding dimethyl maleate first alone for 2 h](image2)
2.2.3.2.4 Effect of temperature

The standard reaction temperature was 50 ºC in previous experiments (Table 16, Entry 1). Two further reactions were made, one at lower temperature (Table 16, Entry 2) and the other at higher temperature (Table 16, Entry 3) in order to analyse their effect on the reaction profile.

Table 16: Effect of temperature, reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dimethyl maleate excess</th>
<th>Temperature/Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>50/100</td>
<td>0.15</td>
<td>0.023</td>
<td>3962/510</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>r.t./100</td>
<td>0.15</td>
<td>0.020</td>
<td>2433/56</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>70/100</td>
<td>0.15</td>
<td>0.020</td>
<td>2234/358</td>
</tr>
</tbody>
</table>

The first reaction was carried out at laboratory room temperature (Figure 48) at approximately 20 ºC. Since the reaction temperature was lower than the critical temperature of CO₂ (31.1 ºC) the reaction was not performed in a supercritical phase but in an expanded liquid phase. With these conditions the conversion decreased rapidly over time and the selectivity towards cross-metathesis accounted for only 5% of the total conversion. Due to the lower conversion compared to the standard reactions the cross-TONs were also lower. Furthermore some IL leaching was observed. The leached IL probably contained the catalyst too.

Figure 48: Methyl oleate and dimethyl maleate cross-metathesis at r.t.
A second reaction was carried out at 70 °C (Figure 49), 20 °C higher than the standard experiments. At higher temperature faster catalyst deactivation was observed as seen in the large decrease in conversion from 71 to 14% in just 8 h, which led to a lower total TON compared with the standard and room temperature experiments. Nonetheless, after the first hour of reaction the selectivity towards cross-metathesis (65%) was higher than in standard reactions at 50 °C (58%). In consecutive samples the same reaction profile was observed as in previous experiments with a rapid decrease of cross-metathesis selectivity. A cross-TON of 358 was achieved which is about 2/3 of that obtained at 50 °C. Despite the higher initial selectivity, reactions at high temperature are not preferred due to faster catalyst deactivation.

![Figure 49: Methyl oleate and dimethyl maleate cross-metathesis at 70 °C](image)

2.2.3.2.5 Effect of pressure

The standard reaction pressure was 100 bar in previous experiments (Table 17, Entry 1). Two further reactions were made, one at lower pressure (Table 17, Entry 2) and the other at higher pressure (Table 17, Entry 3) in order to analyse their effect on the reaction profile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dimethyl maleate excess</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 5 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>2473/716</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>50/50</td>
<td>0.15</td>
<td>0.018</td>
<td>1753/232</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>50/150</td>
<td>0.15</td>
<td>0.019</td>
<td>1458/330</td>
</tr>
</tbody>
</table>
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The first reaction was performed at 50 bar of pressure (Figure 50). Here again, at a pressure lower than the CO$_2$ critical pressure (73.8 bar) the reaction took place in an expanded liquid phase. The reaction profile was similar to previous ones, not improving the cross-metathesis selectivity with only 232 cross- TON and besides, green coloured samples were recovered indicating catalyst leaching. Before analysing the samples, the leached catalyst was quenched by the addition of ethyl vinyl ether. A fast colour change in the samples from green to brown was observed. Further NMR analysis confirmed substantial IL leaching.

![Figure 50: Methyl oleate and dimethyl maleate cross-metathesis at 50 bar](image)

The cross-metathesis of MO and DMM was carried out next at 150 bar of pressure (Figure 51). As this pressure is higher than the critical pressure of CO$_2$ the reaction was performed under supercritical conditions.

![Figure 51: Methyl oleate and dimethyl maleate cross-metathesis at 150 bar](image)
Colourless samples were again recovered suggesting no catalyst leaching and this was confirmed by NMR analysis. Conversion initially at 67% decreased to 53% after 7 h of reaction, which represents a smaller catalyst deactivation in time than previous reactions, but the cross-metathesis selectivity was much lower than self-metathesis accounting only for 330 cross- TONs out of the 1458 total TONs.

2.2.3.2.6 Effect of CO$_2$ as a carrier gas

In order to test the stability of the SILP/scCO$_2$ system a reaction was carried out with nitrogen gas instead of CO$_2$ (Figure 52). The reaction was performed at room temperature and 30 bar of nitrogen with a substrate flow of 0.15 ml/min of a mixture MO/DMM (1 : 8) over 4.4 g of a SILP containing 0.02 wt% Ru/SiO$_2$ and 29 wt% BMIM NTf$_2$/SiO$_2$.

![Figure 52: Methyl oleate and dimethyl maleate cross-metathesis with N$_2$ as carrier gas](image)

The replacement of CO$_2$ by nitrogen drastically altered the reaction. When nitrogen was used as a carrier gas a typical liquid phase reaction took place and most of the IL leached out along with the catalyst as seen visually and after analysis on the first two samples recovered (Figure 53). Conversion started at 69% and decreased to 11% in less than four hours due to heavy leaching. The selectivity towards cross-metathesis was always lower than the selectivity towards self-metathesis, accounting only for 366 cross- TON out of the 1057 total TON. Despite the outcome of the reaction being disappointing, it was useful to prove the importance scCO$_2$ in preventing IL and catalyst leaching.
2.2.3.2.7 Effect of CO₂ flow

Having demonstrated the importance of CO₂, the effect of its flow rate was examined. All metathesis reactions previously carried out employed a CO₂ gas flow of 0.64 l/min (Table 18, Entry 1). Two reactions were run, one using a lower CO₂ flow (Table 18, Entry 2) another at a higher CO₂ flow (Table 18, Entry 3) and compared with previous standard reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CO₂ flow (l/min)</th>
<th>Temperature/Pressure (°C)/bar</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.64</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>2473/716</td>
</tr>
<tr>
<td>2</td>
<td>0.18</td>
<td>50/100</td>
<td>0.15</td>
<td>0.021</td>
<td>1928/503</td>
</tr>
<tr>
<td>3</td>
<td>1.16</td>
<td>50/100</td>
<td>0.15</td>
<td>0.020</td>
<td>2327/785</td>
</tr>
</tbody>
</table>

A lower flow rate of CO₂ led to a similar pattern as previous reactions. Conversion started at 74% and finished at 59% after 6 hours of reaction with selectivity towards cross-metathesis slightly higher than for self-metathesis in the first hour (Figure 54). Subsequent samples showed a decrease in cross-metathesis selectivity as in previous experiments. Nevertheless, a big difference with previous reactions was noticeable in the IL leaching, which, at lower CO₂
flow rate was quite large. This arises from the fact that the partitioning of substrates into the supercritical phase becomes more difficult when less CO\textsubscript{2} is available, thus probably the reaction was performed in an expanded liquid phase which in some extent was miscible with the IL causing its leaching.

![Figure 54: Methyl oleate and dimethyl maleate cross-metathesis with low CO\textsubscript{2} flow](image)

When the reaction was performed with a higher CO\textsubscript{2} flow rate (Figure 55) the IL leaching was minimal as in previous reactions. Nevertheless, catalyst deactivation was also present with conversions decreasing from 78 to 60\% in 6 h. A slightly higher rate to cross-metathesis was achieved with 785 cross- TON out of the 2327 total TON and a similar selectivity pattern was observed as in previous standard reactions but, if we take in account the higher CO\textsubscript{2} excess feed, it did not make the experiment much more cost-effective.

![Figure 55: Methyl oleate and dimethyl maleate cross-metathesis with high CO\textsubscript{2} flow](image)
2.2.3.2.8 Effect of boomerang ligand

Because of the dramatic change in selectivity observed towards cross-metathesis, we wondered whether some change in the catalytically active species might be occurring during the reaction.

Boomerang catalysts (Figure 56) are generally believed to work by decoordination of the ether to create a site at which the alkene coordinates. The alkene then undergoes metathesis with the carbene from the boomerang ligand to introduce a carbene derived from the reacting alkene. The modified boomerang ligand is then believed to remain free in solution until the end of the reaction, when it undergoes metathesis with a metal-bound carbene (formed from a reacting alkene) and recoordinates the ether oxygen.$^{27}$ Recent studies involving fluorescence (fluorescent aryl ether) or $^{19}$F NMR studies (fluorinated aryl ether) have, however, cast doubt on this interpretation,$^{17}$ suggesting that the boomerang ligand does not recoordinate.

We thought it possible that the boomerang ligand might be required for the activation of DMM but not for MO. If this were the case, cross-metathesis would be observed as long as the boomerang ligand would be capable of reacting back with the catalyst, but not if it diffused away from the active site. We therefore carried out a reaction (Table 19, Entry 2) in which we added an excess of boomerang ligand precursor 3 (Figure 57) and compared the results with a previous standard reaction without any boomerang ligand added (Table 19, Entry 1).

When adding a 5 fold excess of boomerang ligand 3 over the catalyst, no improvement in the selectivity occurred. On the contrary only 3% selectivity towards cross-metathesis was found in just one of the samples (Figure 58), whilst in standard reactions, even if the selectivity to
cross-metathesis decreased with time, it accounted for around 30% of the total conversion. Thus only 14 TON out of the 2154 total TON corresponded to cross-metathesis.

Table 19: Effect of boomerang ligand excess, reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boomerang ligand excess</th>
<th>Temperature/Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>2473/716</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>50/100</td>
<td>0.15</td>
<td>0.019</td>
<td>2154/14</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>50/100</td>
<td>0.1</td>
<td>0.020</td>
<td>2027/0</td>
</tr>
</tbody>
</table>

Another reaction was carried out with an 8 fold excess of boomerang ligand 3 (Table 19, Entry 3) but similar results were obtained with only self-metathesis produced. Unexpectedly, an excess of boomerang ligand 3 had an inhibitory effect on the cross-metathesis.

Figure 58: Methyl oleate and dimethyl maleate cross-metathesis with extra boomerang ligand added

2.2.3.2.9 Effect of dimethyl fumarate possible crystallisation

Another possible cause for the decrease in cross-metathesis selectivity could lie in the possible crystallisation of dimethylfumarate (DMF) during the reaction. DMM is a cis diester and can perform self-metathesis to yield two products, the cis DMM and the trans dimethyl fumarate (Scheme 23).

Scheme 23: DMM self-metathesis
While DMM is liquid at room temperature, DMF is a solid with a melting point over 100 °C thus its crystallisation in the reactor could hinder the cross-metathesis because less of the diester is available and it may block the silica pores obstructing the substrates access.

In order to check if that could be the case, metathesis reactions were carried out between MO and the ethyl homologue of DMM, namely diethyl maleate (DEM), as both its cis and trans isomers are liquid at room temperature and thus crystallization would be avoided (Scheme 24). In these reactions, we also replaced BMIM NTf₂ by OMIM NTf₂.

```
\[
\text{O=C-C=O} + \text{O=C-C=O} \rightarrow \text{O=C-C=O} + \text{O=C-C=O} \\
\text{Cross-metathesis}
\]
```

```
\[
\text{O=C-C=O} + \text{O=C-C=O} \rightarrow \text{O=C-C=O} + \text{O=C-C=O} \\
\text{Self-metathesis}
\]
```

Scheme 24: Methyl oleate and diethyl maleate cross-metathesis

However, when the reaction was performed using DEM (Table 20, Entry 2) instead of DMM (Table 20, Entry 1) no change in the reaction profile was observed (Figure 59). Conversion started at 77% and finished at 62% after 6 h of reaction. The selectivity towards cross-metathesis was higher initially compared to self-metathesis and decreased with time. Interestingly it did not decrease to zero as in previous experiments and thus a slightly higher rate of 30% ((cross TON/total TON) * 100) towards cross-metathesis products was achieved than in previous reactions with DMM where 28% was obtained.

**Table 20: Effect of dimethyl maleate possible crystallisation, reaction conditions**

(DEM = diethyl maleate, DEF = diethyl fumarate)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (excess)</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMM (8)</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>2473/716</td>
</tr>
<tr>
<td>2</td>
<td>DEM (8)</td>
<td>50/100</td>
<td>0.15</td>
<td>0.019</td>
<td>2091/641</td>
</tr>
<tr>
<td>3</td>
<td>DEF (8)</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>1807/2</td>
</tr>
<tr>
<td>4</td>
<td>DEM/DEF (4+4)</td>
<td>50/100</td>
<td>0.15</td>
<td>0.017</td>
<td>2120/285</td>
</tr>
</tbody>
</table>
A metathesis reaction was also tried between MO and the *trans* diester DEF (Figure 60). The reaction showed good stability with conversions starting at 62% and finishing at 58%, but surprisingly cross-metathesis accounted for only 2% of the total conversion in the first hour and nothing more afterwards giving the reaction a total selectivity towards MO self-metathesis. This “bad” result was actually very important because it made us aware of the importance of the substrates *cis/trans* configuration. *Trans* substrates, unlike the *cis* ones, present a more hindered approach to the catalytic species which implies their unavailability to coordinate and therefore to perform cross-metathesis.

One last metathesis reaction was tried between MO and a mixture of DEM/DEF in a ratio (1 : 4 : 4) in order to check if DEF was acting as an inhibitor in the previous reaction. Similar conversion was observed, which started at 70% and finished at 58% after 6 h of reaction.
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(Figure 61). The selectivity was found to be intermediate between those of DEM and DEF on their own, showing that DEF does not act as an inhibitor of the cross-metathesis. On the other hand, the trans diester DEF confirmed its unavailability to coordinate to the catalytic species and as a result a lower selectivity towards cross-metathesis was obtained then by the cross-metathesis of MO and exclusively DEM.

![Figure 61: Methyl oleate and diethyl maleate/diethyl fumarate cross-metathesis](image)

2.2.3.2.10 Batch mode reaction

Since none of these previous factors improved the cross-metathesis of MO with DMM, the cross-metathesis under batch conditions in the ionic liquid OMIM NTf₂ was studied. Using a catalyst loading of 1 mol% and a 4 fold excess of DMM at 50 ºC, all the MO was converted to the desired cross-metathesis products within 10 min. We believe that this is the first time that this particular cross-metathesis reaction has been successfully carried out.

In order to better appreciate the evolution of the reaction the catalyst loading was reduced to 0.2 mol% and fascinating results were obtained (Figure 62). Initially, the only products formed were those of the self-metathesis of MO, but as the reaction progressed, cross-metathesis built up until it became predominant and finally exclusive with 100% conversion towards cross-metathesis products after 2 h of reaction.

It should be noted that significant conversion to cross-metathesis products was not observed for the first 5 min of the reaction, despite a much higher catalyst loading than in the flow system. What these results demonstrate is that the rate of self-metathesis is very much faster
than the rate of cross-metathesis. Thus self-metathesis products can be regarded as the kinetically favoured products and cross-metathesis products as the thermodynamically favoured ones.

![Figure 62: Methyl oleate and dimethyl maleate cross-metathesis in batch mode](image)

In other batch reaction with only 0.08 mol% of catalyst the same behaviour was observed. When the conversion to cross-metathesis products exceeded that of self-metathesis a fresh load of substrate was added (Figure 63) observing the same process as before. Self-metathesis products formed faster but cross-metathesis became predominant with time.

![Figure 63: Methyl oleate and dimethyl maleate cross-metathesis in batch mode with substrate refill](image)

2.2.3.2.11 Effect of residence time

Given the results obtained in batch systems, it is surprising that we saw any cross-metathesis at all in the flow system, since the residence time in the reactor under our normal flow
conditions was only 30–130 min and the catalyst loading was very low. However, what we should find is that cross-metathesis is increased if the residence time in the reactor is increased.

We then performed two reactions with higher residence times and compared them with a previous standard reaction (Table 21, Entry 1). In the first of these reactions a higher residence time was achieved by decreasing the substrate flow rate (Table 21, Entry 2) and in the second reaction two consecutive reactors were used instead of one (Table 21, Entry 3).

Table 21: Effect of residence time, reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dimethyl maleate excess</th>
<th>Temperature /Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Ru/SiO₂)</th>
<th>TON (total/cross) after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>50/100</td>
<td>0.15</td>
<td>0.018</td>
<td>2473/716</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>50/100</td>
<td>0.05</td>
<td>0.019</td>
<td>827/483</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>50/100</td>
<td>0.15</td>
<td>0.020</td>
<td>1198/235</td>
</tr>
</tbody>
</table>

By decreasing the flow rate the total conversion increased slightly compared to previous reactions, starting at 91% and decreasing to 73% after 6 h of reaction (Figure 64). Moreover, as was expected, the selectivity towards cross-metathesis was much better than in previous reactions.

![Figure 64: Methyl oleate and dimethyl maleate cross-metathesis at lower flow rate](image-url)
In the first sample recovered cross-metathesis accounted for 75% of the total conversion. Nevertheless, although the selectivity was higher towards cross-metathesis than towards self-metathesis it also decreased with time as in previous experiments, again being lower in the last of the samples taken. However, a higher rate of 58% cross-TON was achieved which is much better than the 16% cross-TON previously obtained at higher flow rates.

A second reaction was carried out where the residence time was increased using a different method. This time the same conditions as in a standard reaction were applied but two consecutive reactors were used instead of one, doubling the length of the reactor bed (Table 21, Entry 3).

Conversions started at 78% and decreased to 58% after 6 h of reaction (Figure 65) but, unlike in the previous reaction, increasing the residence time did not increase the selectivity towards cross-metathesis and a similar pattern as in standard reactions was observed with cross-metathesis slightly higher only in the first sample. After that self-metathesis was predominant and at the end of the reaction cross-metathesis accounted for only 19% of the total TON.

![Figure 65: Methyl oleate and dimethyl maleate cross-metathesis in 2 consecutive reactors](image)

2.2.3.2.12 Phase behaviour

Since the previous reactions with higher residence times gave unclear results the phase behaviour of the reaction was examined in more detail. In order to do this, the tubular reactor was exchanged for another reactor which incorporated a sapphire viewing window.
In the tubular reactor the substrates enter at the bottom and exit at the top (Figure 66), and in the sapphire window reactor substrates enter at the top via a dip tube that reaches the bottom of the reactor and exit at the top (Figure 67).

![Diagram of tubular reactor](image)

**Figure 66: Reactor flow scheme**

![Diagram of sapphire window reactor](image)

**Figure 67: Sapphire window reactor flow scheme**

With this reactor configuration the phase behaviour under the reaction conditions was recorded. A red LED with a battery was fixed inside the reactor to illuminate it. First the reactor was heated at 50 ºC and CO\textsubscript{2} flowed through at 100 bar in order to check the appearance of scCO\textsubscript{2}, which looked much like a boiling liquid filling all the volume of the reactor (Figure 68).

![Image of reactor with CO\textsubscript{2}](image)

**Figure 68: Reactor’s inside flowing CO\textsubscript{2} at 50 ºC and 100 bar**

![Image of reactor with substrate and CO\textsubscript{2}](image)

**Figure 69: Reactor’s inside flowing substrate and CO\textsubscript{2} at 50 ºC and 100 bar**
Next, the MO/DMM mixture was also flowed at a standard rate of 0.15 ml/min. To our surprise, different phase behaviour was observed when adding the substrate mixture and a liquid layer appeared at the bottom of the reactor after a few minutes (Figure 69), the reactor containing a mixture of a supercritical CO$_2$ phase rich in substrate plus a liquid substrate phase expanded by CO$_2$. The reaction conditions we had been using all along did not provide the supercritical environment we had supposed and, as the formation of the liquid layer in time matched the decrease of cross-metathesis in time we related one to the other. We propose then that cross-metathesis was inhibited in the expanded liquid layer while self-metathesis could still proceed.

With this suggestion in mind, we explored why cross-metathesis was predominant most of the time when the reaction was performed at a lower substrate flow rate. The phase behaviour of both MO and DMM was examined by feeding each separately at a flow rate of 0.15 ml/min observing in both cases the formation of a liquid layer. Then, the phase behaviour of the mixture was examined with a substrate flow of 0.05 ml/min and compared to that at 0.15 ml/min. A picture of the reactor’s inside was taken after 10 min flowing substrates at 0.15 ml/min (Figure 70) and compared with a picture of the reactor’s inside flowing substrates at a rate 3 times lower (0.05 ml/min) but at a time 3 times longer (30 min) (Figure 71).

As seen in both pictures, the same amount of liquid was formed indicating that lower flow rates, which means lower substrates flows, did not allow for a better solubility of substrates in the scCO$_2$. Therefore the only difference was that at lower flow rates the liquid layer (cross-metathesis inhibitor) took more time to build up allowing cross-metathesis to carry on for a longer time. Therefore the reaction profile at lower flow rate represents an expansion of
the one at higher flow rate as seen in Figure 72. That means that the selectivity we saw in the first hour using a flow rate of 0.15 ml/min (plain square in Figure 72) was similar to that obtained at a rate 3 times lower (0.05 ml/min) but at a time 3 times longer, thus at the 3rd hour. Consequently the selectivity observed in the 2nd hour using a flow rate of 0.15 ml/min (dashed square in Figure 72) was similar to the one at the 6th hour using a flow rate of 0.05 ml/min.

In conclusion the decrease of substrate flow represents an improvement on the reaction selectivity but not a solution since the cross-metathesis, despite the lower rate, is still inhibited.

2.2.3.3 Dimethyl maleate and 2-octene cross-metathesis

From the results discussed above, DMM seems to be the cause of the not very successful cross-metathesis with MO since the cross-metathesis of the later with 2-octene gave very
good stable results. In order to check if that was the case, cross-metathesis of DMM with 2-octene was performed (Scheme 25) and was expected to be similar to the cross-metathesis between MO and DMM.

\[
\text{Scheme 25: Dimethyl maleate and 2-octene cross-metathesis}
\]

The reaction was carried out under standard conditions of 50 °C and 100 bar of pressure with a mixture DMM/2-octene (4 : 1) at a flow rate of 0.1 ml/min over 4.4 g of a SILP catalyst containing 0.022 wt% Ru/SiO\(_2\) and 29 wt% BMIM NTf\(_2\)/SiO\(_2\).

The total conversion was not very high with values around 50% (Figure 73). As expected the selectivity towards cross-metathesis was lower than that towards self-metathesis and decreased with time accounting for only 265 out of the 1701 total TON.

\[
\text{Figure 73: Dimethyl maleate and 2-octene cross-metathesis at ratio (4 : 1)}
\]

Similar behaviour was observed when repeating the reaction also at 50 °C and 100 bar but with a mixture DMM/2-octene (8 : 1) over 4.4 g of a SILP catalyst containing 0.019 wt% Ru/SiO\(_2\) and 29 wt% BMIM NTf\(_2\)/SiO\(_2\).

The conversion was slightly higher than in the previous reaction, starting at 83% and decreasing to 39% after 6.5 h of reaction (Figure 74). Selectivity towards cross-metathesis was again lower than the selectivity towards self-metathesis and accounted for only 308 out of the 1737 total TON.
It seems clear after these experiments that DMM was responsible for the change in selectivity in its cross-metathesis reaction with MO.

### 2.2.3.4 Methyl oleate and methyl acrylate cross-metathesis

Since DMM lowered selectivity in cross-metathesis with MO, methyl acrylate (MA) was used as an alternative and its cross-metathesis with MO carried out. MA, unlike DMM, is not symmetric around its double bond and therefore 8 possible products can be formed from its cross-metathesis with MO (Scheme 26).

![Scheme 26: Methyl oleate and methyl acrylate cross-metathesis](image-url)
The reaction was carried out under standard conditions of 50 ºC and 100 bar with a mixture MO/MA (1 : 8) at a flow rate of 0.15 ml/min over 4.4 g of a SILP catalyst containing 0.022 wt% Ru/SiO$_2$ and 28 wt% BMIM NTf$_2$/SiO$_2$.

The conversion that started at 61% increased to 85% in the second hour but decreased abruptly to 0 after 2 more hours (Figure 75). This is due to the fact that MA is a terminal alkene, which we already concluded in Sections 2.2.1 and 2.2.2.1, degrade the Ru catalyst via formation of methylidene species which dimerise to form inactive Ru catalysts. Besides only a low selectivity towards cross-metathesis was observed in the first hour that accounted only for 5 out of the 631 total TONs.

![Figure 75: Methyl oleate and methyl acrylate cross-metathesis](image)

### 2.2.3.5 Implications of the phase behavior

As we previously saw in the phase behavior for the metathesis reactions a supercritical phase was not present under the standard conditions of 50 ºC and 100 bar. Instead, two phases were observed, a CO$_2$ expanded liquid phase containing the substrates and products and a CO$_2$ gas phase (Figure 76). Thus, the distribution of the substrates into the IL and CO$_2$ layers could control the selectivity of the reaction as we propose next. A similar phase behavior is expected for hydrogenation reactions.
Initially the IL phase contains only CO₂. Once the flows are switched on, both DMM and MO will be partially taken up by the IL and CO₂, and the expanded liquid phase will contain both. As the reaction proceeds the proportion of MO self-metathesis products in the expanded liquid and IL phases will increase. If the build up of self-metathesis products causes the DMM to partition more favourable into the liquid phase (or less favourably into the IL phase containing self-metathesis products), the concentration of DMM in the IL phase where the catalyst resides will decrease so the rate of cross-metathesis will also decrease. The amount of cross metathesis product would then decrease as the amount of self metathesis products increases.

2.2.4 Conclusions and further work

We have described in this chapter the first catalytic system that allows continuous flow metathesis using a homogeneous catalyst. It involved a boomerang catalyst with an imidazolium tag on the reactive carbene. With terminal alkenes as substrates, a rapid decrease in activity was observed due to catalyst degradation. As long as the double bonds in the alkenes were not terminal high reactivity was observed over at least 10 h. However, a slight fall off in activity with time on stream suggested some catalyst instability.

Total turnover numbers higher than 10,000 were possible over 9 h, with the products containing low ruthenium and ionic liquid content. In the most favourable cases, 6 g of substrate per hour could be converted to an equilibrium mixture of products in a 9 cm³ reactor.
Complete conversion was obtained using batch conditions in the cross-metathesis of methyl oleate and dimethyl maleate when carried out in the ionic liquid OMIM NTf$_2$ with a catalyst loading of 0.2 mol%. Higher selectivity was observed initially towards kinetic self-metathesis products but was totally inverted during the reaction to favour the thermodynamic cross-metathesis products.

Under flow conditions an initially reasonable activity towards the cross-metathesis products dropped rapidly whilst the self-metathesis of methyl oleate continued. Studies on the effect of different reaction parameters gave important conclusions:

- the ionic tag on the catalyst reduces its leaching
- scCO$_2$ avoids IL leaching, which on the other hand was quantitative when the reaction was performed under nitrogen flow
- trans alkenes give poorer results than cis ones due to a more hindered approach to the catalytic species
- higher selectivity towards cross-metathesis was found at lower flow rates

Further observations on the phase behaviour confirmed that at the reaction conditions of 50 °C and 100 bar of pressure two phases are present, a supercritical phase and an expanded liquid phase which we propose is a cross-metathesis inhibitor. If this is the case, the higher selectivity to cross-metathesis at low flow rates derives from the slower formation of the liquid phase at these lower rates.

Cross-metathesis of methyl oleate and 2-octene was successful in continuous flow with stable conversions around 90% and selectivity to cross-metathesis accounting for 67% of the total conversion.

Dimethyl maleate proved to be responsible for the decrease in cross-metathesis selectivity as it also did not work well when metathesised with 2-octene.

Overall, we have developed a green system for alkene metathesis that allows the products to be obtained with high yields and with very low metal contamination. No solvent is present in the collected product and the only purification needed is fractional distillation of the equilibrium mixture of products.
Further work can be done to establish the phase diagram of the mixture methyl oleate/dimethyl maleate. Furthermore, different diesters should be tested in order to replace dimethyl maleate which seems to be the cause of the cross-metathesis selectivity decrease.
2.3 NOTES AND REFERENCES


Chapter 3

Methoxycarbonylation reactions
Methoxycarbonylation reactions

Carbonylation reactions involve the introduction of carbon monoxide (CO) into an organic or inorganic compound. The reaction has a 100% atom economy with no waste since all the atoms present in the substrates are combined to form the final carbonyl products. The carbonyl products that arise from carbonylation reactions include carboxylic acids, aldehydes, esters, lactones, ketones, amides, carbamates, etc. and constitute the most important functional group in organic chemistry due to their reactivity. Carbonylation reactions of alkenes involve regiochemistry (branched / linear products) and stereochemistry (r/s chiral carbons) giving rise to a vast number of possible products. Some of the most common carbonylation reactions are presented in Table 22.

Table 22: Different carbonylation reactions

<table>
<thead>
<tr>
<th>Carbonylation reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monsanto Process</td>
<td>CH$_3$OH + CO $\rightarrow$ CH$_3$COOH</td>
</tr>
<tr>
<td>Hydroformylation</td>
<td><img src="image" alt="Hydroformylation Reaction" /></td>
</tr>
<tr>
<td>Hydroxycarbonylation</td>
<td><img src="image" alt="Hydroxycarbonylation Reaction" /></td>
</tr>
<tr>
<td>Alkoxy carbonylation</td>
<td><img src="image" alt="Alkoxy Carbonylation Reaction" /></td>
</tr>
<tr>
<td>Alkyne carbonylation</td>
<td><img src="image" alt="Alkyne Carbonylation Reaction" /></td>
</tr>
<tr>
<td>Copolymerisation with olefins</td>
<td><img src="image" alt="Copolymerisation Reaction" /></td>
</tr>
<tr>
<td>Pauson-Khand reaction</td>
<td><img src="image" alt="Pauson-Khand Reaction" /></td>
</tr>
</tbody>
</table>

3.1 HISTORY

The carbonylation reaction dates as far back as the 1930s when Otto Roelen discovered the hydroformylation reaction between ethylene and synthesis gas (syngas), an equimolecular mixture of CO and H$_2$, to produce propanal$^2$ and Walter Reppe discovered the hydroxy and
alkoxycarbonylation reactions of acetylene, using CO and compounds with one reactive hydrogen atom to produce $\alpha$-$\beta$ unsaturated carboxylic acids and their derivatives.$^3$

Since the work of this chapter of the Thesis is based on alkoxycarbonylation reactions I will focus on their development from the first applications to date, leaving aside the hydroformylation and hydroxycarbonylation reactions.

In the early years alkoxycarbonylation reactions were performed under drastic conditions ($>200$ atm, $>200$ °C) with catalytic systems based on nickel or cobalt metals. These high pressures and temperatures on the other hand also promoted unwanted side reactions. For industrial applications and in order to avoid side reactions, milder conditions were required and therefore different catalytic systems had to be envisaged. Although milder reaction conditions were shortly found with nickel$^4$ and cobalt$^5$ catalysts, the focus on the catalyst choice turned to the, less toxic palladium catalysts which were highly active at low temperatures, with the first examples published in the 1960s by researchers at BASF in Germany$^6$ and Toyo Rayon in Japan.$^7$

The next breakthrough in alkoxycarbonylation reactions came in the 1980s when Drent and co-workers at Shell introduced palladium catalytic systems bearing phosphine ligands. The success of this discovery led Shell to file a large number of patents in the field.$^8$-$^{17}$ These catalysts nowadays represent the state of the art due to their high activity and easy tuneability of phosphines.

Two mechanisms$^{18}$ have been proposed for alkoxycarbonylation reactions. (Scheme 27)
The mechanism can start either from a hydrido-palladium species (cycle A) or carboalkoxy-palladium species (cycle B). In the latter, the first step involves alkene insertion into the Pd-C bond of the carboalkoxy complex bond followed by alcoholysis to give an alkoxy-palladium complex and the final ester products. Then coordination of a CO molecule followed by migratory insertion regenerates the initial carboalkoxy-palladium complex. In the hydride cycle, the first step involves alkene insertion into the Pd-H bond to give an alkyl complex followed by coordination and migratory insertion of a CO molecule to yield an acyl species. Then alcoholysis of the Pd-acyl regenerates the initial Pd-hydrido species and produces the final ester products.

Later Tooze et al. found evidence that when the ligand used was 1,2-bis(di-tert-butylphosphinomethyl)benzene (BDTBPMB) the reaction followed the hydride mechanism pathway in methoxycarbonylation reactions of ethylene via statistically designed experiments coupled with HPLC-MS and deuterium labelling.¹⁹, ²⁰

The choice of phosphine ligand plays a crucial role in the activity and selectivity towards linear or branched products. Generally, for linear terminal alkenes, monodentate phosphines favour the branched products while bidentate phosphines favour the linear ones.²¹ There are exceptions to this general behaviour as Sugi et al.²² and van Leeuwen et al.²³ reported. The former showed how the catalyst PdCl₂(Ph₂P(CH₂)₉PPh₂) with a diphosphine ligand gave different regioselectivities depending on the length of the alkyl chain and the latter showed how the introduction of electron withdrawing substituents onto the diphosphine ligands inverted the regioselectivity towards branched products. Despite the growing number of mechanistic studies the cause for the regioselectivity has not yet been established.²⁴

One of the most important bidentate phosphine ligands and the one used in our experiments is 1,2-bis(di-tert-butylphosphinomethyl)benzene (DTBPMB)(Scheme 28).

Scheme 28: DTBPMB ligand

This ligand, originally reported by Moulton et al.,²⁵ was later complexed with Pd and showed outstanding activity (> 50,000 TOF) when treated with a sulfonic acid co-catalyst (MeSO₃H)
in the methoxycarbonylation of ethylene. Furthermore, selectivity higher than 99% was found favouring the linear products over formation of CO/ethylene copolymers and oligomers. Variations of this ligand with electron releasing or electron withdrawing groups incorporated into the benzene ring showed no significant effect on its catalytic performance.

This catalytic system patented by Lucite is used in the first step of their “Alpha process” (Scheme 29) to produce methyl propionate. In the second step of this process the condensation of methyl propionate with formaldehyde produces methyl methacrylate (MMA), an essential building block for acrylic based products with an annual demand of 3 million t/annum.

Lucite with an actual production of 120 mt of MMA per annum and with another plant under construction with a capacity of 250 mt/annum, is the world leading manufacturer of MMA.

The DTBPMB ligand not only shows an astonishing performance in alkoxycarbonylation reactions but also in the tandem isomerisation-alkoxycarbonylation reactions as reported by Jimenez et al.

They showed not only that the methoxycarbonylation of 1-octene yields methyl nonanoate with high activity (97.8% conversion) and selectivity (99%) at 1 bar and 25 °C in a 3 h reaction, but also that they could arrive at the same product starting from the 1-octene isomers (2-, 3- and 4-octene) with similar levels of activity (> 95% conversion) and selectivity (> 94%) (Scheme 30).
These results proved that a catalytic system composed of Pd/DTBPMB isomerised the double bond along the alkyl chain and that it was selectively methoxycarbonylated only in the terminal position. A mechanism for this transformation was proposed in the same paper (Scheme 31).

Scheme 31: Isomerisation-methoxycarbonylation mechanism

The scope of this catalytic system was later expanded by the same group to oleochemicals’ isomerisation-methoxycarbonylation (Scheme 32) and alkyne dicarbonylations (Scheme 33) to produce α,ω-diesters.

Scheme 32: Oleochemicals isomerisation-methoxycarbonylation

The selectivity of the Pd/DTBPMB system was higher than 95% towards the linear product in the methoxycarbonylation of these oleochemicals regardless of whether the double bond was deep in the alkyl chain or even conjugated to the carbonyl group. The substrates with more than one double bond were also believed to yield the saturated diester by means of carbonylation and transfer hydrogenation of the remaining double bonds, although a subsequent study has called this result into question.31
In the case of aliphatic alkyne carbonylation they found that $\alpha,\beta$-unsaturated esters were produced after short reaction times and then by isomerisation-methoxycarbonylation were converted into $\alpha,\omega$-diesters with high yields and selectivities.

Carbonylation reactions have proven to be a successful alternative in carbon-carbon bond forming reactions, which have been widely studied and even rewarded with several Noble prizes throughout history. These include the prizes in 1912 to Victor Grignard and Paul Sabatier, in 1950 to Otto Diels and Kurt Alder, in 1979 to Herbert Brown and Georg Wittig, in 2005 to Yves Chauvin, Robert Grubbs and Richard Schrock and in 2010 to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.
3.2 RESULTS AND DISCUSSION

This chapter is based on the results obtained during one year of research on the subject. The aim was to find optimal conditions for the continuous flow methoxycarbonylation of simple terminal alkenes such as 1-octene and transfer them to a more challenging substrate such as methyl oleate where an isomerisation-methoxycarbonylation could be performed.

Unfortunately, most of the experiments carried out did not work even with 1-octene and therefore the transition to more challenging substrates was never carried out. Furthermore, the lack of positive results made it very difficult to generate conclusions suitable for publication.

After one year of frustrating results the project was dropped. Due to the amount of time invested on this project and even if the results were not very successful a summary of them is presented in this chapter.

The methoxycarbonylation of 1-octene (Scheme 34) was previously studied in our group and the optimal conditions founded for batch systems.\textsuperscript{28} These were 80 °C and 30 bar of CO with a catalyst composed of Pd\(_3\)(dba)\(_3\) precursor, DTBPMB ligand and methanesulfonic acid (MeSO\(_3\)H) in a ratio (1 : 5 : 10). With a palladium loading of 0.8 mol% octene conversions higher than 95% were achieved after 3 hours with selectivity towards the desired linear product higher than 94%. These reaction temperature and catalysts ratios were used in our experiments unless otherwise stated.

![Scheme 34: 1-octene methoxycarbonylation](image)

In order to immobilise the catalyst into the IL for the preparation of SILP catalysts a backbone sulfonated version of the DTBPMB ligand\textsuperscript{32} (Figure 77) was prepared and tested in the methoxycarbonylation of 1-octene.

![Figure 77: Sulphonated DTBPMB](image)
3.2.1 Gas uptake reactions

The first experiments were done in a special autoclave in which the internal pressure could be maintained by feeding gas from a ballast vessel. The autoclave was charged with the starting materials 1-octene and methanol in a ratio (1 : 5) and the catalyst system composed of \( \text{Pd}_2(\text{dba})_3 \), the backbone sulphonated DTBPMB ligand 4 and \( \text{MeSO}_3\text{H} \) in a ratio (1 : 5 : 10). Then the autoclave was heated to 80 °C and 30 bar of CO were added. A pressure controller injected the CO needed to maintain the pressure constant at 30 bar from a ballast vessel, the pressure of which was recorded electronically.

First a reaction was carried out at a low catalyst loading of 0.02 mol% with the sulfonated ligand 4 (Figure 78) and compared to the same reaction using the original DTBPMB ligand (Figure 79).

![Figure 78: 1-octene methoxycarbonylation with 0.02 mol% Pd loading and ligand 4](image)

![Figure 79: 1-octene methoxycarbonylation with 0.02 mol% Pd loading and DTBPMB](image)
The sulfonated ligand 4 showed similar but slightly higher activity than the DTBPMB ligand. However, at these low catalyst loadings the reaction took more than 15 hours to completion which would be incompatible with the continuous flow system since resident times are very much smaller. The linear selectivity was a remarkable 95% when using the sulfonated DTBPMB ligand 4 and 96% when using the simpler DTBPMB ligand.

Nevertheless, another reaction with ligand 4 at a much higher catalyst loading (1 mol%) and the same reaction conditions showed that the reaction was completed within an hour making this a more viable system for application in a continuous flow system. The linear selectivity in this case was a noteworthy 97%.

![Conversion vs. Time Plot](image)

**Figure 80: 1-octene methoxycarbonylation with 1 mol% Pd loading and 4**

### 3.2.2 Continuous flow reactions

The experiments were carried out in a continuous flow system where the pure substrates (previously distilled and passed through an alumina column) and scCO$_2$ flowed through the SILP catalyst bed (the continuous flow system will be explained in detail in Section 6.4). Samples were collected each hour and the products analysed by GC-MS, $^1$H and $^{19}$F NMR to check conversion, linear to branch ratio (L/B) and both IL and catalyst leaching.

The first experiment was carried out at 80 °C and 100 bar. A mixture of 1-octene and methanol (1 : 5) was flowed at a rate of 0.15 ml/min with CO at a rate of 0.05 l/min over 4.4 g of SILP containing 29 wt% of BMIM NTf$_2$ and a mixture of catalyst precursor (Pd$_2$dba$_3$), sulfonated DTBPMB ligand 4 and MeSO$_3$H acid in a ratio (1 : 5 : 10) with a catalyst loading of 0.1 wt% Pd/SiO$_2$. 

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The reaction outcome was not satisfactory as seen in Figure 81. The majority of the conversion corresponded to isomerised 1-octene and the products accounted for only 6% of conversion. Nevertheless, conversion to products showed an excellent regioselectivity higher than 95% towards the linear products.

![Figure 81: 1-octene methoxycarbonylation](image)

In subsequent reactions the alteration of different parameters such as methanol excess, pressure, substrate flows and CO flows was studied. Unfortunately, none of them showed an improvement in the reaction profile and most of them only produced 1-octene isomerisation. From this point the sulfonated DTBPMB ligand 4 was not used anymore and the more simple DTBPMB ligand was used instead.

A different IL (OMIM NTf₂) was used in the following reactions but no improvement was obtained. A reaction was also made without any IL at all. The catalyst leached out of the system in this case and no conversion to products was observed. Other reactions were made without acid or with an acidic IL 5 (Figure 82) as the source of the acid but did not show any conversion either.

![Figure 82: Acidic IL](image)
Reactions with 30 bar of CO and without CO\textsubscript{2} were also tried but did not show any conversion.

### 3.2.3 Batch reactions

Since all the previous experiments did not work in a satisfactory way, the methoxycarbonylation of 1-octene was studied in batch systems in order to find better conditions in less time that it would take for the continuous flow reactions.

**Table 23: 1-octene methoxycarbonylation reactions in batch**

<table>
<thead>
<tr>
<th>Entry</th>
<th>OMIM/BMIM (g)</th>
<th>SiO\textsubscript{2} (g)</th>
<th>Pd/ligand/acid</th>
<th>Pd (% oct)</th>
<th>T\textsuperscript{a} (ºC)</th>
<th>P\textsubscript{CO} (bar)</th>
<th>P\textsubscript{CO\textsubscript{2}} (bar)</th>
<th>P\textsubscript{after heating} (bar)</th>
<th>Total conversion (%)</th>
<th>To product (%)</th>
<th>linear (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.32</td>
<td>1</td>
<td>1:4.2:7.6</td>
<td>0.13</td>
<td>80</td>
<td>30</td>
<td>40</td>
<td>140</td>
<td>87</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.33</td>
<td>-</td>
<td>1:5.2:9.8</td>
<td>0.09</td>
<td>80</td>
<td>30</td>
<td>50</td>
<td>155</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.32</td>
<td>-</td>
<td>1:4.7:9.2</td>
<td>0.11</td>
<td>80</td>
<td>30</td>
<td>50</td>
<td>160</td>
<td>28</td>
<td>34</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>1:3.4:6.2</td>
<td>0.17</td>
<td>80</td>
<td>30</td>
<td>20</td>
<td>70</td>
<td>98</td>
<td>34</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>1:3.3:0.0</td>
<td>0.17</td>
<td>80</td>
<td>30</td>
<td>30</td>
<td>80</td>
<td>57</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>1</td>
<td>1:6.1:10.9</td>
<td>0.10</td>
<td>80</td>
<td>30</td>
<td>35</td>
<td>95</td>
<td>71</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.32</td>
<td>-</td>
<td>1:5.2:10.3</td>
<td>0.11</td>
<td>80</td>
<td>30</td>
<td>20</td>
<td>60</td>
<td>97</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>0.32</td>
<td>-</td>
<td>1:4.3:8.6</td>
<td>0.12</td>
<td>80</td>
<td>30</td>
<td>20</td>
<td>60</td>
<td>97</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>0.29</td>
<td>1</td>
<td>1:5.0:9.8</td>
<td>0.11</td>
<td>80</td>
<td>30</td>
<td>20</td>
<td>70</td>
<td>52</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>0.31</td>
<td>1</td>
<td>1:4.4:7.4</td>
<td>0.14</td>
<td>80</td>
<td>30</td>
<td>20</td>
<td>65</td>
<td>97</td>
<td>9</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>0.27</td>
<td>1</td>
<td>1:4.3:7.4</td>
<td>0.13</td>
<td>80</td>
<td>50</td>
<td>-</td>
<td>60</td>
<td>96</td>
<td>10</td>
<td>93</td>
</tr>
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<td>0.31</td>
<td>1</td>
<td>1:4.0:7.4</td>
<td>0.14</td>
<td>120</td>
<td>50</td>
<td>-</td>
<td>115</td>
<td>97</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>0.29</td>
<td>1</td>
<td>1:5.1:9.6</td>
<td>0.10</td>
<td>120</td>
<td>30</td>
<td>-</td>
<td>45</td>
<td>96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>0.02 acid</td>
<td>-</td>
<td>1:6.3:4.5</td>
<td>0.09</td>
<td>80</td>
<td>45</td>
<td>-</td>
<td>60</td>
<td>98</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td>0.31 + 0.052 acid</td>
<td>1</td>
<td>1:5.2:10.2</td>
<td>0.11</td>
<td>80</td>
<td>45</td>
<td>-</td>
<td>55</td>
<td>97</td>
<td>15</td>
<td>95</td>
</tr>
</tbody>
</table>
All reactions were done in an autoclave. The substrates 1-octene and methanol were added in a ratio 1 : 5 and the catalyst precursor Pd$_2$(dba)$_3$ was added at a loading of 0.1 mol% Pd/1-octene. The DTBPMB ligand and the acid (either MeSO$_3$H or acidic IL 5) were added in ratios of 5 and 10 respectively relative to Pd. Silica was added when required at a ratio 0.1 wt% Pd/SiO$_2$. The IL, either BMIM NTf$_2$, OMIM NTf$_2$ or the acidic IL 5 were added at a loading of 29 wt% of SiO$_2$ when required. For the Entries 1 and 2 in Table 23 all the components of the reaction (1-octene, methanol, Pd$_2$(dba)$_3$ precursor, DTBPMB ligand, acid, IL and silica) were charged in situ, the desired pressure of CO and CO$_2$ added and the autoclave heated to the desired temperature. For the rest of reactions, (Table 23, Entries 3 - 15) all the components were previously mixed in a Schlenk to form the active catalyst and then transferred to the autoclave. The desired pressure of CO and CO$_2$ was added and the autoclave heated to the desired temperature. All the reactions were stopped after 1 h.

Studies were made of whether the absence or presence of BMIM NTf$_2$, OMIM NTf$_2$, silica or CO$_2$ had any influence on the reaction, but no apparent correlations were observed. The use of acidic IL 5 as the source of acid was also tested and the particular reaction where 5 was used without any other IL added (Table 23, Entry 14) gave the best conversion to products.

After analysing all the samples one noticeable conclusion was that all the reactions that gave some conversion to products (Table 23, Entries 4, 7, 8, 10, 11, 14, 15) had in common that the final pressure after heating the autoclave was in the short range at 55 - 70 bar, indicating that the reaction might be pressure dependant.

### 3.2.4 Continuous flow reactions at lower pressures

Since the best conversions in batch systems were achieved at pressures between 55 bar and 70 bar, the next reactions in continuous flow were carried out in this range of pressures. Given that these pressures lay below the critical pressure of CO$_2$ (73.8 bar), the reactions were carried out in a liquid phase. The 1-octene/methanol ratio in these reactions was around 1 : 10 and the mixture was pumped at a rate of 0.05 ml/min in all of them. The Pd loading was 0.1 wt% of SiO$_2$ and the IL used was BMIM NTf$_2$ at a loading of 29 wt% of SiO$_2$ throughout all the reactions.
Methoxycarbonylation reactions

The first two reactions were carried out at 60 bar of CO pressure and without CO$_2$ (Table 24, Entries 1 and 2). The acidic IL 5 was the source of acid in both reactions which were only distinguished by the reaction temperature.

### Table 24: 1-octene methoxycarbonylation at low pressures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid source</th>
<th>Temperature</th>
<th>CO$_2$ Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acidic IL</td>
<td>80</td>
<td>60*</td>
</tr>
<tr>
<td>2</td>
<td>Acidic IL</td>
<td>100</td>
<td>60*</td>
</tr>
<tr>
<td>3</td>
<td>Acidic IL</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Acidic IL</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>MeSO$_3$H</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>MeSO$_3$H</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>MeSO$_3$H</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

* Without CO$_2$, the pressure was reached only with CO

The best results were obtained when the reaction was run at 80 ºC (Figure 83). The conversion started at 85% and decreased to 33% after 9 hours. Abundant IL leaching was observed in the products which may be the reason for the decrease in conversion. The SILP initially yellow became white by the end of the reaction confirming IL and catalyst leaching.

![Figure 83: 1-octene methoxycarbonylation at 60 bar CO and 80 ºC](image-url)
Nevertheless, for the first time significant conversion towards the products was achieved and this ranged between 74 and 52% of the total conversion. Furthermore, the selectivity towards the desired linear regioisomer was constant at 96% throughout all the reaction.

When the reaction was run at 100 °C (Figure 84) the total conversion was constant around 90% and decreased to 82% in the last sample, which is better than when the reaction was done at 80 °C. However, the conversion towards the methoxycarbonylation products ranged between 49 and 10% of the total conversion which is lower than the previous reaction and the linear selectivity achieved (94%) was lower too. IL leaching in the products did also occur and at the end of the reaction the SILP catalyst was dark grey indicating catalyst decomposition and formation of Pd(0).

![Figure 84: 1-octene methoxycarbonylation at 60 bar CO and 100 °C](image)

Next, a reaction was carried out also at 80 °C and 60 bar of pressure, but the pressure was reached with CO$_2$ and CO was flowed at a rate of 0.2 l/min (Table 24, Entry 3). The acidic IL 5 was used as the source of acid and Pd(dba)$_2$ was used as Pd precursor. The total conversion started at 80% and decreased to 60% afterwards where it remained stable (Figure 85). The conversion towards methoxycarbonylation products increased during reaction ranging from 2% to 59% of the total conversion and the linear selectivity increased from 85% to 94%. IL leaching was detected in the two last samples where the conversion to products was higher indicating that the polar ester products are miscible with the IL causing its leaching when working in a liquid phase at lower pressure than the critical pressure of CO$_2$. That presents a dilemma, since at high pressure where a supercritical phase is in place.
and the IL is more insoluble in the reaction medium, the reaction does not proceed (See section 3.2.2).

For the next reaction (Table 24, Entry 4) the pressure was raised to 70 bar of CO$_2$ with the rest of the conditions being similar to those of the previous reaction. The increase of just 10 bar of pressure had a deleterious effect on the reaction outcome. The conversion had a maximum value of 20% which corresponded only to isomerised 1-octene with no sign of products observed in the collected samples (Figure 86). On the other hand, the IL leached from the reaction and could be observed in the collected samples.
This last reaction was repeated with MeSO₃H as the source of acid instead of the acidic IL 5 (Table 24, Entry 5). The total conversion started at 93% which is much higher than in the previous reaction (Figure 87). However, it decreased to 0 after 4 hours. As in the previous reaction, the conversion corresponded exclusively to 1-octene isomers.

![Figure 87: 1-octene methoxycarbonylation at 70 bar CO₂ pressure with MeSO₃H](image)

In the next reaction (Table 24, Entry 6), the Pd loading was increased to 1 wt% Pd/SiO₂ (Figure 88). The reaction was carried out at 70 bar of CO₂ pressure and with MeSO₃H as the source of acid. After the 5th hour the pressure was decreased to 60 bar (grey area) in order to check the reaction’s dependence on pressure.

![Figure 88: 1-octene methoxycarbonylation with 1 wt% Pd/SiO₂ at 70 bar and 60 bar CO₂ pressure](image)

The total conversion was almost quantitative during most of the reaction and decreased to 84% after 9 hours. At the beginning, when the pressure was set at 70 bar, the conversion to
methoxycarbonylation products built up until it was constant around 70% meanwhile the isomerisation decreased progressively to 28%. The selectivity towards linear products was constant at 94%. After the 5th hour, 10 bar of pressure were released from the reactor leaving the pressure at 60 bar, and consequently, a change in the products distribution was produced straight away. The conversion to products decreased and the isomerisation increased at the same time until both were in a similar range around half of the total conversion. Nonetheless, the decrease in conversion towards methoxycarbonylation products did not alter the selectivity towards the linear isomer which was still constant at 94%.

In the last reaction (Table 24, Entry 7), the previous SILP which gave interesting results at 70 bar was reused the next day at 70 bar throughout all the reaction (Figure 89).

![Conversion vs. time graph]

Figure 89: 1-octene methoxycarbonylation at 70 bar CO₂ pressure with previous SILP again

The total conversion in this case started at only 25% and decreased to 12% after 6 hours of reaction indicating catalyst decomposition. The conversion to methoxycarbonylation products started at 19% and decreased to 1% in the last sample whilst the isomerisation started at 6% but increased to 11%. Even if the linear selectivity was higher than 94% during all the reaction, the storage of the catalyst in the reactor overnight caused its degradation making it unsuitable for use in daily sequential reactions, which would be preferred to continuous reactions (day + night) for safety reasons.
3.2.5 Continuous flow reactions after the rig upgrade

From this point the rig was upgraded with a new CO₂ delivery pump and a back pressure regulator which allowed for better control of pressure and liquid CO₂ flow. The rig scheme will be explained in more detail in Section 6.5.1.

The first reaction was performed at 80 °C and 80 bar of CO₂, which is just over the critical pressure of CO₂ (73.8 bar). CO was added at a rate of 0.1 l/min, liquid CO₂ at a rate of 1 ml/min and the substrate mixture 1-octene/MeOH (1 : 10) at a rate of 0.05 ml/min. The total conversion started at 52% in the first recovered sample and decreased to 0 after 8 hours (Figure 90). The conversion towards methoxycarbonylation products started at 12% which represents 23% of the total conversion, and decreased progressively. This decrease of conversion was due to IL and catalyst leaching as observed in \(^{19}\)F, \(^{1}\)H and \(^{31}\)P NMR. The leaching of IL and catalyst suggests that the reaction medium was an expanded liquid phase and not a supercritical phase where leaching is avoided. The regioselectivity, as in previous reactions, was favourable to the linear products with percentages higher than 93%.

![Figure 90: 1-octene methoxycarbonylation at 80 bar CO₂ pressure](image)

Next, a reaction was performed at 70 bar of CO₂ pressure. The total conversion was higher than 98% during the 10 hours of reaction, but no traces of methoxycarbonylation products were found and the conversion corresponded only to isomerised octene. This reaction, same as the previous one, was performed with a catalyst loading of 0.1 wt% Pd/SiO₂. Thus, the next reaction was performed also at 70 bar but with a higher catalyst loading of 1 wt% Pd/SiO₂ (Figure 91).
CO was added at a rate of 0.05 l/min, liquid CO$_2$ at a rate of 2 ml/min and the substrate mixture at a rate of 0.05 ml/min. The total conversion was higher than 90% during the first 5 hours but it corresponded mainly to isomerised octene, the conversion to methoxycarbonylation products being only around 3% of the total conversion. After the 5$^{th}$ hour the first change ① was made in the reaction where the CO flow was increased to 0.2 l/min and the substrate flow decreased to 0.025 ml/min. As a result the total conversion decreased to values around 20% and the conversion towards methoxycarbonylation products increased to 40% of the total conversion. After the 7$^{th}$ hour another change ② was made, where the CO flow was decreased back to a rate of 0.05 l/min and the pressure was increased to 150 bar of CO$_2$. As a result in the 8$^{th}$ hour the total conversion remained stable whereas the conversion towards methoxycarbonylation products increased to 75% of the total conversion. This increase arises from the first change ① since in the 9$^{th}$ hour the conversion to products dropped to 18% which is the consequence of being in a supercritical phase after change ②. This is consistent with previous reactions where it was shown that conversion to products was not observed in supercritical conditions. After the 9$^{th}$ hour the last change ③ was made where the liquid CO$_2$ flow rate was decreased to 1 ml/min. As a consequence, the total conversion increased to 93% which corresponded exclusively to isomerised octene. Despite all the changes during the reaction the regioselectivity remained higher than 93% favouring the linear products.
Two further reactions were performed under supercritical conditions at 80 ºC and 150 bar or 100 bar showing full conversion to isomerised octene.

All the previous reactions were run using a mixture 1-octene/MeOH (1 : 10). Due to the low conversion towards products in supercritical conditions, the 1-octene/MeOH rate was increased to (1 : 25) for the next reactions.

Thus, the next reaction was carried out at 80 ºC, 150 bar of CO₂ pressure and a 1-octene/MeOH ratio of (1 : 29). For this reaction low flows were used in an attempt to increase the residence time of the substrates in the reactor. CO was added at a rate of 0.02 l/min, liquid CO₂ at 0.5 ml/min and the substrates mixture at 0.025 ml/min. The total conversion was higher than 94% throughout the reaction, but corresponded mainly to isomerised octene (Figure 92). The conversion to products was constant around 10% until the 6th hour, when the liquid CO₂ flow was increased to 1 ml/min. As a consequence the conversion to methoxycarbonylation products decreased to 0 a few hours later. The linear selectivity was higher than 90% throughout the reaction.

The next reaction was carried out with the same conditions as the previous reaction but with an increased CO flow rate of 0.05 ml/min instead of the previous 0.02 ml/min. The total conversion was constant at 97% throughout the reaction but again the 1-octene isomerisation was predominant (Figure 93). Nonetheless, the conversion to methoxycarbonylation products was higher than in the previous reaction reaching 20% after 4 hours, after which the CO flow was further increased to 0.1 l/min and as a consequence
the conversion to methoxycarbonylation products increased to 30% in the 8th hour. After this 8th hour the CO flow was decreased to 0.02 l/min (same value as in the previous reaction) and the next sample, taken two hours later, showed that the conversion to products decreased to 20% confirming the beneficial effect of higher CO flow rates. The linear selectivity was higher than 90% throughout the reaction.

Figure 93: 1-octene methoxycarbonylation at 150 bar CO₂ pressure and higher CO flow

In the next reaction, also performed at 150 bar of CO₂ pressure, the effect of the temperature was studied (Figure 94). The starting conditions were 80 °C and flow rates of 0.025 ml/min for the substrates, 0.5 ml/min for liquid CO₂ and 0.1 l/min for CO.

Figure 94: 1-octene methoxycarbonylation at 150 bar CO₂ pressure and different temperatures

In the first sample recovered after two hours the total conversion was 32% whereas the conversion to methoxycarbonylation products represented only 1% of the total conversion.
The CO flow was then increased to 0.2 l/min and as a consequence the next sample (4th hour) showed a small increase in conversion to 42%, the desired products comprising 5% of the total conversion. The temperature was then raised from 80 °C to 100°C. The outcome of this increase in temperature was a large increase in conversion from the previous 42% to 91%. The conversion towards methoxy carbonylation products also increased a little to reach 9% of the total conversion. Next, the temperature was further raised to 120 °C. The total conversion increased a little to 98% but most importantly, the conversion to methoxy carbonylation products increased from 9% to 17% of the total conversion. Finally, the temperature was raised to 140 °C. The total conversion remained stable but the conversion to methoxy carbonylation products decreased to 3% of the total conversion. Besides, the linear selectivity which was around 90% throughout the reaction decreased to 80% in the last sample due to the high temperature.

Another reaction was carried out afterwards at the optimal conditions of the previous reaction, namely 150 bar and 120 °C. The reaction showed a total conversion higher than 94% throughout the reaction but the conversion to methoxy carbonylation products could only be observed during the first sample with a value of 15%. All subsequent samples showed zero conversion.

We wondered if the catalyst deactivated during the time between when it was made until it was used for a reaction (usually next day). Therefore another SILP catalyst was made and used straight away. The reaction was carried out at 80°C and 150 bar of pressure with flow rates of 0.1 ml/min for the substrates, 2 ml/min for liquid CO\(_2\) and 0.3 l/min for CO. The total conversion started at 47%, increased to 69% in the 2nd hour and then decreased to 19% in the 4th hour (Figure 95). IL and catalyst leached from the reaction, possibly due to the high flows used, so this is probably the cause of the conversion decrease.
With exception of the first sample the conversion towards methoxycarbonylation products was constant between 9% and 5% and the regioselectivity higher than 96% favourable to the linear product.

This reaction was repeated but lowering the flow rates to 0.05 ml/min for the substrates mixture, 1 ml/min for liquid CO$_2$ and 0.2 l/min for CO in order to avoid leaching. Nevertheless, IL leaching was observed again suggesting that the contact time during the SILP preparation was not long enough so the IL remained adsorbed onto the silica, so this may also be the cause of the leaching in the previous reaction and not the higher flows.

3.2.6 Conclusions and further work

We can conclude that the methoxycarbonylation reactions in continuous flow proved to be a much more difficult process than the previous metathesis reactions. First, a much higher catalyst loading was needed to reduce the reaction times. As we saw in the gas uptake reactions, with catalyst loadings of 0.02 mol% more than 15 hours were needed for the reactions to finish. Increasing the catalyst loading to 1 mol% reduced the reaction time to 1 hour, a value more suited to the continuous flow system but still far from the less than 10 minutes that the metathesis reaction needed for completion at the same catalyst loading.

In the first continuous flow reactions under standard conditions of 80 °C and 100 bar of pressure we saw that the conversion was predominantly, if not exclusively, to 1-octene isomerised products. It was also shown that the presence of IL in the SILP system is essential, otherwise the catalyst leached out of the reactor very quickly. Several reactions
under different conditions showed no improvement in the conversion towards methoxycarbonylation products.

Several batch reactions were run in an attempt to find better conditions in a faster way. None of the studied parameters (absence or presence of either BMIM NTf₂, OMIM NTf₂, silica or CO₂) had any influence on the reaction, but when observing the results it was noticed that the reactions that gave the best results were performed over a short range of pressures between 55 and 70 bar, indicating that the reaction might be pressure dependent.

Further continuous flow reactions in that range of pressures gave the best conversions to methoxycarbonylation products. The best of all was obtained when using 60 bar of CO pressure without CO₂. The conversion to methoxycarbonylation products was greater than the isomerisation throughout all the reaction. Unfortunately, at this pressure and without CO₂ the reaction took place in a liquid phase and thus substantial IL and catalyst leaching were observed, causing a decrease in conversion and making this reaction unfeasible under continuous flow conditions.

In another reaction IL leaching was only detected in the samples where the conversion to products was substantial indicating that the polar ester products are miscible with the IL, causing its leaching when working in a liquid phase at lower pressure than the critical pressure of CO₂.

Also, the dependence on pressure was observed when altering the pressure from 70 to 60 bar in the middle of the reaction. The conversion towards methoxycarbonylation products, that was predominant at 70 bar, decreased straight away when the pressure was changed to 60 bar to a similar level as that of the isomerisation products.

Finally, some reactions were carried out at 150 bar of pressure and showed almost quantitative conversion with the products mainly composed of isomerised 1-octene. Conversion towards methoxycarbonylation products was increased a little by increasing the CO flow rate and by increasing the temperature to 120 °C. Further increases in temperature caused a decrease in the linear selectivity.
Although the results are not very encouraging, the catalyst system composed of Pd, DTBPMB ligand and acid showed an excellent linear selectivity, usually higher than 90%, both in batch and continuous flow reactions.

Further work may be done with even easier and more reactive substrates such as alkynes in order to find optimal conditions for the continuous reaction.
3.3 NOTES AND REFERENCES


2. O. Roelen, DE Pat No, 849548, 1938/1952.


17. E. Drent, Pat No, GB2240545A 1991 (Much more patents were issued at that time but they are omitted due to space issues).


Methoxycarbonylation reactions


Chapter 4

Asymmetric hydrogenation reactions
Asymmetric hydrogenation reactions

Hydrogenation reactions consist of the introduction of a hydrogen molecule into a multiple bond that leads to its reduction. They differ from protonation or hydride addition in the fact that the products have the same charge as the reactants. Different hydrogenation reactions are shown in Table 25.

Table 25: Different hydrogenation reactions

<table>
<thead>
<tr>
<th>Hydrogenation reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkene hydrogenation</td>
<td><img src="image" alt="alkene" /></td>
</tr>
<tr>
<td>Alkyne hydrogenation</td>
<td><img src="image" alt="alkyne" /></td>
</tr>
<tr>
<td>Aldehyde hydrogenation</td>
<td><img src="image" alt="aldehyde" /></td>
</tr>
<tr>
<td>Ketone hydrogenation</td>
<td><img src="image" alt="ketone" /></td>
</tr>
<tr>
<td>Ester hydrogenation</td>
<td><img src="image" alt="ester" /></td>
</tr>
<tr>
<td>Amide hydrogenation</td>
<td><img src="image" alt="amide" /></td>
</tr>
</tbody>
</table>

Hydrogenation reaction products range from alkanes to alcohols or amines depending on the starting materials employed. Usually they are performed with the help of a catalyst, although they can also be done in its absence but high temperatures and pressures are needed in these cases.

4.1 HISTORY

The first report of a catalysed hydrogenation dates as far back as 1897 when Paul Sabatier described how a stream of ethylene directed onto freshly reduced nickel at 300 ºC produced a gas that was mainly composed of ethane.¹ Hydrogen was generated by the partial decomposition of ethylene and transferred to the double bond of ethylene with the help of the nickel metal. Since then, the development of catalysts has played a crucial role in hydrogenation reactions. In 1927 Murray Raney patented the preparation of a finely divided...
nickel catalyst that was much more active than the best one at that time. This catalyst, known as Raney nickel, is still used nowadays for industrial applications such as margarine production.

The next breakthrough involved the switch to homogeneous catalysis and it came in 1966 when Sir Geoffrey Wilkinson published the preparation of the \([\text{RhCl}(\text{PPh}_3)_3]\) catalyst that bears his name. The possibility of incorporating chiral phosphine ligands into this catalyst opened the door for asymmetric catalysis of prochiral substrates.

This led to many studies focused on asymmetric hydrogenation reactions with Knowles et al. publishing in 1968 the first asymmetric hydrogenation reaction of \(\alpha\)-phenylacrylic acid with a rhodium complex bearing optically active tertiary phosphine ligands (Scheme 35).

\[
\text{Scheme 35: Asymmetric hydrogenation of } \alpha\text{-phenylacrylic acid}
\]

In 1983, Knowles summarised the expansion of the chiral phosphine ligands library that took place at that time (Figure 96). Nowadays, there are more than 3000 known chiral phosphine ligands.
In 1987 Ryoji Noyori wrote another chapter in the asymmetric hydrogenation history with the development of the chiral ligand BINAP (Figure 97) used for ketone, aldehyde and imine hydrogenations. A few years later, in 1991, Burk reported the preparation of 1,2-bis(phospholano)benzene (DuPhos) ligand. He showed how these ligands offered much better catalytic efficiency and enantiomeric excess than previous phosphine ligands. This type of ligand was used in our research, which concentrated on Rh-MeDuPhos 6 (Figure 98).

A close examination of the mechanism (Scheme 36) is necessary to understand how this catalyst induces enantioselectivity.
The mechanism was first published by Halpern in 1982 and consists of four steps:

1. substrate coordination to the solvated catalyst (the only reversible step),
2. oxidative addition of a hydrogen molecule to the catalyst,
3. migratory insertion of hydrogen to the β-carbon of the double bond,
4. reductive elimination that yields the product and a solvated catalyst molecule.

The key to the success of the mechanism lies in the reversible substrate coordination to the catalyst. The substrate coordinates via the carbonyl group and the C=C double bond in a $\eta^2$ fashion. The coordination of the C=C double bond leaves the adjacent CO$_2$R group pointing either up or down, and its interaction with the chiral ligand MeDuPhos provides the origin of the enantioselectivity. The complex MeDuPhos Rh (Figure 99) has four methyl groups on the cyclopentane-phosphine rings, two directed to the front (red) and two directed to the back.

![Figure 99: MeDuPhos Rh complex view with the benzene ring on the back](image)

The two methyl groups directed to the front (red) hinder any approach of substrates from the top-left and the bottom-right quadrants and are responsible for the enantioselectivity of the substrate binding. When the substrate coordinates with the CO$_2$R group pointing to the less hindered quadrants of the catalyst, it forms the more stable complex giving rise to the major enantiomeric complex. On the other hand when the substrate coordinates with the CO$_2$R group pointing to the more hindered quadrants, it forms the more unstable complex giving rise to the minor enantiomeric complex.

However, this is an example of an anti-lock and key mechanism where the less stable (Minor) complex is much more reactive than the more stable one and therefore yields the major product.
Another way to visualise this reactivity difference is David Cole-Hamilton’s interpretation⁹ as pictured in Figure 100 and Figure 101. One can imagine the metal centre surrounded by the ligand bulk (blue). When the substrate (in red) approaches in a less hindered fashion (Figure 100), both the ligand and the substrate surround completely the metal leaving no gaps for the further approach of hydrogen. On the other hand when the substrate approaches in a hindered fashion (Figure 101), it leaves a gap where the hydrogen can access easily and fast to initiate the reaction.

In this chapter we also report our studies on asymmetric hydrogenation with Rh-McDuPhos catalyst immobilised on Al₂O₃ via heteropoly acids (Figure 102). This immobilisation technique was reported first by Augustine et al. in 1999.¹⁰ Phosphotungstic acid (PTA) was the heteropoly acid used since it is more active and selective than other heteropoly acids such as phosphomolybdic acid (PMA), silicotungstic acid (STA) or silicomolybdic acid (SMA).¹¹
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The heteropoly acid coordinates both to the support and to the metal atom of the catalyst via its surface oxygen atoms. Since the ligands on the metal complex are not involved in the anchoring of the catalyst the chirality is not altered and the catalyst can be as active and selective as its homogeneous counterpart. Besides, there is no significant limitation on the type of ligands that may be used.

Asymmetric hydrogenation reactions have proven to be an easy and reliable method for synthesising chiral molecules. Great interest from the scientific community was placed on the development of chiral ligands, and as an outcome the Nobel Prize was awarded in 2001 to William Knowles and Ryoji Noyori for their contributions on this field. Barry Sharpless was also honoured at the same time because of his pioneering work on asymmetric oxidation reactions.
4.2 RESULTS AND DISCUSSION

The experiments were carried out in a continuous flow system where the substrates, hydrogen and scCO$_2$ flowed through the SILP catalyst bed (the continuous flow system will be explained in detail in Section 6.4). Samples were collected each hour and the products analysed by $^1$H NMR to check conversion, GC-FID (Mega-Dex DMP chiral column, 25m length, 0.25 id, 0.25 microns film thickness) to check the enantiomeric excess and $^{19}$F NMR and ICP-OES to check both IL and catalyst leaching respectively. A paper based on the results of this chapter is in preparation.

4.2.1 Gas uptake reaction

Before carrying out reactions in the continuous flow system, a batch reaction was made in a special autoclave in which the internal pressure, and therefore the H$_2$ consumption, could be monitored. The autoclave was charged with the starting material dimethyl itaconate (DMI, 1.81g, 11 mmol), purged with H$_2$ and dry MeOH (9 ml) added to dissolve the DMI. The autoclave was heated to 50 ºC and the pressure set to 12 bar of H$_2$. The catalyst (R,R)-Rh-MeDuPhos 6 (0.0069 g, 0.014 mmol, 0.1% of DMI) was dissolved in dry MeOH (1 ml) and added to the autoclave to start the reaction (Scheme 37). A pressure controller monitored the decrease of pressure in the autoclave and injected the H$_2$ needed to maintain the pressure constant at 12 bar from a ballast vessel. The reaction was followed by measuring the pressure drop in the ballast vessel from which hydrogen was being fed to the autoclave.

![Scheme 37: Dimethyl itaconate asymmetric hydrogenation](image)

Despite the low catalyst loading the reaction was finished in less than 5 min (Figure 103). This reaction time is much lower than that of metathesis and methoxycarbonylation reactions, suggesting that good conversions might be obtained if the reactions were carried out in continuous flow, since the residence times would be higher than the reaction time. Besides, GC analysis of the reaction products showed a significant e.e. of 94% favouring the (R) enantiomer.
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Figure 103: DMI asymmetric hydrogenation with Rh-MeDuPhos (0.1%) at 50 ºC and 12 bar H₂

4.2.2 Continuous flow reactions before the rig upgrade

As DMI is a solid at room temperature (m.p. = 37 ºC) it needs to be dissolved in a solvent in order to be introduced into the rig through the liquid pump. Alcoholic solvents are usually preferred\textsuperscript{13, 14} but in a continuous flow system they would also dissolve the IL causing its leaching along with the catalyst. Therefore, the less polar toluene was used as a solvent in the first continuous reactions (Table 26).

Table 26: DMI hydrogenation. Reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature/Pressure (ºC)/(bar)</th>
<th>Substrate flow (ml min(^{-1}))</th>
<th>H(_2) flow (L min(^{-1}))</th>
<th>Catalyst loading (wt% Rh/SiO(_2))</th>
<th>TON after 5 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>50/100</td>
<td>0.1</td>
<td>0.2</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>50/100</td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
<td>172</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>50/150</td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
<td>174</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>50/150</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>417</td>
</tr>
</tbody>
</table>

DMI was dissolved in a 2 fold excess of toluene and OMIM NTf\(_2\) was used in all SILP catalysts at a loading of 29 wt% IL/SiO\(_2\).
The first reaction (Table 26, Entry 1) was performed under similar conditions to those of the metathesis reactions, namely 50 °C, 100 bar of CO₂ pressure and substrate flow of 0.1 ml/min. Hydrogen was introduced into the rig at a flow of 0.2 l/min and a SILP with a high catalyst loading of 1 wt% Rh/SiO₂ was used.

High conversions were achieved as predicted from the batch reaction. The conversion in the continuous flow started at 99% and decreased to 78% after 7 hours (Figure 104). On the other hand the enantioselectivity was not as good as the 94% e.e. obtained in the batch reaction. In continuous flow the e.e. started at 16% and increased to 39% in the 7th hour. IL leaching was observed in the recovered samples (¹H and ¹⁹F NMR data) and is most probably the cause of the conversion decrease.

![Figure 104: DMI hydrogenation at 1 wt% Rh/SiO₂ loading](image)

As the conversions were high with a catalyst loading of 1 wt% Rh/SiO₂, in the next reaction (Table 26, Entry 2), the catalyst loading was decreased to 0.5 wt% Rh/SiO₂. The conversion in this case started at 95% and decreased to 75% (Figure 105) which is in the same range as with 1 wt% catalyst loading. The TON increased from 78 after 5 hours with catalyst loading of 1 wt% to 172 in the same time period with 0.5 wt% catalyst loading.

As before, the e.e. was also low starting at 11% and increasing to 30% in the 5th hour. IL leaching was also detected in the collected samples so may be the cause of the conversion decrease over time.
Since the IL leaching was believed to have caused the decrease in conversion and catalyst would be lost with it, IL leaching had to be avoided in order to obtain constant conversions. Leaching was reduced (Table 26, Entry 3) by increasing the pressure from 100 bar where an expanded liquid phase occurred, to 150 bar where a supercritical phase is present. Without IL leaching from the system the conversions were stable around 90% (Figure 106) and produced 174 TONs in 5 hours. The e.e. on the other hand did not show any improvement, ranging between 30% and 15%.

In the next reaction (Table 26, Entry 4), also performed at 150 bar of pressure, the catalyst loading was further decreased to 0.2 wt% Rh/SiO₂. Since IL did not leach in this case either, the conversions were stable but slightly lower (≈ 80%) than in the previous reaction. On the
other hand, the TON after 5 hours increased from 174 in the previous reaction with 0.5 wt% Rh/SiO₂ to a value of 417. Once again, the e.e.’s. were not high and stayed in a range between 28% and 16% (Figure 107).

![Figure 107: DMI hydrogenation at 0.2 wt% Rh/SiO₂ loading and 150 bar of pressure](image)

### 4.2.3 Continuous flow reactions after the rig upgrade

From this point the rig was updated with a new CO₂ delivery pump and a back pressure regulator which allowed for better control of pressure and liquid CO₂ flow. The rig scheme will be explained in more detail in Section 6.5.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>H₂ flow (L min⁻¹)</th>
<th>CO₂ flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Rh/SiO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>50/100</td>
<td>0.05</td>
<td>0.1</td>
<td>0.5</td>
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<tr>
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<td>MeOH</td>
<td>50/150</td>
<td>0.05</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>50/150</td>
<td>0.05</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The first reaction after the rig upgrade (Table 27, Entry 1) was carried out in MeOH as solvent at 50 °C and 100 bar of CO₂ pressure. As we previously predicted, MeOH dissolved the IL contained in the SILP catalyst causing its leaching. The conversion was very low and therefore the e.e. was not even measured (Figure 108).
The next reaction (Table 27, Entry 2) was also performed using MeOH as solvent but at higher pressure (150 bar) in an attempt to avoid IL leaching. However, IL leaching still occurred and only a small conversion was observed in the first sample (Figure 109), the rest of the samples being composed only of the starting material, DMI. Due to the low conversion the e.e.’s. of the samples were not analysed.

The next reaction (Table 27, Entry 3) was performed under the same conditions as the previous one but with DMI dissolved in toluene instead of MeOH. The IL did not leach this time from the reactor confirming that MeOH, which is the preferred solvent for batch reactions, is not compatible with continuous reactions using SILP catalysts. Nevertheless,
with toluene as solvent the conversions were also very low (Figure 110) and the e.e.’s. were again were not measured.

![Figure 110: DMI hydrogenation in toluene at 150 bar](image)

Since DMI is a solid at room temperature its hydrogenation has to be carried out in a solvent, but the miscibility of the solvent with ILs presents an extra problem when the reaction is carried out in continuous flow. In order to avoid this problem, the rest of the reactions were carried out with dibutyl itaconate (DBI) because, unlike DMI, DBI is liquid at room temperature and therefore no solvent is needed to pump it into the reactor.

### 4.2.4 Batch reactions with dibutyl itaconate

Dibutyl itaconate hydrogenation (Scheme 38) was first attempted in batch reactions where it was compared to DMI hydrogenation. Whether the IL or silica had any influence in the reaction was also checked.

![Scheme 38: Dibutyl itaconate asymmetric hydrogenation](image)

All reactions (Table 28) were done in an autoclave which was charged with a stirrer, DBI, silica (0.5 g) when required and BMIM NTf₂ (0.15 g) when used. The catalyst (0.1% DBI) was added and the mixture stirred until the catalyst was dissolved. Generally the catalyst
dissolved very fast in the samples which contained IL but did not dissolve completely in the ones that did not, forming a suspension. The desired pressure of H₂ and CO₂ was applied and the autoclave heated to the desired temperature. All the reactions were stopped after 1 h.

**Table 28: DBI batch hydrogenation conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>T° (°C) / (P_{H_2}) (bar) / (P_{CO_2}) (bar)</th>
<th>IL (g)</th>
<th>SiO₂ (g)</th>
<th>Subs/Rh ratio</th>
<th>Conversion (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>50/20/0</td>
<td>-</td>
<td>-</td>
<td>1540</td>
<td>&gt;99</td>
<td>96.2</td>
</tr>
<tr>
<td>2</td>
<td>50/20/0</td>
<td>-</td>
<td>-</td>
<td>1039</td>
<td>&gt;99</td>
<td>95.1</td>
</tr>
<tr>
<td>3</td>
<td>r.t./25/0</td>
<td>-</td>
<td>-</td>
<td>1041</td>
<td>&gt;99</td>
<td>97.2</td>
</tr>
<tr>
<td>4</td>
<td>r.t./20/60</td>
<td>-</td>
<td>-</td>
<td>1039</td>
<td>&gt;99</td>
<td>92.2</td>
</tr>
<tr>
<td>5</td>
<td>r.t./20/60</td>
<td>-</td>
<td>0.5</td>
<td>1039</td>
<td>&gt;99</td>
<td>97.6</td>
</tr>
<tr>
<td>6</td>
<td>r.t./20/60</td>
<td>0.15</td>
<td>-</td>
<td>1093</td>
<td>&gt;99</td>
<td>96.9</td>
</tr>
<tr>
<td>7</td>
<td>r.t./20/60</td>
<td>0.15</td>
<td>0.5</td>
<td>1005</td>
<td>&gt;99</td>
<td>96.8</td>
</tr>
</tbody>
</table>

* DMI in MeOH used as substrate instead of DBI

The DBI hydrogenation products could not be separated by GC on the chiral column and therefore a transesterification reaction with MeOH (Scheme 39) catalysed by HCl was performed for each sample to obtain the lighter methyl substituted products which can be separated to analyse the e.e.

![Scheme 39: DBI hydrogenation products transesterification](image)

Since hydrogenation reactions are usually substrate dependant for each catalyst, a reaction was first made with DMI (Table 28, Entry 1) and compared with another reaction under the same conditions but with DBI as substrate (Table 28, Entry 2). These reactions were done at
Asymmetric hydrogenation reactions

50 °C and 20 bar of H₂ pressure without any CO₂ added. Analysis of the reaction mixture after 1 hour showed quantitative conversion in both cases. The e.e. were also similar, being 96.2% when using DMI and 95.1% when using DBI, indicating that both substrates behave similar in their hydrogenation with the Rh-MeDuPhos catalyst.

The next reaction, carried out at room temperature (Table 28, Entry 3), showed that neither the conversion nor the e.e. were affected by the decrease of temperature.

In the next reaction (Table 28, Entry 4) 60 bar of CO₂ were also added to the autoclave but again no substantial decrease of conversion or e.e. was apparent.

Using the same conditions as in the last reaction, 3 other reactions were performed where SiO₂ alone (Table 28, Entry 5), IL alone (Table 28, Entry 6), or SiO₂ plus IL (Table 28, Entry 7) were added in order to check if they had any influence in the reaction outcome. The reaction mixtures showed full conversion after analysis in all 3 reactions with similar e.e. as previous reactions, showing that IL or SiO₂ had no detrimental effect in the reaction outcome.

4.2.5 Continuous flow reactions with dibutyl itaconate

After checking that DBI hydrogenation was feasible with the Rh-MeDuPhos catalyst and that both IL and SiO₂ had no effect on it, the reaction was attempted in the continuous flow system (Table 29).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>Substrate flow (ml min⁻¹)</th>
<th>H₂ flow (L min⁻¹)</th>
<th>CO₂ flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Rh/SiO₂)</th>
<th>TON after 5 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/150</td>
<td>0.05</td>
<td>0.3</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>50/20</td>
<td>0.05</td>
<td>0.2</td>
<td>-</td>
<td>0.2</td>
<td>764</td>
</tr>
<tr>
<td>3*</td>
<td>50/20</td>
<td>0.05</td>
<td>0.2</td>
<td>-</td>
<td>0.2</td>
<td>831</td>
</tr>
</tbody>
</table>

* Without IL.

The first reaction (Table 29, Entry 1) was carried out in a supercritical regime at 50 °C and 150 bar of CO₂ pressure but surprisingly no conversion at all was observed (Figure 111).
Next a reaction was attempted without any CO$_2$ in a typical liquid phase (Table 29, Entry 2). Nothing was recovered in the first 4 hours because this is the time the substrate takes to flow through the whole rig when it is not dissolved in scCO$_2$. Full conversion was achieved afterwards from the first recovered sample and throughout the remainder of the reaction (Figure 112) producing 764 TONs in 5 h. The e.e. started at 82.7% and decreased to 40.7% at the end of the reaction. Since the reaction was carried out in the liquid phase, abundant IL leached from the reaction which probably caused the decrease of e.e.

A reaction was performed next under the same conditions as the previous one but without any IL (Table 29, Entry 3). In this case a heterogeneous catalyst system was obtained by deposition of the Rh-MeDuPhos catalyst onto the silica. The conversion was quantitative throughout the reaction (Figure 113) and the e.e.’s. were low but constant at $\approx 17\%$ showing
good stability. Rh leaching between 12000 and 6000 ppb were found. Comparing this reaction with the previous one we can conclude that the IL in the SILP catalyst helps in maintaining higher enantioselectivities and thus, its loss via leaching, decreases the e.e. probably down to the level obtained with heterogeneous catalysts without IL.

Next, an approach similar to that used for batch reactions was employed for the reactions in continuous flow, and the effect of the CO$_2$, IL and SiO$_2$ on the reaction was analysed.

4.2.5.1 Effect of CO$_2$ phase

The effect of the CO$_2$ in the reaction was analysed first, and had different outcomes depending on whether the CO$_2$ was in the liquid, gas or supercritical state. The three reactions were made using the same catalyst loading (0.2 wt% Rh/SiO$_2$), CO$_2$ flow (1 ml/min) and substrate flow (0.05 ml/min).

When the reaction was performed with liquid CO$_2$ (Table 30, Entry 1 and Figure 114) the conversion initially at 64% decreased to 28% where it remained stable (Figure 115). IL leached from the reactor and the e.e. decreased from 74% to 7% observing the same behaviour as in previous reactions. At the end of the reaction 474 TONs were obtained.
Table 30: DBI hydrogenation. Reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature/Pressure (°C)/(bar)</th>
<th>CO₂ phase</th>
<th>H₂ flow (L min⁻¹)</th>
<th>CO₂ flow (ml min⁻¹)</th>
<th>Catalyst loading (wt% Rh/SiO₂)</th>
<th>IL leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/80</td>
<td>Liquid</td>
<td>0.3</td>
<td>1</td>
<td>0.2</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>50/150</td>
<td>Supercritical</td>
<td>0.3</td>
<td>1</td>
<td>0.2</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>100/54</td>
<td>Gas</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 114: CO₂ in liquid (1), supercritical (2) and gas (3) states

Figure 115: DBI hydrogenation in liquid CO₂
When the reaction was performed with supercritical CO$_2$ (Table 30, Entry 2 and Figure 114) no conversion at all was observed (Figure 116), but on the other hand the IL did not leach from the silica out of the reactor.

![Figure 116: DBI hydrogenation in supercritical CO$_2$](#)

Finally, when the reaction was performed with CO$_2$ gas (Table 30, Entry 3 and Figure 114) full conversion was achieved until the 7th hour (Figure 117), and decreased afterwards because the substrate flow was increased from 0.05 ml/min to 0.15 ml/min. The IL leached out of the reactor but unlike in previous liquid phase reactions the e.e. did not decrease drastically, starting at 37% and decreasing more smoothly to 29% where we increased the substrate flow and then decreased further to 10%. At the end of the reaction 1345 TONs were accumulated, half of which were obtained in the last two hours run at a higher substrate flow rate.

![Figure 117: DBI hydrogenation in CO$_2$ gas](#)
4.2.5.2 Effect of IL

In the previous reaction with CO\textsubscript{2} gas, where the best results were obtained, the IL used was BMIM NTf\textsubscript{2}. The effect of the IL chain length was studied for this case and therefore the reaction was repeated under the same conditions but with the longer chain IL OMIM NTf\textsubscript{2}. No difference was observed in the conversion which was quantitative during the first 3 samples and decreased slightly to 96% in the last sample (Figure 118). OMIM NTf\textsubscript{2} also leached from the reaction while the e.e. remained stable again but at a much lower value (12%) than when BMIM NTf\textsubscript{2} was used as IL (e.e. \( \approx 30\% \)). At the end of the reaction 996 TONs had occurred.

![Figure 118: DBI hydrogenation in CO\textsubscript{2} gas with OMIM NTf\textsubscript{2}](image)

Next, 2 reactions were run again, one using BMIM NTf\textsubscript{2} and the other using OMIM NTf\textsubscript{2}, but without CO\textsubscript{2}. The rest of the conditions were: room temperature, 20 bar of H\textsubscript{2} pressure, DBI flow of 0.05 ml/min and H\textsubscript{2} flow of 0.2 l/min with a SILP containing 0.02 wt\% Rh/SiO\textsubscript{2} and 29 wt\% IL/SiO\textsubscript{2}. These 2 reactions were compared with each other and with the similar reactions using BMIM NTf\textsubscript{2} and OMIM NTf\textsubscript{2} where CO\textsubscript{2} gas was added (Figure 117 and Figure 118 respectively).

When BMIM NTf\textsubscript{2} was used without CO\textsubscript{2}, the conversion initially >99% decreased to 81% at the end of the 10th hour (Figure 119). BMIM NTf\textsubscript{2} leached from the reactor and the e.e. decreased from 92% to 38%. Comparing this result to the one when CO\textsubscript{2} was added (Figure 117) we can see that much better e.e. were obtained without CO\textsubscript{2} in the system. At the end of the reaction 916 TONs were obtained.
When OMIM NTf₂ was used without CO₂, the conversion initially >99% decreased to 75% at the end of the 10th hour (Figure 120) which represents a slightly higher decrease in conversion than when using BMIM NTf₂. OMIM NTf₂ also leached from the reactor and the e.e. decreased from 93% to 60% which in this case represents a lower decrease in e.e. than when using BMIM NTf₂. Comparing this result to the reaction when CO₂ was added (Figure 118) we can see that much better e.e.’s. were obtained again without CO₂ in the system. We can conclude that the presence of CO₂ hinders the enantioselectivity. At the end of the reaction 912 TONs were obtained.

Since the IL leaching had a negative influence on the conversion and e.e., 2 reactions were attempted using in each case an IL immobilised on the SiO₂. The first reaction used BMIM
OTf as IL which we thought could be immobilised by hydrogen bonding with the silica OH groups (Figure 121).

![Figure 121: Possible IL immobilisation](image1.png)

However, IL leaching was observed when the reaction was performed making us discard this approach. The conversion initially at 99% decreased to 53% (Figure 122) and the e.e. decreased from 94% to 65%. 460 TONs were obtained at the end of the reaction.

![Figure 122: DBI hydrogenation without CO$_2$ and with BMIM OTf](image2.png)

The second reaction used an IL covalently grafted onto silica (Figure 123).

![Figure 123: IL grafted onto silica](image3.png)

The IL did not leach in this case but very low activity was observed. The conversion initially at 20% decreased to 9% and the very low e.e. decreased from 4% to 1% (Figure 124).
4.2.5.3 Effect of SiO₂

Two reactions without CO₂ were performed using silica with a smaller pore size since it has been shown to increase the e.e.,\textsuperscript{15} possibly due to higher steric constrains inside the pores. Thus, the previous SiO₂ used (Sigma Aldrich, Merck Silica Gel 100, grade 10184, 63-200 μm particle size, 100 Å pore diameter) was replaced by SiO₂ Fluorochem LC201, 35-70 μm particle size and 60 Å pore diameter.

Both reactions were run at 50 °C, 20 bar of hydrogen, a substrate flow of 0.05 ml/min and a H₂ flow of 0.2 l/min. The first reaction was run with a SILP containing BMIM NTf₂ and complete conversion was observed throughout the reaction (Figure 125). The IL leached as had occurred in previous reactions and consequently the e.e. decreased from 64% to 22%. In this case, against what was expected, by using smaller pore size silica the e.e. did not increase but decreased instead, since in previous reactions with larger pore size silica the e.e. had higher initial values of around 80% and decreased to values around 40% at the end of the reaction, with in average 20% higher e.e. than when using smaller pore size silica. This different behaviour arises from the fact that the SILP catalyst is a homogeneous catalyst and therefore not comparable with the reported examples\textsuperscript{15} where truly heterogeneous catalysts were used.

Figure 124: DBI hydrogenation without CO₂ and with IL grafted onto SiO₂
The second reaction was performed under the same conditions as the previous one but without any IL. In this case a truly heterogenised catalyst system was obtained by deposition of the Rh-MeDuPhos catalyst onto the silica. The conversion was also quantitative throughout the reaction (Figure 126) and the e.e. showed good stability. This time, as expected, higher e.e.’s. were obtained by using smaller pore size silica (≈30%) instead of larger pore size silica (≈17%). However, despite the almost 2 fold increase, the e.e. was still very low.
4.2.5.4 Catalyst deactivation

Since high e.e. could not be achieved in continuous flow unlike in batch reactions we wondered whether some catalyst deactivation might be occurring during the reaction due to impurities in the reaction components.

Given that in previous reactions both silica and DBI were used as received from the suppliers, for the next reactions the DBI was distilled under inert atmosphere and the silica was preheated under vacuum in order to purify them.

Two reactions were carried out, one with IL in the supported catalyst (homogeneous) and one without IL in the supported catalyst (heterogeneous), at 50 °C, 20 bar of hydrogen, a substrate flow of 0.05 ml/min and a H₂ flow of 0.2 l/min. When the IL was added complete conversion was observed throughout the reaction and the e.e. initially at 66% decreased to 45% at the end of the reaction (Figure 127) due to IL leaching. Although the initial e.e. was lower than in previous reactions without purified substrate and silica (82%), it decreased only 21% in 5 h which is an improvement compared to that of unpurified substrate and silica where the e.e. decreased by 42% in the same time range.

Next a reaction with purified substrate and silica and without IL was carried out. Complete conversion was achieved again throughout the reaction and the e.e. started at 49% but decreased slightly to stabilise at 35% (Figure 128). Although the e.e. was very low it represented a 2 fold increase compared to that of the reaction where unpurified substrate and silica were used (≈17%).

![Figure 127: DBI hydrogenation with pretreated silica, distilled substrate and with IL.](image)

Next a reaction with purified substrate and silica and without IL was carried out. Complete conversion was achieved again throughout the reaction and the e.e. started at 49% but decreased slightly to stabilise at 35% (Figure 128). Although the e.e. was very low it represented a 2 fold increase compared to that of the reaction where unpurified substrate and silica were used (≈17%).
Although these results confirm a slower catalyst deactivation than when using unpurified substrate and silica, the e.e.’s have to be improved much more to be considered acceptable. Usually the catalyst was prepared in one day, stored under inert atmosphere overnight and used the day after so we wondered if the catalyst was deactivated during this inactive period. Therefore, for the next reaction the catalyst (without IL) was prepared and the reaction carried out just after finishing the catalyst preparation, using the same conditions as for the previous reaction. The silica was pretreated but DBI was used as received this time. Complete conversion was achieved throughout the reaction and the e.e. was stable at 73% (Figure 129) which represented more than a 2 fold e.e. increase compared with the previous reaction and confirmed that some catalyst deactivation was produced when storing the catalyst overnight.
Interestingly, the hydrogenation of DMI in MeOH, which showed poor conversion previously, could be achieved by running the reaction just after finishing the catalyst preparation. The reaction was run at 50 °C, 20 bar of hydrogen, a substrate flow of 0.1 ml/min and a H₂ flow of 0.2 l/min. Full conversion was achieved in the first hour but decreased after 6h to 71% (Figure 130) due to catalyst leaching as visually observed in the coloured samples. The e.e. was low and more or less stable around 35%.

![Figure 130: DMI hydrogenation. Reaction made just after finishing catalyst](image)

### 4.2.5.5 Relationship between enantiomeric excess and catalyst leaching

It is clear from many of the reactions described above that leaching of the ionic liquid leads to a decrease in e.e., whilst the conversion is not greatly affected. This suggests that some non-selective but active catalyst may be being formed, possibly as a result of leaching of the ligand rather than the catalyst. Since the catalyst is ionic, it is not expected to be soluble in toluene or in DBI, but the neutral diphosphine, which contains the chiral information would be soluble in both if it decoordinates from the rhodium.

### 4.2.6 Continuous flow reactions with alumina/heteropoly acid systems

In the previous reactions we saw how heterogeneous catalysts obtained by supporting the catalyst directly onto silica (without IL) were more stable than the homogeneous ones (catalyst dissolved in IL) and complete conversion with constant e.e. of 73% could be achieved in a continuous flow reaction. Another heterogenised catalyst system, first introduced by Augustine et al. in 1999,10 and based on the support of metal complexes onto alumina via heteropoly acids, was used next (Figure 131).
The first reaction was run at room temperature, 20 bar of H₂ pressure, 0.05 ml/min of DBI flow and 0.2 l/min H₂ flow over a catalyst composed of 6.5 g of Al₂O₃, 1.45 g of phosphotungstic acid (PTA) and 40 mg of a Rh-MeDuPhos complex which represented a loading of 0.1 wt% Rh/Al₂O₃. Complete conversion was achieved throughout the reaction and more importantly, constant e.e.’s. of around 83% were achieved (Figure 132), which represents an increase of 10% e.e. compared with the previous heterogeneous catalysts. Colourless samples were recovered indicating no apparent catalyst leaching.

At the end of the reaction, the reactor was not taken apart for cleaning as usual and the catalyst was left inside for 74 h under the reaction conditions, but without flow in order to check the catalyst stability over time. Quantitative conversion was also obtained after the 74 h period but the e.e. decreased slightly during reaction from 84% to 79% after 5h (Figure
Asymmetric hydrogenation reactions

After this 5\textsuperscript{th} hour liquid CO\textsubscript{2} was introduced in the system at a rate of 1 ml/min and the temperature and pressure raised to 50 °C and 150 bar respectively to achieve supercritical conditions. As a consequence, the conversion dropped substantially in the next 4 h, reaching almost zero showing the negative influence on the reaction by using scCO\textsubscript{2}.

![Figure 133: DBI hydrogenation with Al\textsubscript{2}O\textsubscript{3}/PTA/Rh-MeDuPhos. Change to supercritical conditions](image)

Next a reaction was carried out under the same conditions as the previous reactions but with a catalyst composed of Rh-MeDuPhos complex directly supported onto Al\textsubscript{2}O\textsubscript{3} without using the heteropoly acid PTA as a connecting bridge. As a result, lightly coloured samples were recovered indicating catalyst leaching and much lower conversions were achieved starting at 57\% and decreasing to 41\% due to the loss of catalyst (Figure 134). Furthermore, the e.e.’s. were very poor with values between 7\% and 3\% demonstrating conclusively that the heteropoly acid linker is required for the reaction to proceed successfully.

![Figure 134: DBI hydrogenation with Al\textsubscript{2}O\textsubscript{3}/Rh-MeDuPhos and without PTA](image)
For the next reaction the Al₂O₃ support was replaced by SiO₂ and the same reaction conditions as before were used. As a result, the conversions and e.e. were very low showing that SiO₂ is not as a suitable support when using the heteropoly acid spacer (Figure 135).

Next, the effect of the pressure on the reaction was studied. A reaction was run at r.t., 0.1 ml/min substrate flow and 0.2 l/min H₂ flow (Figure 136). The pressure initially set at 20 bar was decreased to 10 bar after 6 h (grey area in Figure 136) and further decreased to 5 bar 2 h later. At 20 bar, the conversion initially at 82% decreased slightly to values around 74% while the e.e. increased from 78% initially to 86%. Then the pressure was decreased to 10 bar and consequently the conversion increased from 76% to 89%, which was the highest conversion value in this reaction, while the e.e. remained stable at 86%. Finally, the pressure was further decreased to 5 bar and as a consequence the conversion decreased from 89% to 82% while the e.e. still remained stable at 86%. Average TOFs of 280 h⁻¹ were achieved which produced 2178 TONs at the end of the reaction.
Asymmetric hydrogenation reactions

Next, the influence of the H₂ flow on the reaction was studied. A reaction was run at r.t., 0.1 ml/min substrate flow and 5 bar of pressure (Figure 137). The H₂ flow initially set at 0.2 l/min was decreased to 0.1 l/min after 3 h (grey area in Figure 137) and further decreased to 0.05 l/min 3 h later. With 0.2 l/min of H₂ flow the conversion initially at 78% increased slightly to stabilise at 84% while the e.e. also increased from 82% to 89%. Then the H₂ flow was decreased to 0.1 l/min and consequently the conversion decreased from 84% to 60% in the next 3 h while the e.e. also decreased slightly from 89% to 82%. Finally the H₂ flow was further decreased to 0.05 l/min and consequently the conversion decreased further from 60% to 23% in the next 3 h while the e.e. also decreased from 82% to 70%. It is very clear, in this case, how lowering the H₂ flow produced a decrease in both conversion and e.e.

![Figure 137: DBI hydrogenation with Al₂O₃/PTA/Rh-MeDuPhos. Effect of H₂ flow](image)

Next, the influence of the substrate (DBI) flow on the reaction was studied. A reaction was run at r.t., 0.2 ml/min H₂ flow and 5 bar of pressure (Figure 138). The DBI flow initially set at 0.1 ml/min was decreased to 0.05 ml/min after 3 h (grey area in Figure 138) and later increased to 0.2 ml/min 3 h later. With 0.1 ml/min of DBI flow the conversion initially at 29% increased to 75% while the e.e. also increased from 57% to 82%. Then the DBI flow was decreased to 0.05 ml/min and consequently the conversion increased from 75% to 95% in the next 3 h, which was the highest conversion value in the reaction, while the e.e. remained stable at 82%. Finally the DBI flow was increased to 0.2 ml/min and consequently the conversion decreased substantially from 95% to 31% in the next 3 h while the e.e. also decreased from 82% to 73%. It is clear in this case too how the lower the DBI flow the better the conversion and e.e. This is what is expected as a result of the increased residence time of the substrate within the reactor at lower flow rates.
For the next reaction we studied the stability of the catalyst over time using the optimal conditions found in the previous reactions. Therefore the reaction was run for 4 days continuously at r.t., 10 bar of pressure, a H$_2$ flow of 0.2 l/min and a DBI flow of 0.05 ml/min (Figure 139). The conversion started at 68% and increased to 92% in the 10$^{th}$ hour of reaction where it remained stable for another 12 h. After, it decreased progressively over time to reach values around 50% where it remained stable after 70 h of reaction. Then the pressure was decreased to 5 bar (grey area in Figure 139) and the conversion increased to 78% to decrease again to 71% at the end of the reaction. The initial e.e. of 93% increased to 96% in the 10$^{th}$ hour and decreased slightly afterwards to 82% at the 70$^{th}$ hour. Then the pressure was decreased to 5 bar and, as a result, the e.e. increased to 90%. Average TOFs of 125 h$^{-1}$ were achieved during 80 h of reaction accumulating a total TON of 9580. Rh leaching between 89 and 46 ppb were found.

Figure 138: DBI hydrogenation with Al$_2$O$_3$/PTA/Rh-McDuPhos. Effect of substrate flow

Figure 139: DBI hydrogenation with Al$_2$O$_3$/PTA/Rh-McDuPhos. Stability on time at 10 bar pressure
Asymmetric hydrogenation reactions

Since the decrease of pressure to 5 bar increased both the conversion and e.e. the reaction was repeated with the same conditions namely, r.t., H₂ flow of 0.2 l/min and a DBI flow of 0.05 ml/min but at 5 bar of pressure (Figure 140). Much better results were obtained at this lower pressure, with the conversion being quantitative over 47 consecutive hours and decreasing to 68% after 83 consecutive hours of reaction. The e.e’s. were also much better, being over 99% during 25 consecutive hours and decreasing to 65% after 75 hours where they remained stable. After 4 days of continuous reaction a total TON of 12,907 was achieved with average TOFs of 160 h⁻¹. Rh leaching between 44 and 625 ppb were found.

![Figure 140: DBI hydrogenation with Al₂O₃/PTA/Rh-MeDuPhos.](image)

**Stability on time at 5 bar pressure**

On the right hand side of Figure 140 there is a photograph of the catalyst after the reaction, where it can be seen how the orange Al₂O₃/PTA/Rh-MeDuPhos catalyst decomposed to some extent during catalysis turning grey, this probably being the cause of the decrease in activity.

### 4.2.7 Batch reactions with different substrates

Asymmetric hydrogenations of different prochiral substrates such as isophorone (Figure 141), 2-methyl-2-pentenal (Figure 142) and acetophenone (Figure 143) were also attempted in batch mode using the Rh-MeDuPhos catalyst alone, all giving unsuccessful results, which was not surprising since hydrogenation catalysts tend to be substrate specific.
No conversion was observed in the case of both isophorone and 2-methyl-2-pentenal. In the case of acetophenone hydrogenation, only 9% conversion towards the alcohol products was observed after 20 h of reaction with 42% e.e.

4.2.8 Conclusions and further work

We have showed in this chapter how Rh-MeDuPhos presents excellent activity (< 5 min to reaction completion) and enantioselectivity (94%) in the DMI hydrogenation reaction performed in a batch mode. When the same reaction was run in continuous flow mode, DMI which is a solid at r.t. had to be dissolved in a solvent. The first continuous flow reactions were performed using toluene as a solvent and showed that the catalyst loading could be decreased to 0.2 wt% Rh/SiO$_2$ while good conversions were still achieved. The e.e’s. on the other hand were under 30%. Also it was shown that CO$_2$ pressures up to 150 bar were required in order to avoid IL leaching.

When the solvent used was MeOH, which is the preferred solvent for batch mode Rh-MeDuPhos hydrogenation reactions, abundant IL leaching was observed even at 150 bar pressure, indicating that it is not compatible with continuous flow reactions.

DBI was afterwards used as a substrate since it required no solvent. Batch mode reactions were carried out first and showed high conversions (>99%) and e.e. (>95%) whether IL, SiO$_2$, CO$_2$ or a combination of them was present in the reaction or not. However, when the reactions were performed in continuous flow, it was noticed that the best results (full conversion throughout the reaction) were obtained whenever CO$_2$ was not present. The absence of CO$_2$ implied that the reaction was performed in a liquid phase and therefore abundant IL leaching was observed along with a decrease in the enatioselectivity from 80% to 40%. Continuous flow reactions were also performed using a typical heterogeneous catalyst composed of Rh-MeDuPhos deposited over SiO$_2$. Full conversions were also possible in this case but the e.e’s. were under 20%. The loss in e.e. over time is proposed to
Asymmetric hydrogenation reactions

arise as a result of loss of the ligand, which dissolves in the mobile phase and gives an achiral, but still active catalyst.

A study of the reaction behaviour when using CO₂ in its different phases (liquid, gas and supercritical) was carried out. Under supercritical conditions IL leaching was avoided but conversion was not observed. When using CO₂ some conversion in its liquid phase and full conversion in its gas phase was observed, but abundant IL leaching caused a decrease in the enantioselectivity.

The IL effect was also studied in continuous reactions without CO₂. BMIM NTf₂ caused a higher decrease in enantioselectivity than OMIM NTf₂ while conversions were similar. Nevertheless, the e.e. in both cases were better than the ones obtained in similar reactions using CO₂.

Reactions with immobilised IL via ionic exchange (BMIM OTf) led to IL leaching confirming a weak immobilisation and thus making this method unsuitable. When the immobilisation was carried out by grafting, the IL (OPIM Br) did not leach but poor conversions and e.e.’s were obtained.

Using SiO₂ with lower pore size did not improve the enantioselectivity. The catalyst deactivation proved to be the main factor causing low enantioselectivities since reactions with purified starting materials and the immediate use of freshly synthesised catalyst gave the best e.e.

Better results were obtained by immobilising Rh-MeDuPhos catalyst onto alumina via heteropoly acids. Full conversion and 80% e.e. could be obtained in a continuous reaction that decreased drastically when scCO₂ was added. The importance of the alumina support and the presence of the heteropoly acid were confirmed by running reactions with SiO₂ as support and without a heteropoly acid respectively. Both reactions showed poor conversions and enantioselectivities.

The effect of pressure, H₂ flow and substrate flow were studied and the long term stability of the reaction examined under the optimised conditions. More than 12,900 TONs were achieved after 4 days of continuous reaction, with conversions higher than 90% during the first 3 days, decreasing to 68% after 83 h of reaction. E.e.’s. higher than 99% could be
Chapter 4

achieved in the same reaction during the first 2 days and decreased to 64% at the end of the reaction.

Finally, hydrogenation of other prochiral substrates was attempted without success which was not surprising since hydrogenation catalyst tend to be substrate specific.

Further work should be done with Rh-MeDuPhos catalyst immobilised onto alumina via heteropoly acids since it gave the best results. Further optimisation of this system in continuous mode could even lead to its application in an industrial environment.
4.3 NOTES AND REFERENCES

Chapter 5

External placement work
One of the requisites for the completion of the Ph.D. was to spend at least 3 months in an external research institution. In my case I spent the 3 months divided between 2 research institutions and therefore have two different projects which I discuss in this chapter.

5.1 SYNTHESES OF MESOPOROUS SILICA MATERIALS

This part of the chapter is the result of a collaboration carried out from the 8th of October to the 26th of November 2010 at the “Institut Charles Gerhardt” in Montpellier (France) which is part of the “Centre National de la Recherche Scientifique” (CNRS) and it was carried out under the supervision of Dr. Anne Galarneau.

5.1.1 Introduction

Continuous flow reactions are more suitable for industrial applications since they present several advantages over batch systems such as time efficiency, long-term production, increased mass and heat transfer, better mixing, possibility of multistep reactions in a continuous sequence,\(^1\) possibility of implementing purification coupled with the reaction,\(^2\) cheaper automation, easier scale up and reaction optimisation,\(^3\) etc.

Microreactors are most common in research laboratories and can be divided into 3 types namely parallel microchannels, packed bed reactors and monoliths (Figure 144).

![Different microreactors types](image)

Figure 144: Different microreactors types
Parallel microchannel reactors consist of a circuit of channels where substrates and reactants are injected and flow through a usually thermally controlled environment. Packed bed reactors consist of a heterogeneous catalyst packed into a cylindrical reactor and monoliths consist of a solid structured network.

Most of the work of this thesis was done using packed bed reactors so a collaboration with Dr. Anne Galarneau in France was set up in order to do some research with monoliths. The use of monoliths can overcome some physico-chemical drawbacks associated with packed bed reactors such as fluid dynamics, pressure drop, heat and mass transfer, low contact efficiency and mechanical attrition. In particular we worked on silica monoliths, which consist of a silica network with macropores (> 50 nm) and mesopores (< 50 nm) which gives a flat flow profile.

Silica monoliths can be functionalised as shown by El Kadib and co-workers. They grafted both basic and acidic functionalities by flowing aminopropyltriethoxysilane and 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane respectively in a continuous cyclic process. Later the functionalised monoliths were evaluated in two reactions, the base catalysed Knoevenagel reaction between benzaldehyde and cyanoethyl acetate (Scheme 40) and the acid transesterification of triacetin (glycerin triacetate) with methanol (Scheme 41).

Furthermore they compared the activity of monoliths in continuous flow with the same monoliths crushed forming a packed bed reactor and also with the same crushed monoliths in a batch reaction. The result couldn’t have been more satisfactory for the monoliths as seen in Figure 145.

In both reactions the productivity increased from batch to continuous flow, and in continuous flow the productivity increased from packed bed to monoliths. In the Knoevenagel reaction switching from batch to continuous flow with a packed bed reactor increased the productivity by a factor of 4, and from continuous flow with a packed bed
reactor to continuous flow with monoliths the productivity increased by a factor of 1.6. Even bigger increments were found for the transesterification reaction. Switching form batch to continuous flow with a packed bed reactor increased the productivity by a factor of 10, and from continuous flow with a packed bed reactor to continuous flow with monoliths the productivity increased by a factor of 3.

The objective of this collaboration was to synthesise several monoliths, both simple and functionalised and then try to do catalysis in continuous supercritical flow back in St Andrews. Unfortunately the monoliths could not be fitted into the continuous flow reactor in St Andrews and therefore no more chemistry could be done with them.

Within this collaboration I also had the opportunity to synthesise ionogels, which are ionic liquids with dimensional stability (entrapped into a solid network). They can be organised into 3 categories depending on the nature of the solid network:

- Organic (low molecular weight gelators or polymers as solid network)(Figure 146)
- Inorganic (oxide nanoparticles, carbon nanotubes or oxide networks arising from sol-gel processes as solid network)(Figure 147)
- Hybrid organic-inorganic (polymers reinforced with inorganic fillers as solid network)(Figure 148)
Ionogels, which keep the main properties of ILs except outflow have found applications in the field of electrolytic membranes in lithium-ion batteries, fuel cells, solar cells, electrochemical sensors, electrochemical biosensors and actuators. They have also found applications in the field of separation membranes, catalytic membranes and drug release.

The SILP systems that are the main catalysts in this thesis are composed of silica, ionic liquids and catalyst. Inorganic ionogels are basically composed of silica and ionic liquids thus they could be used as SILP substitutes.

### 5.1.2 Analysis of silica and SILP catalysts

The surface area, pore diameter and pore volume of both silica and SILP catalysts were measured by porosimetry analyses of the silica support before and after impregnation with ILs and are represented in Figure 149.
The results are summarised in Table 31. The silica by itself had a surface area of 328 m$^2$/g that decreased to 182 m$^2$/g when IL and catalyst were added to it in order to form the SILP catalyst. This decrease in the surface area is due to the increase of particle size by adding IL and catalyst which form a layer over the silica. When increasing the particle size there are less particles per gram and that makes the surface area smaller than when having more, smaller, particles per gram.

### Table 31: Results from Nitrogen adsorption isotherm of silica and SILP

<table>
<thead>
<tr>
<th></th>
<th>Silica + IL + catalyst</th>
<th>SILP</th>
<th>$\Delta$ (Silica – SILP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area (m$^2$/g)</td>
<td>328</td>
<td>182</td>
<td>146</td>
</tr>
<tr>
<td>Pore diameter (nm)</td>
<td>11.5</td>
<td>10.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Pore volume (ml/g)</td>
<td>0.93</td>
<td>0.58</td>
<td>0.35</td>
</tr>
</tbody>
</table>

The pore diameter also decreased from 11.5 nm to 10.4 nm when adding IL and catalyst. If we visualise a pore (Figure 150), from the decrease of the pore diameter we can experimentally calculate the IL layer thickness by Eq 1. Theoretical IL layer thickness on the same SILP was calculated also by Eq 2.

![Figure 150: Silica particle with IL layer (green) showing the pore diameter of silica and SILP](image)

**Eq 1**

\[
IL \text{ layer thickness (nm)} = \frac{D_{Silica} - D_{SILP}}{2}
\]

**Eq 2**

\[
IL \text{ layer thickness (nm)} = \frac{mass_{IL}}{mass_{Silica} \times surface \ area_{Silica}} \times 1000
\]
The IL layer thickness had a theoretical value of 0.574 nm and an experimental value of 0.55 nm. Both results are in a close range thus validating the theoretical data.

The last row of Table 31 shows that the volume of the pore also decreased from 0.93 ml/g in the silica to 0.58 ml/g in the SILP representing a decrease of 0.35 ml/g. The percentage of pore filling can also be calculated both experimentally (Eq 3) and theoretically (Eq 4).

\[
\text{Eq 3} \quad \text{Pore filled (\%)} = \frac{\Delta_{(\text{silica-SILP})}}{Pore \text{ volume}_{\text{silica}}} * 100
\]

\[
\text{Eq 4} \quad \text{Pore filled (\%)} = \frac{\text{mass}_{\text{IL}}/\text{density}_{\text{IL}}}{\text{mass}_{\text{silica}} \times Pore \text{ volume}_{\text{silica}}} * 100
\]

The theoretical percentage of pore filling was 20%, but the experimental value was 37% which is almost double. This might arise from the high IL viscosity preventing the complete penetration of the IL into the silica pores leaving an empty space inside as suggested in Figure 151.

![Silica particle](Figure 151: Pore filled by an IL (green) creating an empty space (blue) inside)

### 5.1.3 Synthesis of silica monoliths

Silica monoliths were synthesised by a sol-gel process based on the reactions of hydrolysis (Eq 5) and polycondensation (Eq 6).

\[
\text{Eq 5} \quad \text{Si(OR)}_4 + \text{H}_2\text{O} \rightarrow \text{Si(OH)(OR)}_3 + \text{ROH}
\]

\[
\text{Eq 6} \quad \text{Si-OH} + \text{Si-OH} \rightarrow \text{Si-O-Si} + \text{H}_2\text{O}
\]

\[
\text{Eq 6} \quad \text{Si-OH} + \text{Si-OR} \rightarrow \text{Si-O-Si} + \text{ROH}
\]
First HNO₃ 68% (4.601 g, 0.05 mol) was weighed into a beaker. Distilled water (46.304 g, 2.65 mol (2.57 mol_{water} + 0.08 mol_{acid})) was weighed into a flask with a stirrer and the nitric acid added to it. The flask was sealed with parafilm and stirred in an ice/water bath. Poly(ethylene glycol) (4.789 g, 0.10 mol) was weighed and added to the previous solution. The mixture was stirred for 1 h to dissolve the PEG completely.

In the meantime the plastic tubes where the monoliths were going to be made were cleaned, dried, sealed at one end and put into the fridge in order to maintain the temperature as constant as possible during all the process.

After the poly(ethylene glycol) was dissolved, tetraethylorthosilicate (TEOS) (37.797 g, 0.18 mol) was weighed and added to the solution. The mixture was stirred for another hour and then it was poured into the plastic tubes sealing them afterwards. Then the tubes were put into a large beaker and filled with enough distilled water to cover the tubes. The beaker was covered with aluminium foil and heated at 40 °C for 3 days. The phase separation/gelification of the monoliths which generated the macroporosity occurred in this step.

Then the monoliths were taken out of the tubes and washed several times with distilled water. In order to create the mesoporosity the monoliths were put in a Teflon container and covered with a solution of NH₄OH 0.1 M, the container was closed and left in the oven overnight at 40 °C. Then the monoliths were taken out of the solution, washed with distilled water and dried in the oven at 40 °C. Finally they were calcined in the oven at 550 °C. A different sound was noticeable when dropping the monoliths onto the bench before calcination (plastic like sound / monoliths still filled with reactants) and after calcination (metallic like sound / monoliths empty inside).

![Figure 152: Silica monoliths](image)
The finished monoliths were analysed by scanning electron microscopy (SEM) to see the macropore structure (Figure 153) and by nitrogen adsorption isotherm to measure the surface area ($S_{BET}$), pore diameter ($D_p$) and pore volume ($V_p$).

The macropores size and therefore $S_{BET}$, $D_p$, and $V_p$ could be altered by changing the average mass of poly(ethyleneglycol) (PEG) as seen in Figure 154. By increasing the average mass of PEG from 20,000 Dalton to 100,000 Dalton the surface area increased from 487 $m^2/g$ to 630 $m^2/g$ due to a reduction in both the pore diameter from 11.5 nm to 8.8 nm and the pore volume from 1.11 ml/g to 1.07 ml/g. (60 $\mu$m scale in both pictures)

\[
\begin{align*}
S_{BET} (m^2/g) &= 487 < 630 \\
D_p (nm) &= 11.5 > 8.8 \\
V_p (ml/g) &= 1.11 > 1.07
\end{align*}
\]
In monoliths with the same macropore size the mesopore size and therefore also the $S_{\text{BET}}$, $D_p$ and $V_p$ could also be altered by changing the temperature of the NH$_4$OH basic treatment as seen in Figure 155. By increasing the temperature of the basic treatment from 40 ºC to 60 ºC to 80 ºC the surface area decreased from 630 m$^2$/g to 489 m$^2$/g to 434 m$^2$/g due to an increase in both the pore diameter from 8.8 nm to 12.8 nm to 16 nm and the pore volume from 1.07 ml/g to 1.14 ml/g to 1.23 ml/g. In the pictures it can be seen how, at higher temperatures, the surface of the cut is rougher due to the larger mesopores. Smaller mesopores on the other hand create a smoother surface.

Atmosphere and $D_p$ and $V_p$ as a function of the basic treatment temperature

![Figure 155: Mesopore size, $S_{\text{BET}}$, $D_p$ and $V_p$ as a function of the basic treatment temperature](image)

Attempts were made to synthesise monoliths with incorporated IL by adding either 1-butyl-3-methylimidazolium tetrafluoroborate or 3-octyl-1-(3-(trimethoxysilyl)propyl) imidazolium bromide (Figure 156) but the results were unsatisfactory in both cases obtaining fragile gel-like monoliths.

![Figure 156: 3-octyl-1-(3-(trimethoxysilyl)propyl) imidazolium bromide](image)
5.1.4 Functionalisation of silica monoliths

In order to functionalise the monoliths, they were cut into 2 cm pieces and put into a plastic tube surrounded by 2 glass tubes. This combination was put into the oven and subjected to a heating ramp (Figure 157) to shrink the plastic and fix the monolith with the glass tubes as seen in Figure 158. The monolith was dried at 150 °C under vacuum for 2 h and then it was put into an oven with a liquid recirculation system (Figure 159).

The amount of grafting reagent needed (basic 3-aminopropyltrimethoxysilane or acidic 2-(4-chlorosulphonylphenyl)ethyltrimethoxysilane)(Figure 160) was calculated for the grafting of 10 molecules/nm$^2$, weighed, dissolved in 50 ml of EtOH and recirculated overnight over the monolith at 60 °C and at a rate of 0.5 ml/min.
Figure 160: Grafting reagents used

The next day the monolith was washed in continuous flow first with 50 ml EtOH, then with 50 ml of a mixture EtOH/H₂O (1:1) and then with 50 ml of acetone. Finally it was dried in the oven at 40 °C and thermogravimetric analysis (TGA) was performed showing an average grafting of 1.80 molec/nm² for the basic reagent and 0.59 molec/nm² for the acidic reagent. A more concentrated solution of acidic reagent was recirculated over another monolith to increase the grafting but the monolith clogged (Figure 161).

Figure 161: SEM picture of clogged monolith

A solution of Grubbs-Hoveyda 2nd generation “like” catalyst (0.0026 g, 2.9 x 10⁻⁶ mol)(Figure 162) in acetone (20 ml) was flowed though the monolith at 0.5 ml/min and 60 °C overnight
to test if catalyst immobilisation could be achieved. The monolith was green afterwards. A clean acetone solution was passed through the monolith then and the catalyst was washed away leaving a white monolith again and suggesting that no permanent immobilisation took place.

![Grubbs-Hoveyda 2nd generation “like” catalyst](image)

**Figure 162: Grubbs-Hoveyda 2nd generation “like” catalyst**

### 5.1.5 Synthesis of immobilised IL

The synthesis of immobilised IL followed a literature procedure.\(^{19}\) Imidazole (5.1 g, 79.5 mmol) was dissolved in 75 ml of toluene. 3-Chloropropyltriethoxysilane (18 ml, 75 mmol) was added to the mixture and refluxed overnight. An oil containing 3-(N-imidazolyl)propyltriethoxysilane was obtained and to it added 1-bromooctane (14 ml, 80 mmol) and refluxed overnight. The product 1 was washed 3 times with cyclohexane, 10 ml of ethanol added and distilled under vacuum to remove the organics (14.91 g, 0.03 mol, 40.6% yield).

![Synthesis of immobilised IL](image)

In order to immobilise the IL onto silica a sol-gel reaction with TEOS was performed. In a polypropylene bottle were placed 100 ml of distilled water, 25 ml of HCl 37% and 8 ml of TEOS and the mixture heated at 40 °C for 3 hours while stirring. Then 3.62 g of 1 (ratio
TEOS/1 = 4.5) were added and stirred for 24 hours. Then the temperature was set at 60 °C and the mixture stirred for a further 24 hours. The product was mixed with ethanol, filtered and dried at 60 °C. 3.428 g of product were recovered and passed through a molecular sieve of 425 mesh size. TGA analysis showed 35.55 wt% of IL which corresponded to a grafting of 1.35 molec/nm².

5.1.6 Synthesis of ionogels

In a typical ionogel synthesis butylmethylimidazolium tetrafluoroborate (0.65 ml, 0.003 mol) was weighed in a Teflon vial, tetramethyl orthosilicate (TMOS)(1 ml, 0.006 mol) was weighed in the same vial and absolute ethanol was added (1.5 ml). The solution was stirred for 10 min. Then HCl (0.5 ml, 0.1 mol dm⁻³, 0.027 mol) was weighed in the same vial. The mixture was stirred for 5 min, the stirrer was removed, and the vial stored closed for 2 days in the oven at 30 °C to gelify. Afterwards the colourless ionogel was opened and weighed every day until the mass was constant. TGA analysis showed an IL content of 67 wt%.

Several attempts were made to incorporate the Grubbs-Hoveyda 2nd generation “like” catalyst into the ionogel synthesis but all the solutions that were initially green became dark brown ionogels suggesting catalyst decomposition (Figure 163).

Figure 163: Ionogel with catalyst

5.1.7 Conclusions and further work

Analysis of the silica and the SILP catalyst showed how, by addition of IL + catalyst onto the silica the surface area, the pore diameter and pore volume decreased. Experimental measurements were in accordance with theoretical values of IL layer thickness. In the case of percentage of pore filled the experimental value was almost double the theoretical value and
that might arise because it is impossible for the IL to reach the bottom of the pores due to its high viscosity.

The synthesis and functionalisation of silica monoliths has been successfully carried out. Both the macroporosity and the mesoporosity of monoliths could be controlled by the choice of different average mass poly(ethyleneglycol) and the temperature of the basic NH₄OH treatment. Grafting of basic and acidic molecules onto the monoliths was achieved through a continuous recirculating flow.

ILs were also immobilised into silica by a sol-gel process with TEOS obtaining 35 wt% of IL into the synthesised silica. Higher loadings of IL were achieved when synthesising ionogels where 67 wt% of the silica structure corresponded to the IL.

Further work should be made towards a reactor design which allows the incorporation of monoliths in a supercritical environment, a task that will not be easy due to the high pressure to which these fragile monoliths would be exposed.
5.2 SYNTHESIS OF Rh/Pd HYBRID CATALYSTS FOR HYDROGENATION REACTIONS

This part of the chapter is the result of a collaboration carried out from the 16th of January to the 20th of February 2012 at the “Istituto di Scienze e Tecnologie Molecolari” in Milan (Italy) which is part of the “Consiglio Nazionale delle Ricerche” and it was carried under the supervision of Dr. Vladimiro Dal Santo.

5.2.1 Introduction

Arene hydrogenations are more challenging than alkyne or alkene hydrogenations since aromaticity has to be broken\(^20\). Despite this, arene hydrogenation has been long studied with the first example published by Sabatier et al. in 1901 when they reported the benzene hydrogenation using reduced Nickel and excess hydrogen at 200 °C.\(^21\) Both homogeneous\(^22\) and heterogeneous\(^23\) catalyst have been previously used for this reaction. Homogeneous catalysts are preferred due to their high activity but difficult and costly catalyst separation and recovery from products and solvents have made them less desirable. One approach to circumvent this problem is to immobilise them on conventional supports such as silica.

In particular, we were interested in hybrid catalysts with a combination of Rh molecular complexes and dispersed Pd nanoparticles supported in silica. This type of catalyst gives improved activity in arene hydrogenation in comparison with the separate components by themselves as shown by Gao et al.\(^24\) which was explained as a consequence of a hydrogen spillover process where hydrogen is indirectly adsorbed onto the support surface. Later on this hypothesis was rejected when a study was performed with a catalyst formed by sol-gel co-entrapment of metallic Pd and \([\text{Rh}(\text{COD})(\mu-\text{Cl})]_2\), suggesting that a synergic effect between both metals may be responsible for the improved activity.\(^25\)

The origin of this synergic effect was explained by Dal Santo et al. in later publications.\(^26, 27\) They performed different arene hydrogenations with 3 types of catalysts supported on silica containing Pd\(^0\) nanoparticles (Pd\(^0\)/SiO\(_2\)), [Rh(cod)(sulphos)] (sulphos = O\(_3\)S(C\(_6\)H\(_4\))-CH\(_3\)C(CH\(_2\)PPh\(_2\))\(_3\)) single sites (Rh\(^1\)/SiO\(_2\)) and [Rh(cod)(sulphos)]-Pd nanoparticles (Rh\(^1\)-Pd\(^0\)/SiO\(_2\)). Taking as an example benzene hydrogenation, the Rh\(^1\)/SiO\(_2\) catalyst did not show any conversion to cyclohexane while the Pd\(^0\)/SiO\(_2\) catalyst showed 4% conversion. Making
different experiments with these two catalysts starting from benzene, cyclohexa-1,3-diene and cyclohexene they proposed the reaction pathway for Rh$^1$/SiO$_2$ (Scheme 42) and Pd$^0$/SiO$_2$ (Scheme 43) where one can see how these two catalysts complement each other.

Scheme 42: Benzene hydrogenation with isolated Rh single sites$^{27}$

Scheme 43: Benzene hydrogenation with isolated Pd nanoparticles$^{27}$

The Pd$^0$ mechanism involves disproportionation of the cyclohexa-1,3-diene and fast cyclohexene hydrogenation meanwhile Rh$^1$ is faster than Pd$^0$ at reducing cyclohexa-1,3-diene but slower at reducing cyclohexene to cyclohexane.

When the hybrid Rh$^1$- Pd$^0$/SiO$_2$ catalyst was used the conversion was increased from 4 to 15%. Although this value is not very high it represented a 4 fold increase in the conversion proving a cooperation between Rh$^1$ and Pd$^0$ in the mixed catalysis. This rate enhancement was also reproducible with different substrates. This cooperation was studied by extended X-ray absorption fine structure (EXAFS) and the outcome was that the Rh$^1$-Pd$^0$/SiO$_2$ reacted with H$_2$ to give a new surface species where the Rh$^1$ and the Pd$^0$ are connected via Rh-Pd bonds as well as bridging hydrides (Scheme 44).

Scheme 44: Rh$^1$-Pd$^0$/SiO$_2$ reaction with H$_2$ $^{27}$
Analysis of the species after benzene hydrogenation showed a structure where Rh atoms were coordinated by a dihapto sulphos ligand and by a C₄ moiety of a benzene molecule, with the other C₂ moiety of benzene coordinated to Pd (Scheme 45).

Scheme 45: Rh⁺-Pd⁰/SiO₂ after benzene hydrogenation

This is the first step in the Rh⁺-Pd⁰/SiO₂ benzene hydrogenation mechanism and differs from the Rh⁺/SiO₂ mechanism by the fact that Rh⁺ either free or immobilised onto SiO₂, and its cationic derivative [Rh(cod)(triphos)]⁺ are unable to coordinate benzene in any fashion, nor are they able to catalyse benzene hydrogenation to any extent. Thus it is the synergic effect of Pd⁰ which adsorbs and activates benzene so as to allow its C₄ coordination to Rh.

The next step in the Rh⁺-Pd⁰/SiO₂ hydrogenation mechanism (Scheme 46) involves reduction from benzene to cyclohexa-1,3-diene by the combined action of both metals. This is followed by the reduction to cyclohexene which is fast and would take place mainly at the Rh⁺ site, thus avoiding problems of disproportionation by Pd⁰. The last step involves the further reduction to cyclohexane which can be done by both metals but is faster on Pd⁰.

Scheme 46: Complete mechanism for benzene hydrogenation over Rh⁺-Pd⁰/SiO₂
Later the same group described a much easier and more active Rh\textsuperscript{1}-Pd\textsuperscript{0}/SiO\textsubscript{2} hybrid catalyst (Scheme 47) which can be extended to any cationic metal complex.\textsuperscript{28} They achieved this by using an electrostatically anchored Rh complex for which the counteranion bonds to the support material instead of the Rh complex being directly coordinated to the support, as in the previous example.

![Scheme 47: Hybrid Rh\textsuperscript{1}-Pd\textsuperscript{0}/SiO\textsubscript{2} with a cationic Rh complex immobilised via ionic bonding\textsuperscript{28}](image)

The objective of the collaboration with this particular group was to synthesise these same hybrid catalysts and a new one and then back in St Andrews perform arene hydrogenations in our continuous flow system. The new catalyst we tried to synthesise is one composed of Pd\textsuperscript{0} nanoparticles and the Rh-MeDuPhos catalyst I used in St Andrews for asymmetric hydrogenations. Potential applications of this chiral hybrid catalyst would point towards the asymmetric hydrogenations of substituted arenes such as xylene.

### 5.2.2 Silica pretreatment

All the catalysts synthesised were supported on silica (Table 32) which was pretreated as follows.

<table>
<thead>
<tr>
<th>Support</th>
<th>Surface area (m\textsuperscript{2}/g)</th>
<th>Pore volume (cm\textsuperscript{3}/g)</th>
<th>Pore diameter (nm)</th>
<th>Particle size (\textmu m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica Davisil A</td>
<td>291</td>
<td>1.28</td>
<td>13.7</td>
<td>60 – 200</td>
</tr>
<tr>
<td>Silica Davisil C</td>
<td>529</td>
<td>0.88</td>
<td>5.4</td>
<td>60 - 200</td>
</tr>
<tr>
<td>Silica Merck grade 10184</td>
<td>349</td>
<td>1.02</td>
<td>11.5</td>
<td>63 - 200</td>
</tr>
</tbody>
</table>
In a typical experiment, silica (≈ 5 g) was heated at 500 °C to remove impurities, first in the open air for 3-4 h and then under high vacuum overnight. High vacuum was reached with the help of a turbomolecular pump which set the vacuum below 9 mbar. The next day the silica was allowed to cool, covered with ultrapure water under an inert atmosphere in order to recover the OH groups on the surface and stirred for 3-4 h. Then most of the water was removed in vacuo and the silica heated at 300 °C under high vacuum to remove the last traces of water. Then the silica was stored in the glove box until further use.

Once the silica was pretreated either Rh or Pd alone could be supported on it. In the case of the hybrid catalysts where both metals were supported together, Pd was supported in the first place followed by Rh. In order to support Pd two different methods were used:

- Chemical vapour deposition (CVD)
- Ionic exchange

### 5.2.3 Synthesis of Pd/SiO₂ by chemical vapour deposition

The chemical vapour deposition technique is based on the sublimation of a metal complex and its deposition onto a surface. In our case we used a [Pd(allyl)(cp)] complex as the source of Pd and silica as a support on which surface the Pd was to be deposited.

In order to deposit Pd nanoparticles onto silica, both silica (≈ 2 g) and the [Pd(allyl)(cp)] complex (≈ 1 wt% Pd/SiO₂) were put into a special Schlenk tube used for chemical vapour deposition (Figure 164), placing the silica in the outer part and the Pd complex in the inner part.

The Schlenk tube was then put under vacuum, covered with aluminium foil and stirred over the weekend in a bath at 35 °C to allow the sublimation of the Pd complex and its deposition over the silica. Then the rest of Pd complex was discarded and the silica transferred to the gas flow Schlenk tube (Figure 165). An argon flow was passed through the Pd/SiO₂ (20 min) followed by a H₂ flow with a heating ramp (Figure 166) in order to reduce Pd⁰ to Pd⁰.
The heating ramp went from r.t. to 200 °C at a rate of 0.5 °C/min. Then it was held at 200 °C for 1 h and then cooled to r.t. under an argon flow. Afterwards a flow of oxygen (30 min) was passed through the mixture to passivate the Pd nanoparticles and finally a flow of argon (20 min) was passed to remove the oxygen. The mild passivation of Pd⁰/SiO₂ is a necessary step to allow for the grafting of Rh, as it takes place in the potentially reactive solvent CH₂Cl₂. However, this does not represent a limitation to catalysis, as the thin oxide layer is rapidly and completely removed under hydrogenation conditions. The solid was finally stored under inert atmosphere. An ICP measurement of a sample gave a Pd content of 0.66 wt%, which is less than the target 1 wt%.

5.2.4 Synthesis of Pd/SiO₂ by ionic exchange

In order to deposit Pd nanoparticles over silica by ionic exchange the silica and the Pd precursor Pd(NH₃)₄Cl₂.H₂O (≈ 1wt% Pd/SiO₂) were weighed in a flask in air. Ultrapure water (40 ml/g SiO₂) was added and the mixture stirred overnight. Then the Pd/SiO₂ mixture was filtered, washed with ultrapure water and dried in the oven overnight.

The Pd/SiO₂ was calcined next using a heating ramp under an oxygen flow (Figure 167). The ramp went from r.t. to 550 °C at a rate of 5 °C/min, held at this temperature for 6 h and then cooled under an argon flow. Then the Pd was reduced using another heating ramp under H₂ flow (Figure 168). In this case the ramp went from r.t. to 300 °C at a rate of 10 °C/min, the sample was held at 300 °C for 1 h and cooled again under argon flow. Afterwards a flow of oxygen (30 min) was passed through the mixture to passivate the Pd nanoparticles and finally a flow of argon (20 min) was passed to remove the oxygen. The solid was finally stored under inert atmosphere. An ICP measurement of a sample gave a Pd content of 0.47 wt%,
which is less than the target 1 wt% and also less than the value reached by CVD (0.66 wt%), which makes the ionic exchange a poorer method to deposit Pd than CVD.

![Figure 167: Calcination heating ramp](image1)

![Figure 168: Reduction heating ramp](image2)

5.2.5 Synthesis of achiral Rh/SiO$_2$

Rh grafting onto the silica was carried out as follows. Silica (≈ 1 g) and [Rh(cod)(dpmm)]OTf (0.5 wt% Rh/SiO$_2$) were mixed in a Schlenk tube in the glove box. Dry dichloromethane (5 ml) was added to dissolve the Rh complex and the mixture stirred for 4 h. Then the yellowish grafted material was collected by filtration under argon (clear solution obtained) and washed three times with dry dichloromethane. Finally, the solid product was dried under vacuum overnight and stored under inert atmosphere. An ICP measurement of a sample gave a Rh content of 0.41 wt%, which is not very far from the target 0.5 wt%.

5.2.6 Synthesis of chiral Rh/SiO$_2$

Silica (≈ 1 g) and Rh-MeDuPhos (0.5 wt% Rh/SiO$_2$) were mixed in a Schlenk tube in the glove box. Dry dichloromethane (5 ml) was added to dissolve the Rh complex and the mixture stirred for 4 h. Then the dichloromethane was removed under vacuum overnight and the solid stored under inert atmosphere.

5.2.7 Synthesis of achiral Rh-Pd/SiO$_2$

The procedure to synthesise the non chiral hybrid Rh-Pd catalyst started by synthesising the Pd/SiO$_2$ via either CVD or ion exchange and then Rh was integrated
following the same procedure used to synthesise the non chiral Rh/SiO$_2$. ICP measurements from different samples where Pd was deposited via CVD gave loading values between 0.64 - 0.73 wt% for Pd and between 0.39 - 0.42 wt% for Rh which are in the range of previous measurements.

5.2.8 Synthesis of chiral Rh-Pd/SiO$_2$

The procedure to synthesise the chiral hybrid Rh-Pd catalyst started by synthesising the Pd/SiO$_2$ via either CVD or ion exchange and then Rh was integrated following the same procedure used to synthesise the chiral Rh/SiO$_2$. ICP measurements from different samples where Pd was deposited via ion exchange gave loading values between 0.43 - 0.50 wt% for Pd and between 0.40 - 0.42 wt% for Rh which are in the range of previous measurements. Another sample where Pd was deposited via CVD gave loadings of 0.71 wt% for Pd and 0.43 wt% for Rh.

5.2.9 Styrene hydrogenation in continuous scCO$_2$ flow with Rh/SiO$_2$, Pd/SiO$_2$ and Rh-Pd/SiO$_2$

Styrene hydrogenation (Scheme 48) was performed in batch reactions with these same catalysts by Dal Santo et al.$^{26}$ With styrene as substrate there is the possibility of differentiating between alkene and arene hydrogenation. They observed almost quantitative conversion to ethylbenzene (EB) when using a Rh/SiO$_2$ catalyst, complete conversion with 3% selectivity towards ethylcyclohexane (ECH) when using a Pd/SiO$_2$ catalyst and complete conversion with 19% selectivity towards ECH when using a hybrid Rh-Pd/SiO$_2$ catalyst. These results proved how Rh-Pd hybrid catalysts performed better in arene hydrogenation than each metal by itself.

![Scheme 48: Styrene hydrogenation](image)

We repeated these reactions in continuous flow with scCO$_2$ as a carrier gas. The reaction conditions were 60 °C, 160 bar of pressure, H$_2$ flow of 0.1 - 0.15 l/min, CO$_2$ flow of 1 ml/min and styrene flow of 0.05 - 0.1 ml/min. As a result we obtained a conversion higher
than 80% towards EB when using Rh/SiO$_2$, complete conversion towards EB when using Pd/SiO$_2$ and complete conversion with 2% selectivity towards ECH when using Rh-Pd/SiO$_2$. These results were not as good as when the reactions were carried out in batch mode, but followed the same pattern which is the improvement of the arene hydrogenation when using the hybrid Rh-Pd catalyst.

5.2.10 Conclusions and further work

The synthesis of various catalysts of Rh, Pd, and Rh-Pd immobilised onto silica has been explored. Different techniques were used to deposit the Pd onto the silica, including chemical vapour deposition and ion exchange. Immobilisation of [Rh(cod)(dppp)]OTf complexes was achieved via hydrogen bonding of the trifluoromethane sulfonyl anion and the silanol groups of the silica surface. Furthermore, immobilisation of chiral Rh-MeDuPhos complexes was achieved by its adsorption onto the silica surface.

Catalytic tests on arene hydrogenation proved to proceed with better yields when using a bimetallic Rh-Pd hybrid catalyst than when the same reaction was performed by each metal on its own.

Further research should be carried out on the optimisation of the reaction parameters in continuous flow since the conversions are not as high as in the batch reactions. Besides, due to time issues and lack of optimisation nothing was attempted with the chiral version of the hybrid catalysts. It will be very interesting to see its performance in asymmetric hydrogenations of substituted arenes such as ortho or meta-xylene.
5.3 NOTES AND REFERENCES


Chapter 6

Experimental work
6.1 MATERIALS AND TECHNIQUES

The starting materials diethyl diallylmalonate 98%, 1-pentene 98%, 1-octene 98%, 2-pentene 99%, 2-octene 97%, methyl oleate 99%, dimethyl maleate 96%, dimethyl fumarate 97%, methyl acrylate 99%, dimethyl itaconate 99%, dibutyl itaconate 96% and SiO₂ (Merck silica gel 100, grade 10184, 70-230 mesh, 10 nm pore diameter) were purchased from Aldrich.

Phosphotungstic acid (PTA) was purchased from Fluka and Al₂O₃ from Acros organics.

The catalysts Ru-Grubbs-Hoveyda 2nd generation “like” and Rh-McDuPhos were kindly donated by S. P. Nolan and ChiroTech Ltd respectively, the catalyst precursors Pd(dba)₂ and Pd₂(dba)₃ purchased from Aldrich.

The ligand DTBPMB was kindly donated by Lucite International Ltd.

The gases H₂ (99.99%), CO (99.97%) and CO₂ (99.99%) were purchased from BOC industrial gases.

NMR analyses were made either with Bruker Avance 300 MHz or Bruker Avance II 400 MHz spectrometers.

GC-MS analyses were made with an HP 6890 series gas chromatogram equipped with a HP-1 column, 30m length, 0.25mm id, 0.25 microns film thickness and chiral GC-FID were made with an Agilent 6890N Network GC system equipped with a Mega-Dex DMP chiral column, 25m length, 0.25 id, 0.25 microns film thickness.
Chapter 6

6.2 SYNTHESIS OF IONIC LIQUIDS

The ILs were prepared as described below, analysed by $^1$H and $^{13}$C NMR and compared to the literature data.$^{1,3}$

6.2.1 Synthesis of 1-butyl-3-methylimidazolium bromide [BMIM] Br

This IL was synthesised as described in Ref. 1.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$, 298 K): δ 0.90 (t, $J = 7.3$ Hz, 3H, CH$_3$), 1.32 (m, $J = 7.6$ Hz, 2H, CH$_2$CH$_3$), 1.85 (m, $J = 7.4$ Hz, 2H, NCH$_2$CH$_3$), 4.05 (s, 3H, NCH$_3$), 4.30 (t, $J = 7.3$ Hz, 2H, NCH$_2$), 7.56-7.64 (dt, $J = 1.8$ Hz, 2H, NCHCHN), 10.27 (s, 1H, NCHN) ppm.

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$, 298 K): δ 12.9 (s, CH$_3$), 19.1 (s, CH$_2$CH$_3$), 32.5 (s, NCH$_2$CH$_3$), 36.1 (s, NCH$_3$), 50.8 (s, NCH$_2$), 122.0, 123.5 (s, NCHCHN), 134.9 (s, NCHN) ppm.

NMR signals were consistent with those described in the literature$^1$.

6.2.2 Synthesis of 1-octyl-3-methylimidazolium chloride [OMIM] Cl

This IL was synthesised as described in Ref. 1.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$, 298 K): δ 0.86 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.27 (m, $J = 7.2$ Hz, 10H, CH$_2$), 1.87 (m, $J = 7.4$ Hz, 2H, NCH$_2$CH$_3$), 4.06 (s, 3H, NCH$_3$), 4.28 (t, $J = 7.3$ Hz, 2H, NCH$_2$), 7.42, 7.59 (s, 2H, NCHCHN), 10.41 (s, 1H, NCHN) ppm.

$^{13}$C NMR (100 MHz, CD$_2$Cl$_2$, 298 K): δ 14.1 (s, CH$_3$), 22.9, 26.5, 29.3, 29.4, 30.5, 32.0 (s, 6 x CH$_3$), 36.7 (s, NCH$_3$), 50.2 (s, NCH$_2$), 122.1, 123.8 (s, NCHCHN), 138.2 (s, NCHN) ppm.

NMR signals were consistent with those described in the literature$^1$. 
6.2.3Synthesis of 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyle)amide [BMIM][NTf₂]

\[
\begin{align*}
\text{N} & \equiv \text{N}^+ \text{Br}^- + (\text{CF}_3\text{SO}_2)\text{NLi}^- \\
& \rightarrow \text{N} \equiv \text{N}^+ (\text{CF}_3\text{SO}_2)\text{N}\text{Li}^-
\end{align*}
\]

This IL was synthesised as described in Ref. 1.

\([^1]H\) NMR (400 MHz, CD₂Cl₂, 298 K): δ 0.97 (t, J = 7.4 Hz, 3H, CH₃), 1.38 (m, J = 7.4 Hz, 2H, CH₂), 1.87 (m, J = 7.4 Hz, 2H, NCH₂CH₂), 3.95 (s, 3H, NCH₃), 4.18 (t, J = 7.4 Hz, 2H, NCH₂), 7.33 (s, 2H, NCHCHN), 8.75 (s, 1H, NCHN) ppm.

\([^{13}]C\) NMR (100 MHz, CD₂Cl₂, 298 K): δ 13.1 (s, CH₃), 19.3 (s, CH₂), 31.9 (s, NCH₂CH₂), 36.3 (s, NCH₃), 49.9 (s, NCH₃), 118.1-121.3 (d, J₁C₂ = 321 Hz, CF₃), 122.2, 123.6 (s, NCHCHN), 136.0 (s, NCHN) ppm.

NMR signals were consistent with those described in the literature.

6.2.4 Synthesis of 1-octyl-3-methylimidazolium bis(trifluoromethanesulfonyle)amide [OMIM][NTf₂]

\[
\begin{align*}
\text{N} & \equiv \text{N}^+ \text{Cl}^- + (\text{CF}_3\text{SO}_2)\text{NLi}^- \\
& \rightarrow \text{N} \equiv \text{N}^+ (\text{CF}_3\text{SO}_2)\text{N}\text{Li}^-
\end{align*}
\]

This IL was synthesised as described in Ref. 1.

\([^1]H\) NMR (400 MHz, CD₂Cl₂, 298 K): δ 0.79 (t, J = 7.4 Hz, 3H, CH₃), 1.22 (m, J = 7.4 Hz, 10H, CH₂), 1.78 (m, J = 7.4 Hz, 2H, NCH₂CH₂), 3.84 (s, 3H, NCH₃), 4.07 (t, J = 7.3 Hz, 2H, NCH₂), 7.20 (s, 2H, NCHCHN), 8.55 (s, 1H, NCHN) ppm.

\([^{13}]C\) NMR (100 MHz, CD₂Cl₂, 298 K): δ 14.1 (s, CH₃), 22.9, 26.2, 29.1, 29.3, 30.3, 31.9 (s, 6 x CH₂), 36.7 (s, NCH₃), 50.7 (s, NCH₃), 118.6-121.8 (d, J₁C₂ = 321 Hz, CF₃), 122.6, 124.0 (s, NCHCHN), 136.2 (s, NCHN) ppm.

NMR signals were consistent with those described in the literature.
6.2.5 Synthesis of 1-butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)amide [BMMIM][NTf₂]

This IL was synthesised as described in Ref. 2.

\(^{1}\)H NMR (400 MHz, CDCl₃, 298 K): δ 0.90 (t, J = 7.4 Hz, 3H, CH₃), 1.31 (m, J = 7.4 Hz, 2H, CH₂), 1.71 (m, J = 7.4 Hz, 2H, NCH₂CH₂), 2.54 (s, 3H, NC(CH₃)N), 3.73 (s, 3H, NCH₃), 3.98 (t, J = 7.4 Hz, 2H, NCH₂), 7.09-7.13 (d, J = 2.1 Hz, 2H, NCHCHN) ppm.

\(^{13}\)C NMR (100 MHz, CDCl₃, 298 K): δ 9.56 (s, NC(CH₃)N), 13.32 (s, CH₃), 19.50 (s, CH₂), 31.44 (s, NCH₂CH₂), 35.31 (s, NCH₂), 48.61 (s, NCH₂), 118.18-121.37 (d, J_CF = 321 Hz, CF₃), 120.82, 122.55 (s, NCHCHN), 143.71 (s, NCN) ppm.

NMR signals were consistent with those described in the literature ².

6.2.6 Synthesis of 1-methyl-3-(butylsulfonate)imidazolium [BMIM-SO₃]

This IL was synthesised as described in Ref. 3.

\(^{1}\)H NMR (400 MHz, D₂O, 298 K): δ 1.63 (m, J = 7.4 Hz, 2H, NCH₂CH₂), 1.91 (m, J = 7.4 Hz, 2H, SCH₂CH₂), 2.83 (t, J = 7.4 Hz, 2H, SCH₂), 3.78 (s, 3H, NCH₂), 4.13 (t, J = 7.4 Hz, 2H, NCH₂), 7.32-7.39 (t, J = 1.8 Hz, 2H, NCHCHN), 8.63 (s, 1H, NCHN) ppm.

\(^{13}\)C NMR (100 MHz, D₂O, 298 K): δ 20.85 (s, SCH₂CH₂), 28.02 (s, NCH₂CH₂), 35.56 (s, NCH₂), 48.82 (s, NCH₂), 49.98 (s, SCH₂), 122.06, 123.54 (s, NCHCHN) ppm.

NMR signals were consistent with those described in the literature ³.
6.2.7 Synthesis of 1-butyl-3-(butylsulfonate)imidazolium [BBIM-SO₃]

This IL was synthesised as described in Ref. 3.

\(^1\)H NMR (400 MHz, D₂O, 298 K): δ 0.80 (t, J = 7.4 Hz, 3H, CH₃CH₂), 1.19 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₃), 1.62 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₃), 1.91 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₃), 2.82 (t, J = 7.4 Hz, 2H, SCH₂), 4.08-4.13 (t, J = 7.4 Hz, 4H, 2 x NCH₂), 7.39 (s, 2H, NCHCHN), 8.70 (s, 1H, NCHN) ppm.

\(^{13}\)C NMR (100 MHz, D₂O, 298 K): δ 12.55 (s, CH₃CH₂), 18.70 (s, CH₃CH₂), 20.89 (s, SCH₂), 28.03 (s, SCH₂), 31.12 (s, CH₃CH₂), 48.88 (s, NCH₂), 49.28 (s, NCH₂), 49.98 (s, SCH₂), 122.20-122.42 (s, NCHCHN) ppm.

NMR signals were consistent with those described in the literature 3.

6.2.8 Synthesis of 1-methyl-3-(butylsulfonate)imidazolium bis(trifluoromethanesulfonyl)amide [BMIM-SO₃H][NTf₂]

This IL was synthesised as described in Ref. 3.

\(^1\)H NMR (400 MHz, D₂O, 298 K): δ 1.60 (m, J = 7.4 Hz, 2H, NCH₂CH₃), 1.88 (m, J = 7.4 Hz, 2H, SCH₂CH₃), 2.80 (t, J = 7.4 Hz, 2H, SCH₂), 3.75 (s, 3H, NCH₂), 4.10 (t, J = 7.4 Hz, 2H, NCH₂), 7.29-7.35 (t, J = 1.8 Hz, 2H, NCHCHN), 8.59 (s, 1H, NCHN) ppm.

\(^{13}\)C NMR (100 MHz, D₂O, 298 K): δ 20.84 (s, SCH₂CH₃), 28.02 (s, NCH₂CH₃), 35.55 (s, NCH₂), 48.83 (s, NCH₂), 49.96 (s, SCH₂), 117.57-120.75 (d, J_CF = 321 Hz, CF₃), 122.09, 123.58 (s, NCHCHN), 135.85 (s, NCN) ppm.

NMR signals were consistent with those described in the literature 3.
6.2.9 Synthesis of 1-butyl-3-(butylsulfonate)imidazolium bis(trifluoromethanesulfonyl)amide [BBIM-SO₃H][NTf₂]

This IL was synthesised as described in Ref. 3.

¹H NMR (400 MHz, D₂O, 298 K): δ 0.80 (t, J = 7.4 Hz, 3H, CH₃CH₂), 1.20 (m, J = 7.4 Hz, 2H, CH₃CH₂), 1.63 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₂), 1.74 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₂), 1.91 (m, J = 7.4 Hz, 2H, CH₂CH₂CH₂), 2.83 (t, J = 7.4 Hz, 2H, SCH₂), 4.08-4.13 (t, J = 7.4 Hz, 4H, 2 x NCH₂), 7.39-7.40 (t, J = 1.8 Hz, 2H, NCHCHN), 8.70 (s, 1H, NCHN) ppm.

¹³C NMR (100 MHz, D₂O, 298 K): δ 15.09 (s, CH₃CH₂), 21.25 (s, CH₃CH₂), 23.44 (s, SCH₂CH₂), 30.59 (s, SCH₂CH₂CH₂), 33.68 (s, CH₃CH₂CH₂), 51.45 (s, NCH₂), 51.88 (s, NCH₂), 52.53 (s, SCH₂), 120.15-123.33 (d, JCF = 321 Hz, CF₃), 124.78-125.00 (s, NCHCHN) ppm.

NMR signals were consistent with those described in the literature³.
6.3 PREPARATION OF POTASSIUM 3,4-BIS(DI-TERT-BUTYLPHOSPHINOMETHYL)BENZENESULFONATE

The following procedure for the sulfonation of DTBPMB ligand was based on the method described by Benjamin Lee Parnham. The synthesis was carried out under inert atmosphere.

To a Schlenk tube equipped with a reflux condenser, oil bubbler and magnetic stirrer was added the DTBPMB ligand (4 g, 10.1 mmol) and the flask cooled to 0 °C in an ice-water bath. Fuming sulphuric acid (15 ml) was added dropwise while stirring with the temperature being maintained below 5 °C. The mixture was heated at 80 °C for 4 hours and stirred at room temperature overnight.

The next day the solution was transferred via cannula to a flask containing degassed ice (20 g) to hydrolyse the acid (CAUTION: This procedure is highly exothermic so should be carried out slowly). The solution was adjusted to pH 8-10 by the addition of a saturated solution of KOH which caused the precipitation of the sulfonated phosphine plus potassium sulfate. The water was removed in vacuo and the mixture was suspended in degassed methanol (50 ml) and stirred for 1 h at 40 °C before filtering. The methanol was removed in vacuo from the filtrate and the resulting solid again suspended in methanol and filtered. The solvent was again removed in vacuo to yield crude product as a white solid.

The removal of the final inorganic sulfate impurity was achieved by passing a methanolic solution of the product through a silica plug with elution of the desired phosphine using a mixture of ethyl acetate/methanol/acetic acid/water (12 : 6 : 1 : 1 by volume).

$^1$H NMR (400 MHz, CD$_3$OD, 298 K): δ 1.07 (m, 36H, 4 x C(CH$_3$)$_3$), 3.05 (s, 4H, 2 x CH$_2$), 7.45 - 7.50 (s, 2H, KSO$_3$CCHCHC), 7.96 (s, 1H, KSO$_3$CCHC) ppm.

$^{13}$C NMR (100 MHz, CD$_3$OD, 298 K): δ 27.9 (s, P(C(CH$_3$)$_3$)), 30.7 (s, PC(CH$_3$)$_3$), 33.3 (s, CH$_3$P), 124.5 (s, KSO$_3$O), 129.9 - 132.4 (s, CHC(KSO$_3$)CCHC), 143.0 (s, PCHC(CCH$_2$)P) ppm.

$^{31}$P NMR (161 MHz, CD$_3$OD, 298 K): δ 26.1, 27.3 ppm.
6.4 PREPARATION OF SUPPORTED IONIC LIQUID PHASE (SILP) CATALYSTS

In these SILP systems the catalyst was dissolved into the ionic liquid and this mixture was supported on silica (Sigma Aldrich, Merck Silica Gel 100, grade 10184, 70-230 mesh, 10 nm pore diameter). The quantity of SiO₂ needed to fill the reactor was measured (usually 3.4 g). The SILP catalysts were prepared as follows:

- The catalyst (measured in wt% of metal with respect to SiO₂) was weighed in the glove box (usually 6.5 mg of Grubbs-Hoveyda 2nd generation “like” catalyst (0.02 wt% Ru/SiO₂), 19 mg Pd₂(dba)₃ (0.1 wt% Pd/SiO₂) and 40 mg Rh-MeDuPhos (0.2 wt% Rh/SiO₂)) and placed into a Schlenck tube equipped with a magnetic stirrer.
- The catalyst was dissolved in dry dichloromethane (15 ml).
- The ionic liquid (usually 29 wt% of SiO₂) was weighed and added to the previous solution.
- The SiO₂, previously heated to remove surface hydroxides (10 h, 500 ºC), was weighed and added to the solution.
- The mixture was stirred for 30 – 60 min.
- After this time, the solution was heated under vacuum (35 ºC) in order to evaporate the dichloromethane (Figure 169). As a result an IL layer of 0.57 nm was deposited over the silica filling around 20% of the pore volume.

*Figure 169: SILP system appearance before and after DCM evaporation*

- The SILP system was transferred to a glove box, loaded into the reactor and the reactor stored there until the next run was carried out.
6.5 PREPARATION OF ALUMINA SUPPORTED CATALYSTS VIA HETEROPOLY ACIDS

In these catalytic systems the catalyst was immobilised via metal bonding to phosphotungstic acid (PTA) previously supported on alumina (Acros organics, aluminium oxide, activated, neutral, 50-200 micron). The quantity of $\text{Al}_2\text{O}_3$ needed to fill the reactor was measured and the catalytic systems prepared under an inert atmosphere following the procedure described by Augustine et al. ⁵

- $\text{Al}_2\text{O}_3$ (6.5 g) was weighed in a Schlenk tube, degassed by several $\text{N}_2$-vacuum cycles and heated under vacuum to remove oxygen.
- PTA (1,45 g) was weighed in a Schlenk tube, degassed by several $\text{N}_2$-vacuum cycles and dissolved in dry EtOH (40 ml).
- The PTA solution was added to the $\text{Al}_2\text{O}_3$ via cannula and stirred for 4 h. Then the liquid was removed via filter-cannula and the solid washed with dry EtOH (4 x 20 ml).
- Rh-MeDuPhos (40 mg, 0.1 wt% Rh/$\text{SiO}_2$) was weighed in a Schlenk tube inside the glove box, dissolved in dry EtOH (20 ml) and the solution passed via cannula to the $\text{Al}_2\text{O}_3$/PTA solution and stirred overnight.
- The liquid was removed via filter-cannula and the solid washed with dry EtOH (4 x 20 ml).
- To finish, the solid catalyst was dried under vacuum, transferred into the glove box, loaded into the reactor and the reactor stored there until the next run was carried out.
6.6 CONTINUOUS FLOW RIG

6.6.1 Apparatus

For this PhD 2 rig setups were built and used. A description of each one is detailed below. The first one was used for metathesis and some of the methoxycarbonylation reactions (Scheme 49) and the second one, which was an improved version of the first, was used for methoxycarbonylation and hydrogenation reactions.

Scheme 49: First rig set up

ACV: auxiliary collection vessel
BV: ballast vessel
DC: decompression chamber
F: filter
FCV: flow control valve
FM: flow meter
GB: gas booster
H: heater
LP: liquid pump
MFC: mass flow controller
NRV: non return valve
P: pressure transducer
PCV: pressure control valve
PH: pre-heater
R: reactor
Sub: substrate
SV: shut-off valve
T: thermocouple
V: vent
All piping, valves and connectors were purchased either from Swagelok or Hoke. The rig can be divided into 4 sections for easier understanding:

- **Gas input.**
  scCO$_2$ was fed through an New Ways of Analytics (NWA) PM 101 supercritical fluid pump and its pressure, and hence the entire system regulated with an NWA pressure control valve. CO was pressurised with a Haskel AG75 gas booster, stored in a ballast vessel and fed into the system through a Bronkhorst F-231M-RAD-11-Z flow meter/controller. Non return valves were installed after the CO line (to avoid CO$_2$ entering into into the mass flow controller) and after the union between both gases to avoid liquids in this gas section.

- **Liquid input.**
  Liquid substrates were fed through a Gilson 305 HPLC pump and mixed with the gases before entering the reactor.

- **Reactor area.**
  The mixture of gases and liquids were preheated in a coil wrapped around a heated aluminium block to reach the supercritical state and then passed through the reactor/s (Figure 170) which are in heated aluminium blocks. A filter was installed after the reactor to avoid silica particles being entrained into the decompression system.

![Figure 170: Reactor diagram for SILP catalysis](image-url)
Recovery area.

The products and remaining substrates were decompressed to ambient pressure and collected in a vessel. An auxiliary collection vessel was installed in case the first one was filled. The flow of decompressed gases was measured with a Brooks 1357 flow meter and the gases vented to the atmosphere. The flow meter was used to regulate the CO\textsubscript{2} flow in the system.

A photograph of the rig is shown in Scheme 50. Note that the flow is from right to left (gas feeding from right and product collection on left).

![Scheme 50: First rig set up picture]

ACV: auxiliary collection vessel
BV: ballast vessel
DC: decompression chamber
F: filter
FCV: flow control valve
FM: flow meter
GB: gas booster
H: heater
LP: liquid pump
MFC: mass flow controller
NRV: non return valve
P: pressure transducer
PCV: pressure control valve
PH: pre-heater
R: reactor
Sub: substrate
SV: shut-off valve
T: thermocouple
V: vent
Experimental work

The second rig (an improved version of the first one) is shown in Scheme 51. The changes in the rig are explained below:

- The NWA PM 101 supercritical fluid pump and the pressure control valve were substituted by a Jasco PU-2080-CO₂ Plus delivery pump which allowed better control and monitoring of the CO₂.
- The decompression control valve was substituted by a Jasco BP-2080 Plus automatic back pressure regulator which allowed a monitored constant pressure in the system.

Scheme 51: Second rig set up

In a later rig update, a gas chromatograph (Shimadzu GC-2010 Plus) was connected via an online sampling loop after the reactor which allowed monitoring of the reaction conversion.
6.6.2 Continuous flow operation procedure

Before each reaction the rig was cleaned by passing acetone through it for several hours. When starting a new reaction, the GC was warmed up first. Next, the pre-heater was set to the desired temperature and switched on and the reactor, previously filled with the SILP, connected to the rig under a flow of the gases required for the reaction. The rig was then pressurised to the desired pressure and checked for leaks and the reactor was heated to the desired temperature. The liquid pump was purged under N\textsubscript{2} with the substrate solution. When the temperature, pressure and flows were stable the substrate was pumped in at the desired flow rate. Inside the reactor (Figure 171), the substrates that were dissolved in scCO\textsubscript{2}, diffused into the ionic liquid layer deposited over the silica pores. The IL was insoluble in the scCO\textsubscript{2}. The catalyst, also insoluble in the scCO\textsubscript{2}, was dissolved into the IL and reacted with the substrates to give the products. The products, soluble in the scCO\textsubscript{2}, flowed out of the reactor into a decompression chamber, collected every hour, weighed to check the mass balance and analysed by the appropriate techniques.

![Diagram of reactor](image)

Figure 171: Reactor’s inside expanded view.
6.7 NOTES AND REFERENCES


