CONTINUOUS FLOW HOMOGENEOUS CATALYSIS USING IONIC LIQUID/SUPERCRITICAL FLUID BIPHASIC SYSTEMS
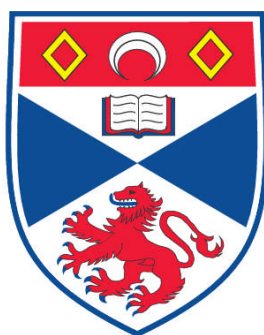
Tânia Isabel Quintas Martins

A Thesis Submitted for the Degree of PhD
at the
University of St. Andrews

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Continuous Flow Homogeneous Catalysis using Ionic Liquid/Supercritical Fluid Biphasic Systems

A thesis presented by

Tânia Isabel Quintas Martins

to the

University of St Andrews

in application for the degree of

DOCTOR OF PHILOSOPHY

To my Parents.

Para ser grande, sê inteiro...

Para ser grande, Sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo que fazes.

Assim em cada lago a Lua toda

Brilha, porque alta vive.

Ricardo Reis

Declaration

I, …………………………………………………………., hereby certify that this thesis, which is approximately ……………… 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.

Date …………......… **Signature of Candidate** ………………………………...…

I was admitted as a research student in October 2004 and as a candidate for the degree of ……………………………......…. in October 2004; the higher study for which this is a record was carried out in the University of St Andrews between 2004 and 2010.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of ……………………..………..…… in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Acknowledgements

Abstract

Ionic liquid/scCO$_2$ biphasic systems have been studied as a possible solution to the main problems concerning homogeneous catalysis reactions such as, the product/catalyst separation, the catalyst retention in the reaction medium and the use of organic solvents. The hydroformylation of long chain alkenes (1-octene) has been carried out as a continuous flow reaction using [OctMIM]Tf$_2$N (OctMIM = 1-octyl-3-methylimidazolium, Tf = CF$_3$SO$_2$) as the reaction solvent and scCO$_2$ as the mobile phase to extract the products. The performance of the rhodium complexes formed with the ionic ligands [PentMIM][TPPTS] (1-pentyl-3-methylimidazolium tri(m-sulfonyl)triphenylphosphine) and [OctMIM][TPPTS] (1-octyl-3- methylimidazolium tri(m-sulfonyl)triphenylphosphine) is described under different sets of experimental conditions.

Continuous flow hydroformylation of 1-octene was also carried out using a SILP (**S**upported **I**onic **L**iquid **P**hase) catalyst formed with the TPPTS-based ionic ligands named above. The SILP system described in this work has the peculiarity of introducing the "without gases" approach: *syn* gas was synthesised *in situ* by the decomposition of formaldehyde.
The performance of both systems is compared in the end.

The extension of the continuous flow ionic liquid/scCO$_2$ biphasic system is shown with the optimisation of the silver-catalysed heterocyclisation of furans. A comparison is carried out with a previously developed and optimised continuous flow heterogeneous system.

Abbreviations

[BDMIM]Br	1-butyl-2,3-dimethylimidazolium bromide
[BDMIM]Cl	1-butyl-2,3-dimethylimidazolium chloride
[BDMIM]TPPTS	1-butyl-2,3-dimethylimidazolium tri(m-sulfonyl)triphenylphosphine
[BMIM]Cl	1-butyl-3-methylimidazolium chloride
[BMIM]PF$_6$	1-butyl-3-methylimidazolium hexafluorophosphate
[EMIM]Tf$_2$N	1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)-amide
[EtNH$_3$][NO$_3$]	Ethylammonium nitrate
[N(CF$_3$SO$_2$)]$^-$	[Tf$_2$N]$^-$
[Octmim]Br	1-octyl-3-methylimidazolium bromide
[OctMIM]Tf$_2$N	1-octyl-3-methylimidazolium bis(trifluoromethanesulfonyl)-amide
[OctMIM]TPPTS	1-octyl-3-methylimidazolium tri(m-sulfonyl)triphenylphosphine
[Octmpyr]Br	1-octyl-3-methylpyridinium bromide
[Octmpyr]Tf$_2$N	1-octyl-3-methylpyridinium bis(trifluoromethanesulfonyl)-amide
[PentMIM]Cl	1-pentyl-3-methylimidazolium chloride
[PentMIM]TPPTS	1-pentyl-3-methylimidazolium tri(m-sulfonyl)triphenylphosphine
[PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)]	1-Propyl-3-methylimidazolium Diphenyl(3-sulfonatophenyl)-phosphine
[PrMIM]Br	1-propyl-3-methylimidazolium bromide
[PrMIM]Cl	1-propyl-3-methylimidazolium chloride
[PrMIM]TPPMS	1-Propyl-3-methylimidazolium Diphenyl(3-sulfonatophenyl)-phosphine
^{1}H NMR	Proton nuclear magnetic resonance
^{31}P NMR	Phosphorus nuclear magnetic resonance

acac	2,4-pentanedione
AgCF$_3$SO$_3$	Silver triflate
AgNO$_3$.SiO$_2$	Silver nitrate on sílica gel
Al$_2$O$_3$	Aluminum oxide
C$_2$F$_4$	Tetrafluoroethylene
C$_4$F$_9$I	Perfluoro-tertiary-butyl iodide
CD$_2$Cl$_2$	Deutered dichloromethane
CDCl$_3$	Deutered chloroform
CO	Carbon monoxide
Co	Cobalt
Cr	Chromium
CSTR	Continuously stirred tank reactor
DCM	Dichloromethane
DMC	Dimethyl carbonate
DME	Dimethyl ether
Et	Ethyl
GC	Gas chromatography
GC	Gás chromatography
GC-FID	Gas chromatography flame ionisation detection
H$_2$	Hydrogen
HCl	Hydrogen chloride
HCO$_2$H	Formic acid
HCOH	Formaldehyde
HF	Hydrogen fluoride
Hg	Mercury
IL	Ionic liquid
K$_2$OsO$_4$.2H$_2$O	Potassium osmate dihydrate
l:b	Linear to branched ratio
Li(Tf$_2$N)	Lithium bis(trifluoromethanesulfonyl)-amide
Me	Methyl
MeI	Methyl iodide
MeOH	Methanol

N_2	Nitrogen
Ni	Nickel
NMR	Nuclear magnetic resonance
P_2O_5	Phosphorus oxide
p_c	Critical pressure
Pd	Palladium
$Ph_2P(3-C_6H_4SO_3Na)$	TPPMS
ppb	Parts per billion
PPh_3	Triphenylphosphine
ppm	Parts per million
Pt	Platinum
PVP	Polyvinylpyrrolidone
Rh	Rhodium
S	Sulfur
$scCO_2$	Supercritical carbon dioxide
SCF	Supercritical fluid
SILP	Supported ionic liquid phase
T_c	Critical temperature
THF	Tetrahydrofuran
TOF	Turnover frequency
TON	Turnover number
TPPDS	Disodium salt of 3,3'-phenylphosphinediyl-benzenesulfonic acid
TPPMS	Mono-sulfonated triphenylphosphine, monosodium salt
TPPTI	tri(*m*-sulfonyl)triphenyl phosphine tris(1-butyl-3-methylimidazolium) salt
TPPTS	tri(*m*-sulfonyl)triphenyl phosphine trisodium salt
UV	Ultraviolet
VOC	Volatile organic compound
XPS	X-ray photoelectron spectroscopy
δ	Chemical shift relative to tetramethylsilane (TMS)

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Chapter 1

General Introduction

1. General Introduction

Parts of this Chapter have been published as T. Quintas and D. J. Cole-Hamilton, *Flow Processes in Non-Conventional Media,* in *Chemical Reactions under Flow Conditions*, Eds. S. V. Luis and E. Garcia-Verdugo, Royal Society of Chemistry, Cambridge, 2010, Chapter 5, pp. 163-195.

1.1 The Need for Alternative Solvents in Flow Catalysis

1.1.1 Homogeneous *vs.* Heterogeneous Catalysis

A chemical process involving reactants and a catalyst is denominated catalysis. If during the catalytic process both the catalyst and the reactants are in the same phase, mostly the liquid phase, it is called homogeneous catalysis. Otherwise, it is called heterogeneous catalysis.

Although homogeneous catalysis has very clear advantages when compared to heterogeneous catalysis, many of the known homogeneous catalytic systems are still not being commercialised because of problems concerning the separation of the catalyst from the product, the retention of the catalyst in the reaction medium and the use of organic solvents.[1, 2]

The advantages of homogeneous catalysts over the heterogeneous catalysts include:

- their higher specificity;

- the availability of all the catalytic centres because of the dissolution of the catalyst in a solvent;

- reproducibility;

- controllability.

Despite this, heterogeneous catalysts can be a cheaper option to the chemical industry because of their higher thermal stability, the lack of need for a large quantity of suitable solvents but most of all, the easy separation of the very expensive catalyst from the product and its easy reuse.

Table 1.1 provides a simple way of illustrating the advantages and disadvantages of homogeneous versus heterogeneous catalysis.

Table 1.1 Homogeneous versus heterogeneous catalysis.[3]

	Homogenous	Heterogeneous
Activity	+++	-
Selectivity	+++	+
Catalyst description	++	-
Catalyst recycling	-	+++
TON	+	+++
Quantity of catalyst	++	+++

Society in general, and scientists in particular, are starting to be aware of the dangers and consequences caused by the damage that is being done to our environment and several efforts are being made, in order to create and/or preserve a better world and environment for all of us. Alongside the catalyst separation problem, there are also the many environmental problems that are starting to concern and affect society. It is well known that volatile organic compound (VOC) vapours can be released by organic solvents to the atmosphere and that their use in large scale by the chemical industry is not benign to the environment. Also, we should beware that eventually the crude oil supplier, which is the source of most organic solvents, will run out. There is a need for non-crude oil based media.

Over the last few decades, the chemical industry has been trying to create, develop and substitute already existing industrial processes for better and cleaner ones. An important part of this research involves the substitution of common solvents by alternative ones, which not only reduce emissions of VOCs to the atmosphere, but also offer processing advantages in terms of allowing reactions that would otherwise be carried out in batch mode to be made continuous.

Homogeneous catalysis is usually carried out in batch or batch continuous reactions. Batch reactions have the disadvantage that the reactor must be opened at the end of the reaction; the product, catalyst and solvent must be separated and, if possible, the catalyst and solvent recycled. This leads to very significant downtime and low production efficiency.

Batch continuous reactions operate continuously (Figure 1.1) with substrates being fed into a reactor, usually a continuously stirred tank reactor (CSTR). Part of the reaction solution flows into a separator where the product, solvent and catalyst are separated in a continuous process, usually distillation or phase separation. The phase or residue containing the catalyst is then fed back into the reactor whilst the products are removed for further processing. The main disadvantage of such batch continuous processes is that some of the catalyst is in the separator or recycling loop. Not only does this mean that a larger amount of catalyst than is necessary to sustain the reaction at the desired rate must be used, but also that it is under conditions very different from those in the catalytic reactor for which it has been optimised. Often the conditions in the separator can be harsh (high temperature, low pressure) and can lead in some cases to catalyst decomposition or to precipitation. In the worst cases, these problems may lead to clogging of the recycling loop and very considerable downtime.

Products

CSTR

Flash
Column
or
Phase
Separator

Substrates

Catalyst recycle
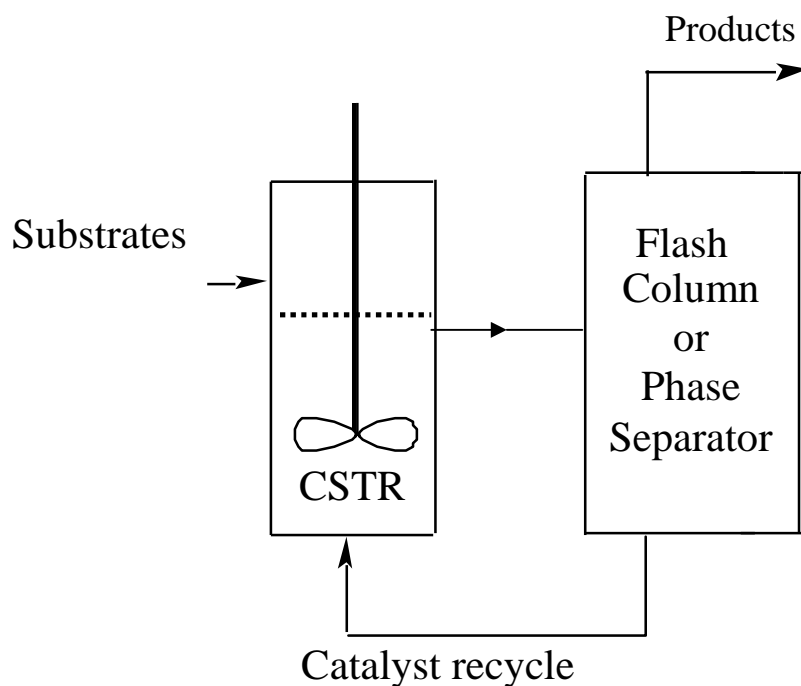
Figure 1.1 Schematic diagram of a batch continuous reactor.

1.2 Continuous Flow Processing using Homogeneous Catalysis

In order to address these disadvantages, it would be ideal if homogeneously catalysed reactions could be carried out under conditions where the substrate flows through the catalyst solution and the product flows out of the reactor, with the catalyst remaining in the reactor at all times (Figure 1.2). Such a system would be very similar to those used for heterogeneous catalysts.
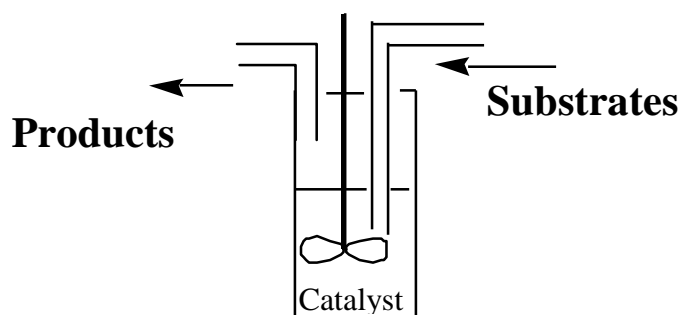
Figure 1.2 Desired process for continuous flow homogeneous catalysis.

Such flow systems are possible if all the reagents are volatile and if all the products can be distilled from the reactor containing a non-volatile solvent and a non-volatile catalyst. An example is the commercial hydroformylation of propene to butanals. This is carried out using Rh/PPh_3 catalysts with aldol condensation products of the formed aldehydes acting as the solvent. Propene, CO and H_2 are fed into the reactor in the gas phase whilst the product is also removed in a continuously flowing process in the gas phase. This is possible because the boiling point of butanal is 75 ^{o}C and the reaction is carried out at about 100 ^{o}C.[4] To continue with the example of hydroformylation, this continuous flow approach is difficult for higher boiling aldehydes derived from longer chain alkenes because the rhodium based catalyst decomposes at *ca*, 110 ^{o}C and most aldehydes boil at higher temperatures than this (Figure 1.3).
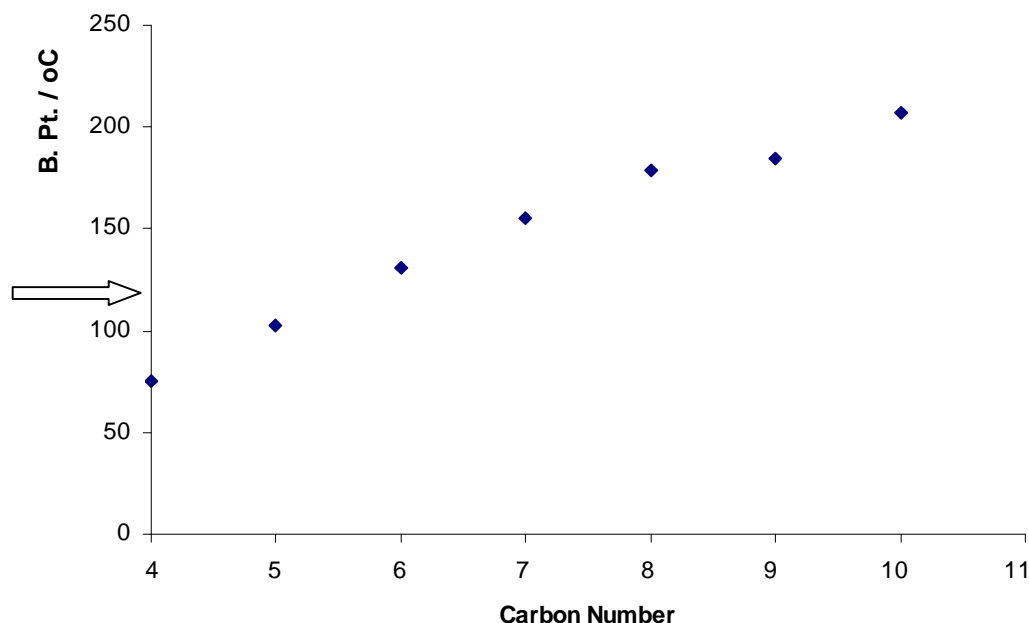
Figure 1.3 The effect of chain length on the boiling point of linear aldehydes. The arrow indicates the temperature of decomposition of Rh/PPh$_3$ alkene hydroformylation catalysts.

Longer chain aldehydes are still manufactured by homogeneous hydroformylation reactions, but not in continuous flow processes, because they are valuable materials used as plasticizers and in the manufacture of soaps and detergents, and because alkenes are relatively cheap. In most cases, cobalt catalysts are employed sometimes with added alkylphosphines.[4, 5] These require more forcing conditions than rhodium and are less selective, either giving much higher amounts of undesired branched products (no phosphine added) or giving significant amounts of alkane side product from hydrogenation of the alkene (phosphine modified; alcohols rather than aldehydes are the predominant products). These reactions are run in batch continuous mode. The product separation involves several washes with sodium hydroxide and neutralisation, leading to salt formation. Only very

recently has Rh/PPh$_3$ been commercialised, by Sasol using technology developed by Kvaerner (now Davey) Process Technology. This is again run in batch continuous mode with the separation being carried out by reduced pressure distillation.[6]

This brief discussion of alkene hydroformylation serves to illustrate some of the difficulties of homogeneous catalysis and the barriers that exist to operation under continuous flow mode. However, recent developments have introduced new types of solvents that do allow homogeneous catalytic reactions to be carried out under genuinely continuous flowing conditions.[2, 7] In this Chapter, we review progress that has been made in the use of non-traditional solvents to allow homogeneous catalysis to be carried out under flow conditions. In addition, we highlight systems where non-conventional solvents have been used in batch continuous processes.

1.3 The Use of Solvents

Solvents are typically described as any material which is capable of dissolving another substance.[8] For many years, industry has been using common organic solvents, like for instance, chloroform, tetrahydrofuran (THF), dichloromethane (DCM) or acetone, with serious consequences to the environment. These consequences come mainly from the fact that solvents are normally used in very large quantities during the chemical processes and also because they are usually volatile liquids (VOCs) that are very hard to contain without spreading vapours to the atmosphere.

Besides being used as reaction media in most chemical processes, solvents are also used as cleaning solutions, to perform a separation or an extraction or even to take part in product synthesis.

Whatever the main aim of the use of a solvent, it is important to choose it properly taking in account its various properties, including:

- viscosity;

- polarity;

- solubilising power;

- volatility.

These properties are very important and should be studied as a whole so that, during any chemical process, the solvent involved should be able to dissolve the reagents and reactants completely, be inert to all the reaction conditions, have an appropriate boiling point and most of all, it should be easily removed from the other products at the end of the process. Because normally the easiest ways to remove the solvent at the end of any chemical process are by evaporation or distillation, volatile solvents have become very popular over the years.

Together with the fact that common solvents emit vapours to the atmosphere, contributing to global warming and sometimes being involved in the depletion of the ozone layer, there are other hazards to take into account when using common solvents, such as their toxicity and flammability. Therefore, it should come as no surprise that these are amongst the most regulated chemicals.[9, 10]

1.3.1 Traditional Solvents *vs.* Non-Conventional Solvents

Considering the points explained above, researchers and industry have been joining forces together over the last decades to develop new classes of solvents, where the main aim is to reduce significantly all the hazards associated with traditional solvents. This can be achieved through the design of new substances, such as ionic liquids for which, because of their very diverse nature, the performance can be tuned to be as good as or even better than conventional solvents. Another alternative is to use no solvents at all, the so-called solventless systems.[11] Other successful examples of applications of new reaction media include the use of water (not previously widely applied in the chemical industry), supercritical fluids and fluorous solvents amongst others. Industry and researchers have been working hard in order to exploit the advantages of these solvents and to implement them in well-known chemical processes. We shall now review recent progress in the use of ionic liquids and of supercritical fluids, highlighting their uses in homogeneous catalysis and especially, where possible, in flow systems.

1.4 Ionic Liquids

1.4.1 The Concept of Ionic Liquids

Ionic liquids (IL) or molten salts are liquids at room temperature consisting only of ions. The main difference between ionic liquids and common molten salts, like for instance NaCl, is the fact that they are liquids at low temperatures.[12]

Although the first room-temperature ionic liquid, [EtNH$_3$][NO$_3$], was discovered in 1914, they were only "rediscovered" a few decades ago; since then, their properties and potential applications have been increasing enormously[13]. Nowadays ionic liquids are considered as a whole "new class of solvents" and have been extensively studied and tested in various chemical processes.[12, 14-19]

One of their many advantages when compared to traditional solvents consists of the possibility of combining several anions and cations in order to synthesise several potential ionic liquids. Basically, it is possible to "design" an ionic liquid to represent the ideal solvent properties for a certain reaction. Amongst the most common types of cations used in the synthesis of ionic liquids there are, for example, the N, N'-dialkylimidazolium ions, the tetraalkylammonium ions, the alkylpyridinium ions or the tetraalkylphosphonium ions. As for anions, the most common ones are [AlCl$_4$]$^-$, [PF$_6$]$^-$, [BF$_4$]$^-$ and [Tf$_2$N]$^-$ (Figure 1.4). Just to give an idea about the potential scope, according to Seddon, it is possible to have around 10^{18} potential ionic liquids only in the imidazolium and pyridinium systems, only by varying the combination of anions and cations.[20]

BF_4^-, PF_6^-, $CF_3SO_2^-$, $(CF_3SO_2)_2N^-$, $CH_3SO_3^-$, $AlCl_4^-$, $Al_2Cl_7^-$, NO_3^-
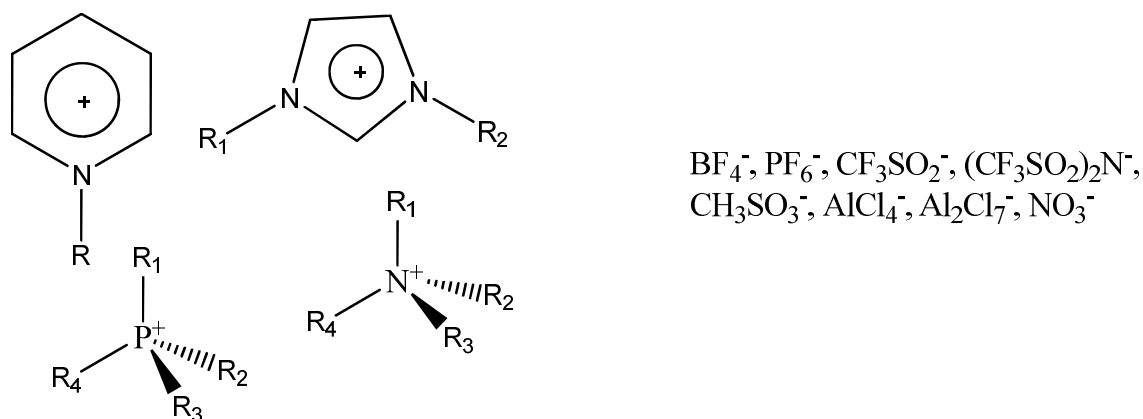
Figure 1.4 Some of the most popular cations and anions used in the synthesis of ionic liquids.

By changing the nature of the cation and anion comprising the ionic liquid, it is possible to change the properties of the ionic liquid itself, such as, its viscosity and solubility.[19] For instance, by increasing the size of the alkyl chain of the cation composing part of the ionic liquid, it is possible to increase its solvating properties for less polar solutes.[16] This ability of adjusting the properties of the ionic liquids through the immense possibilities of cation-anion combination, gave them the well deserved name of "designer solvents".

Two of the greatest advantages of ionic liquids when compared with traditional solvents are their non-measurable vapour pressure and their non-flammability. This potentially makes them environmentally benign as they do not release vapours into the atmosphere. Other factors must also be considered however, such as, environmental persistence, toxicity, corrosivity and the environmental impact of their synthesis. Since there are so many different possible combinations of ionic liquids, it is impossible to generalise, but it should be possible to find ionic liquids which will have minimum negative environmental impact throughout their

life cycle. Also, the absence of a measurable vapour pressure is very advantageous in terms of product separation from the reaction medium and the catalyst by distillation.[12] Most of the ionic liquids used are also very thermally stable, which allows chemical reactions or separations to be carried out at very high temperatures without negative effects on the ionic liquid.

In summary, some of the properties of ionic liquids which allow some liquids to be considered as alternatives to replace traditional solvents and stand as a "new class of solvents" are:

- tuneable solvation properties;

- non-measurable vapour pressure;

- non-flammable below decomposition temperature;

- high thermal stability;

- very good solvents for a variety of organic and inorganic compounds;

- high electrical conductivity;

- very cheap and easy to prepare (in some cases).

In 1972, Parshall reported the first successful platinum catalysed hydroformylation reaction carried out in an ionic liquid reaction medium.[21] He introduced the use of tetraalkylammonium salts of $GeCl_3^-$ and $SnCl_3^-$ as solvents - then referred to as non-conventional molten salts - in several catalytic reactions because of their non-volatility, thermal stability and the possibility of retaining the metal catalyst and increasing the reaction selectivity.

1.4.2 Continuous Flow Catalysis using Ionic Liquids

1.4.2.1 Liquid-Liquid Biphasic Catalysis

One of the main applications of ionic liquids as solvents is in liquid-liquid biphasic catalysis (Figure 1.5). In such systems there are two immiscible solvents but only one of the phases contains the catalyst; this allows the very easy separation of the product by decantation and recycling of the catalyst phase.[12, 19] The characteristics of these biphasic systems may allow homogeneous systems to behave almost like heterogeneous systems.
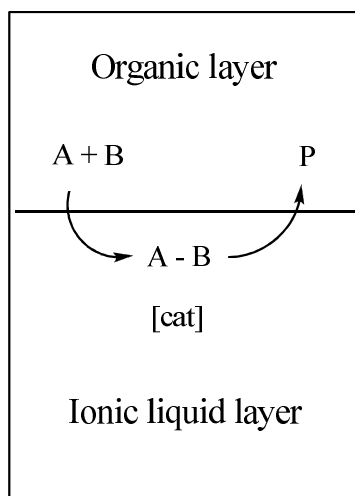
Figure 1.5 Liquid-liquid biphasic catalysis using ionic liquids for catalyst retention.

Due to their tunable solvating properties it is possible to "design" the right ionic liquid to guarantee that the catalyst will be totally dissolved in the ionic liquid phase. The main result of this is the verified reduction in the catalyst leaching from the reaction medium into the product phase. In terms of industry, this is a big advantage when considering the price of the metal catalysts, which can now be used for longer periods of time.

The first ionic liquid based process to be used in industry, which was introduced by Eastman Chemical Company in 1998,[22] involved the use of long-chain tetraalkylphosphonium salts in a Lewis acid catalysed isomerisation of monoepoxidised butadiene to dihydrofuran, an important intermediate from which higher added products can be synthesised.
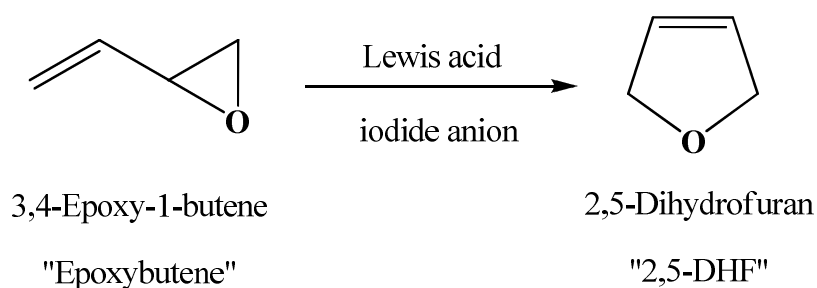
Scheme 1.1 Isomerisation of 3,4-epoxy-1-butene to 2,5-dihydrofuran (DHF).

In this process, certain very polar low molecular weight oligomeric side products develop. The reaction is carried out in the presence of the phosphonium salt, which has very low polarity and is soluble in heptane. After the volatile products have been distilled from the reactor, a concentrated solution containing the catalyst and the phosphonium salt is continuously fed to a counter-current extractor, where the catalyst, phosphonium salt and polar side products are separated using heptane. The catalyst and phosphonium salt dissolve, but the side-products do not. The separated side products are sent for incineration, whilst the non-polar extract is distilled to remove heptane and to leave the catalyst and the phosphonium salt, which are recycled back into the reactor. This batch continuous process, which unusually exploits the very low polarity of the liquid phosphonium salt ran for 8 years with minimal losses of phosphonium salt (Figure 1.6).
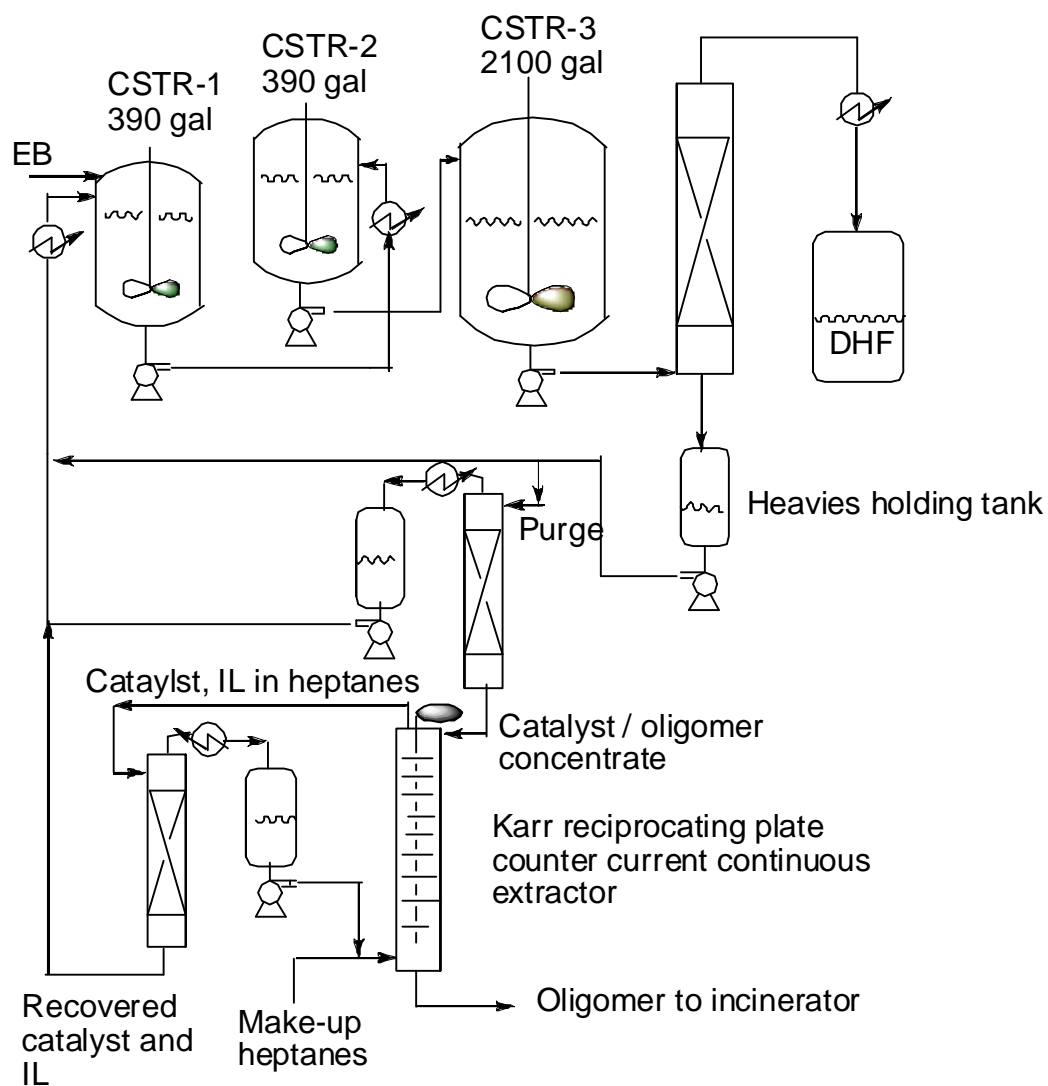
Figure 1.6 Schematic diagram of the reactor and separator used by the Eastman Chemical

Company for the isomerisation of epoxybutadiene to dihydrofuran. The catalyst consists

of a Lewis acid and an apolar quaternary phosphonium salt.[22, 23]

In 2002, BASF[TM] introduced another commercial use of ionic liquids, the BASIL[TM] (**B**iphasic **A**cid **S**cavenging utilizing **I**onic **L**iquids) process.[24] Alkoxyphenylphosphines are used as raw materials for the production of photoinitiators to cure coatings and printing inks by exposure to ultraviolet (UV) light. Their synthesis (Scheme 1.2) has the major drawback of also producing HCl as a co-product. Conventionally, tertiary amines can be used to scavenge the HCl, but the thick, non-stirrable slurry resulting from the scavenging decreases enormously the efficiency of the process. It was also necessary to carry out the process in batch mode in order to filter the product after the reactor. As a result, throughput was very low and the process was difficult to operate.

$$PhPCl_2 + 2\,EtOH + 2\,R_3N \longrightarrow PhP(OEt)_2 + 2\,R_3N.H^+Cl^-$$
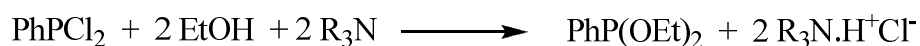
Scheme 1.2 The synthesis of diethylphenylphosphonite.

By introducing 1-methylimidazole, an ionic liquid precursor, as the HCl scavenger in the production of the diethyphenylphosphonite, Maase and co-workers[25] greatly improved the rate and efficiency of the process because 1-methylimidazolium chloride, which forms, is a colourless mobile liquid, which separates from the product. The imidazole has a nucleophilic catalytic action in the process, so the whole reaction can take place in less than one second, leading to an enormous increase on the reaction rate and process productivity (by a factor of 8×10^4 to 690 000 kg m^{-3} h^{-1}).

In 2004, the BASIL process was initiated using a large vessel with the actual reaction being carried out in very small jet reactors (Figure 1.7).[25] It is also possible to regenerate the imidazole and release HCl on heating.

Figure 1.7 The BASIL process is run in a small jet reactor. The plant has a total capacity of 690 000 kg m^{-3} h^{-1}.[25]

Another good example of these systems is the Dimersol X process, which was developed by the Institut Français du Pétrole (IFP).[26-28] The dimerization of butene into octene is catalyzed by Ni(II) salt complexes activated with an alkylaluminium co-catalyst. Although it has all the advantages of a homogeneous process, it also comes with the main associated drawback, the big loss of catalyst when carried out continuously.

Chauvin, Olivier-Bourbigou and other researchers from the IFP, identified a suitable biphasic system by using 1,3-dialkylimidazolium chloroaluminate as a solvent for this process. This ionic liquid creates a good liquid-liquid biphasic system since it is a good solvent for butenes but not for the dimerisation products. The expulsion of the product leads to fewer secondary products. Furthermore, the ionic liquid can also dissolve and stabilise the Ni catalyst without even needing the help of a ligand.

Tests were run using a continuous flow through a CSTR followed by a phase separator (Figure 1.8). For a period of 5500 h, Raffinate II (industrial feed composed by 70 wt% butenes, of which 27 wt% was 1-butene) was fed continuously into the reactor where the ionic liquid layer was vigorously mixed with the organic layer. The mixture then passed to the phase separator, where gravity separation happened very fast and cleanly. The upper organic phase containing the products escaped through an overflow for collection and processing, whilst the lower ionic liquid phase containing the catalyst was recycled back to the reactor. After deliberately stopping the tests, the researchers concluded that it was not necessary to add more ionic liquid during the tests and that the Ni leaching had decreased dramatically when compared with the homogeneous Dimersol process.
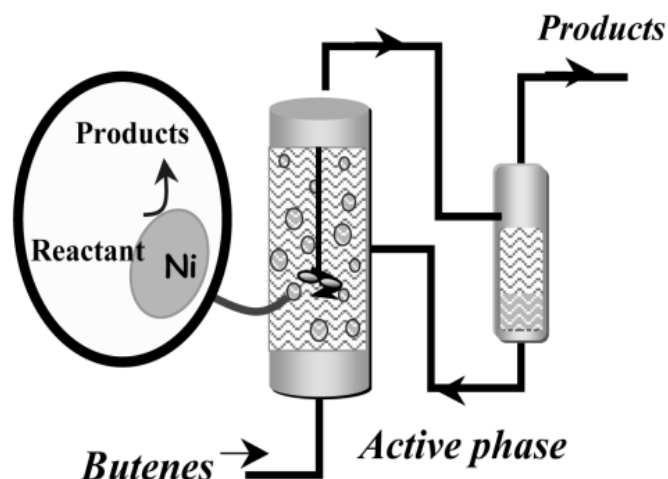
Figure 1.8 Continuous dimerisation of butenes using 1,3-dialkylimidazolium chloroaluminate to immobilize the Ni-catalyst.[12]

All these examples involve batch continuous processing where part of the catalytic solution is continuously removed for product separation and catalyst recovery (recycling). One possible way in which such catalysts might be used for genuine continuous operations might be to use a counter-current in a loop type reactor. The catalyst dissolved in the ionic liquid would be fed from the bottom of the counter-current separator, whilst the substrates were fed from the top. The reaction would occur within the separator and product would be bled from the bottom of the column. The ionic liquid containing the catalyst would then be recycled from the top to the bottom of the reactor. The conditions throughout the reactor would be the same and the product catalyst separation would be integrated with the reaction. In practice, such a process has never been described.

Two genuinely continuous flow processes involving ionic liquids have been, however, suggested and demonstrated. One is to support a thin film of ionic liquid within a porous support and to use it in a tubular heterogeneous reactor – so called supported ionic liquid phase catalysts (SILP).[29] The other is to transport substrates

and products into and out of the ionic liquid by using a supercritical fluid as the transport vector.[30-32]

1.4.2.2 Supported Ionic Liquid Phase Catalysis

Continuous flow hydroformylation of long chain alkenes (1-octene) has been carried out in a supported homogeneous system using a SILP (**S**upported **I**onic **L**iquid **P**hase) catalyst, where a thin layer of ionic liquid catalyst is immobilized at the surface of an inert solid support, like for instance, silica gel.

SILP catalysts have the ability to combine the advantages of both homogeneous and heterogeneous catalysts. By using a fixed-bed reactor in a homogeneous system, it is possible to achieve a better catalyst/product separation and still expect the same performance in terms of selectivity as a "normal" homogeneous catalyst.[29, 33]

SILP catalysis can be carried out in the liquid[29, 34-37] or gas[28, 37-40] phases. When using liquid phase substrates, there is a possibility that the catalyst and ionic liquid may leach from the support, especially if the ionic liquid has been designed to dissolve the substrate so as to reduce problems with mass transport. One way of getting around this problem is chemically to anchor the ionic liquid to the support. Mehnert and co-workers[29] investigated the hydroformylation of 1-hexene using Rh/[BDMIM]$_3$[P(3-C$_4$H$_6$SO$_3$)$_3$] (BDMIM = 1-butyl-2,3-dimethylimidazolium) and a series of ionic liquids supported in the pores of silica, from which the surface hydroxyl groups had been removed by reaction with an imidazolium modified triethoxysilane. This gives a layer of imidazolium salt anchored to the

silica, which may aid in the immobilisation of the ionic liquid. In general, it was found that turnover frequencies were low ($< 55 - 65$ h^{-1}) compared with the ones for an analogous homogeneous system using Rh/PPh$_3$ (400 h^{-1}), but higher than the ones for the bulk biphasic system (23 h^{-1}). Leaching of the ionic liquid and the catalyst was significant but less when very polar ionic liquids, such as [BMIM]PF$_6$, were used or if the conversion of the non-polar alkenes to the more polar aldehydes was kept to a minimum. Despite the leaching, the SILP process provides a very elegant solution to the catalyst product separation problem.

Hydrogenation of alkenes does not produce a polar product, so a similar system to the one described above for the hydroformylation of liquid alkenes was used in the hydrogenation of 1-hexene to give enhanced activity compared with the homogeneous or bulk biphasic systems without any measurable leaching. The catalyst could be reused 18 times without any loss of activity.[41] Continuous reactions in a flow reactor were not reported.

One other problem that can arise when using SILP catalysts for liquid phase substrates in reactions which also involve gases, is severe gas depletion. The aspect ratio of the pores within the support is high, so that gases have to diffuse a long way to arrive at the catalytically active centres. Once the gas that is initially dissolved in the substrate has been consumed, the reaction rate will drop significantly as it becomes gas transport limited.

None of the problems occur if the reaction is carried out in the gas phase. Here, diffusion to the catalytic sites is fast and, being essentially involatile, neither the catalyst nor the ionic liquid is transported out of the reactor. Thus, continuous

flow propene[33] or butene hydroformylations have been performed over a SILP catalyst for several hundred hours using, for example, a Rh/sulpho-xantphos catalyst in supported [BMIM][n-$C_8H_{17}OSO_3$].[42] The support must first be treated to remove acid sites which protonate the ligand, but under optimised conditions, the system works very well. There is a small fall off in rate at longer reaction times because aldol condensation products of the C_4 aldehydes formed block the pores and/or catalyst, but these products can be removed by evacuating the catalyst at elevated temperature. Following this treatment, the catalyst returns to its initial activity and selectivity.[33, 37, 38, 40, 43-45]

The main problem with using all gas phase reactions is their limited scope. There are rather few reactions, methanol carbonylation being another that have been investigated[36] where the substrates and products are all in the gas phase at the reaction temperature. An alternative is to use high temperatures and very low flow rates of the less volatile substrates. However, the total throughput of such a system will be rather low.

One other alternative is to carry out the SILP catalysis using relatively low volatility substrates transported over the catalyst bed dissolved in a supercritical fluid.[46] This type of system has a number of potential advantages. Gas diffusion is fast in the supercritical phase. With the substrates and gaseous reagents all being contained in the one phase, they all have very good access to the pores of the support and hence the catalytic centres. By using ionic liquids and ionic catalysts that are insoluble in the supercritical fluid, leaching should be minimised. Supercritical carbon dioxide (scCO$_2$) has been shown to increase the solubility of permanent gases within ionic liquids[47-49], so that the rate of transport of gases into

the ionic liquid should be improved. Finally, any heavy products that form may be soluble in the supercritical fluid, so that fouling of the catalyst can be avoided.

A system for the hydroformylation of 1-octene using a SILP catalyst consisting of a rhodium complex formed *in situ* from [Rh(acac)(CO)$_2$] (acacH = 2,4-pentanedione) and [PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)] (PrMIM = 1-propyl-3-methylimidazolium), dissolved in a thin film of [OctMIM]Tf$_2$N (OctMIM = 1-octyl-3-methyimidazolium; Tf = CF$_3$SO$_2$) with CO$_2$ flow has been demonstrated and is shown schematically in Figure 1.9.[46] The reaction works best close to the critical point of the mobile phase producing over 500 catalyst turnover h^{-1} continuously for 40 h, with Rh leaching of only 0.5 ppm. Aldol condensation products from the C$_9$ aldehydes were also detected in the collected products, suggesting that fouling will not be a problem of long term use.
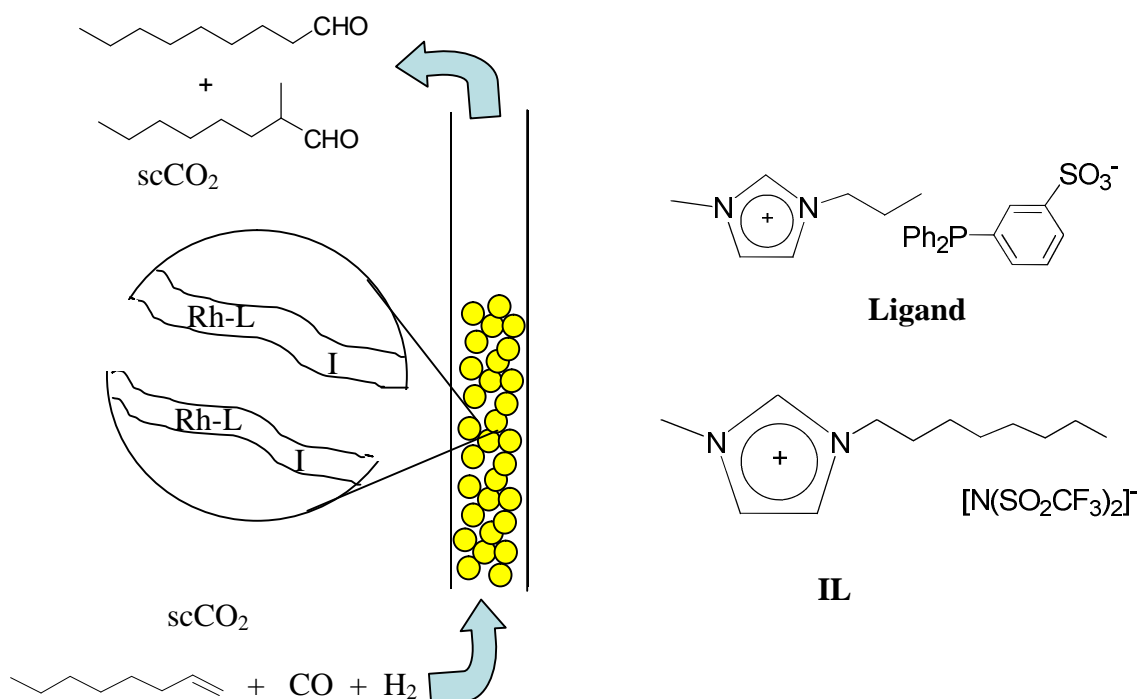
Figure 1.9 Schematic diagram of SILP catalyst with supercritical flow for the hydroformylation of 1-octene.[46]

1.4.2.3 Ionic Liquid/scCO$_2$ Biphasic Systems

The precursor to the SILP catalysts with supercritical flow were the IL/scCO$_2$ biphasic systems, which are amongst the most recent and promising alternatives to deal with the catalyst/product separation problem. These systems are based on the separation of the product and the retention of the catalyst in the solvent. The scCO$_2$ transports the products from the reactor and they can then be precipitated from the solution after the decompression of the gas.[30-32]

Having been involved in showing that scCO$_2$ can be very soluble in some ionic liquids (up to 60 mol %), whilst the same ionic liquids have no measurable

solubility in CO_2[50], Blanchard and Brennecke described how it is successfully possible to recover organic products from the ionic liquid [BMIM][PF$_6$] using scCO$_2$.[51] They consider this separation technique as being quite reliable and environmentally friendly. Although this is a biphasic system, both phases are liquid. However, it is helpful that the scCO$_2$ is highly soluble in the ionic solution. As for the ionic solution, it has to be insoluble in the scCO$_2$ to allow the product separation and the catalyst retention.

Brennecke and co-workers studied the high-pressure phase behaviour of these systems.[52] They tested the solubility of carbon dioxide in ten different imidazolium salts, varying both the anion and the size of the alkyl chain. The results revealed that, for all ionic liquids tested, the solubility of the carbon dioxide increased with increasing pressure and decreased with increasing temperature. Its solubility also increased when using ionic liquids with fluoroalkyl groups present in the anion, such as [Tf$_2$N]$^-$ or [methide]. As for the alkyl chain of the cation, the solubility of the carbon dioxide increased with increasing the length of the chain.

Sellin *et al.* (hydroformylation of long chain alkenes)[31] and Leitner, Wasserscheid and co-workers (asymmetric hydrovinylation of styrene with ethene)[53] were the first to describe continuous flow in IL/scCO$_2$ biphasic systems, although others had shown that catalytic reaction products could be extracted from an ionic liquid reaction medium using scCO$_2$[54] and that reactions in ionic liquids could be carried out in the presence of scCO$_2$. The products could be removed and the ionic liquid containing the catalyst recycled.[55]

As a brief explanation of the continuous flow hydroformylation process, the reactants (CO, H_2 and the alkene) and the CO_2 are introduced into the reactor in separate and continuous flows. Inside the CSTR, that already contains the ionic catalyst dissolved in the ionic liquid, the reactants become dissolved in the ionic liquid solution and react with the Rh catalyst. Both the ionic liquid and the catalyst are insoluble in the $scCO_2$, but the $scCO_2$ is soluble in the ionic liquid. The $scCO_2$ also increases the solubility of the CO and hydrogen in the ionic liquid.[47, 56, 57] The products dissolve in the $scCO_2$ and pass to the separator, where, by decreasing the pressure, the density of the CO_2 will also decrease and the products will precipitate from the solution into the collection vessel. The CO_2 can, in principle, be recycled (Figure 1.10).
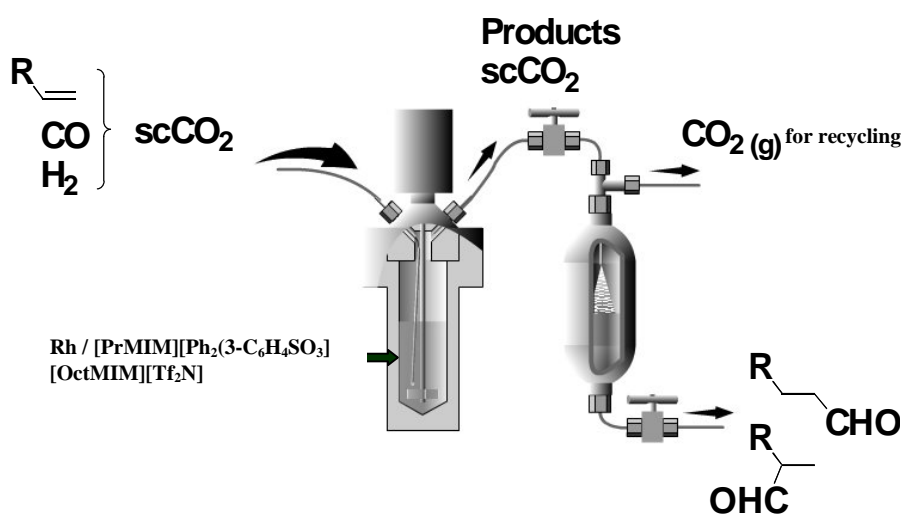
Figure 1.10 Schematic diagram of the continuous flow supercritical fluid - ionic liquid biphasic system applied in the hydroformylation of an alkene.[32, 58]

The first experiments involved the use of Rh/[PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)]. (Ph$_2$P(3-C$_6$H$_4$SO$_3$Na) was insufficiently soluble in the ionic liquid) in [BMIM]PF$_6$.[31] A stable reaction rate and linear selectivity were maintained over several hours, suggesting that the catalyst was stable, but the rate was very low (5 catalyst turnover h^{-1}). By increasing the length of the alkyl chain on the imidazolium salt and changing from [PF$_6$]$^-$ to [Tf$_2$N]$^-$ (desirable also because [PF$_6$]$^-$ reacts with water produced by aldol condensation of the product aldehydes to produce [O$_2$PF$_2$]$^-$ and HF),[31] the rate was increased by an order of magnitude[32] because the solubility of the 1-octene substrate in the ionic liquid was increased.[16] Further rate enhancements were achieved by varying the substrate flow and, especially the flow of CO/H$_2$.

Increasing the proportion of permanent gases in the flowing medium reduces the solubilising power of the CO$_2$ so that more of the substrate partitions into the ionic liquid, where the catalyst resides. In addition, it makes the flowing medium a poorer solvent for the catalyst so that rhodium leaching, which was already low, is reduced still further. At relatively high levels of CO/H$_2$, the reaction becomes limited by the intrinsic catalyst kinetics rather than by mass transport effects, but care must be taken because the flowing medium may become such a poor solvent for the reaction products that it no longer extracts them properly, they build up in the reactor and eventually a liquid mixture containing substrate, products, catalyst and ionic liquid fills the reactor and flows into the separator, necessitating extensive cleaning and causing substantial downtime.

Under the optimised conditions, steady state reaction rates of > 500 h^{-1} (in the commercially interesting region) with very low rhodium leaching (12 ppb) were maintained over many hours.[32]

The main disadvantages of this process were the very high pressure required to extract the products from the reaction solution (200 bar) and the poor selectivity to the linear product (~3:1).[32] The first problem can be alleviated in the SILP system, described above, because there it is possible to work in the expanded liquid phase without forming a homogenous mixture and removing the catalyst and ionic liquid, or by removing the necessity for product extraction by dissolving the catalyst in the reaction product (see Section 1.4.1.6).[59, 60]
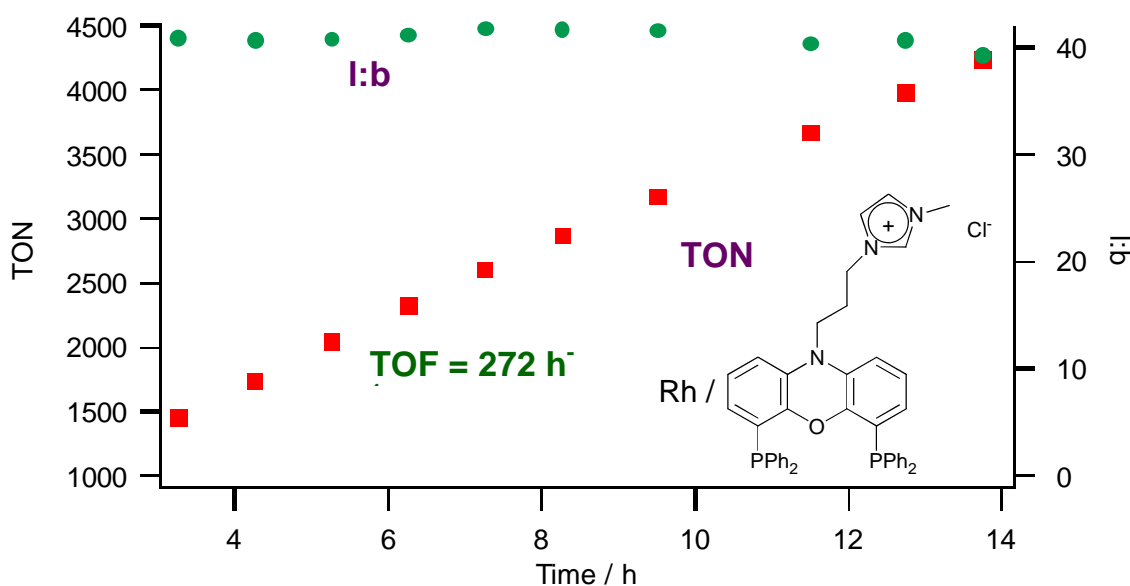
Figure 1.11 Hydroformylation of 1-octene in a continuous flow [OctMIM]Tf$_2$N/scCO$_2$ system using a rhodium complex of the ligand shown. The selectivity to the linear aldehyde was 92 %.[58]

The problem of product linearity was addressed by using a different ligand based on the highly selective xantphos core, modified to bear a pendant imidazolium functionality as shown in Figure 1.11, which gave linear/branched aldehyde ratios of 40:1 over an 8 h period with turnover rates of 280 h^{-1}. Rhodium leaching was increased to about 0.2 ppm.[58]

The hydrovinylation of styrene was performed in a continuous flow system at 0 ^{o}C in [EMIM]Tf$_2$N (EMIM = 1-ethyl-3-methylimidazolium), because the specially designed catalyst is thermally sensitive. Since the system was considerably below the critical temperature of CO_2, the reaction was probably carried out in liquid CO_2. Nevertheless, continuous operation was possible over > 60 h with good conversion and 60 - 66 % enantiomeric excess (ee).[61]

This type of process has now been applied in a wide range of catalytic reactions. These have been reviewed.[30]

1.5 Supercritical Fluids

A supercritical fluid (SCF) is normally defined as a substance (highly compressed gas) above its critical temperature (T_c) and critical pressure (p_c), where the critical point represents the highest temperature and pressure at which the substance can exist as a vapour and liquid in equilibrium.[62]
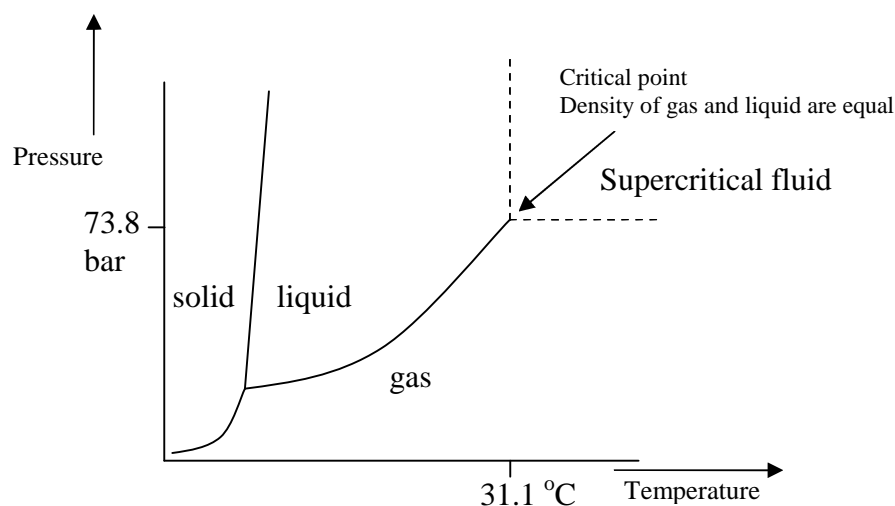
Figure 1.12 Phase diagram for pure carbon dioxide showing its critical parameters, p_c = 73.8 bar and T_c = 31.1 ℃.

Figure 1.12 shows the phase diagram for pure carbon dioxide which can, like many other materials, exist in the solid, liquid or gaseous forms. The tie lines shown represent phase transitions and in particular, that between the liquid and the gas, represents evaporation or condensation. For non-ideal materials, the critical temperature, T_c, is the temperature above which the gas will not condense, no matter how high the pressure is raised. Above this temperature and above the critical pressure (the boiling pressure at T_c) the material is termed a supercritical fluid and it has some properties that resemble those of a liquid (densities > 0.4 g cm^{-3}, ability to dissolve a range of organic compounds) and some that are gas-like (fills all the space available, flows like a gas, high diffusivity, total miscibility with permanent gases). In addition, the solubilising power of a supercritical fluid can be altered by changing the temperature and/or pressure. The critical point of CO_2 is 73.8 bar and 31.1 ℃, conditions which are readily accessible in both research and industrial environments. This, along with the low toxicity,

flammability and cost of CO_2 makes it the supercritical fluid of choice for many applications. The ability to dissolve organic materials at the same time as permanent gases, as well as the excellent flow properties makes it an ideal medium for transporting compounds, even of quite low volatility, in flow systems. Several other supercritical fluids have, however, also been studied for use in chemical processes. Table 1.2 shows the critical parameters for various compounds.[62]

Table 1.2 Critical parameters for several supercritical fluids.[62]

Compound	Tc (K)	pc (bar)
Carbon dioxide	304.1	73.8
Ethane	305.4	48.8
Ethene	282.4	50.4
Propane	369.8	42.5
Propene	364.9	46.0
Trifluoromethane (Fluoroform)	299.3	48.6
Chlorotrifluoromethane	302.0	38.7
Trichlorofluoromethane	471.2	44.1
Ammonia	405.5	113.5
Water	647.3	221.2
Cyclohexane	553.5	40.7
n-Pentane	469.7	33.7
Toluene	591.8	41.0

There are many advantages associated with the use of supercritical fluids as reaction media[63, 64], but the main one is related to the environmental advantage of replacing common solvents as reaction media. Supercritical fluids also provide the added advantage of being able to release the products from the reaction medium by decreasing the pressure in the system.

1.5.1 Supercritical Fluids for Product Separation in Homogeneous Catalysis

1.5.1.1 All Homogeneous Supercritical Systems

Two main approaches have been developed for using supercritical fluids to affect the separation of products from catalysts in supercritical systems. In one the catalyst is designed so that it is soluble in the $scCO_2$, whilst in the other the substrate and product are transported in the $scCO_2$, but the catalyst is insoluble. In general, the substrates are soluble in $scCO_2$, so easier separation and adaptation to flow conditions occurs when the catalyst is insoluble. Nevertheless, many $scCO_2$ catalysts have been developed, either using alkyl phosphine ligands such as PMe_3[65] or PEt_3[66] or using fluorinated ponytails,[67] anions or both.[68, 69] All these homogeneous systems can still be used for catalyst/product separation because the catalyst is usually less soluble than the substrate in $scCO_2$. Using pressure and temperature swings it is possible to precipitate the catalyst in the reactor, remove the substrate dissolved in the supercritical fluid, precipitate the substrate in a separate vessel and recompress the $scCO_2$ for passage back into the reactor. This CESS process (**C**atalysis and **E**xtraction using **S**upercritical **S**olutions) has been demonstrated for the asymmetric hydroformylation of styrene using a rhodium complex with a fluorinated BINAPHOS ligand in a semi-batch process.[70, 71] Yields and enantioselectivities were high, but some rhodium (0.2 - 2 ppm) and ligand loss occurred (as indicated by a drop in enantiomeric excess after the fourth

cycle, which could be restored by the addition of extra ligand). A design concept for batch continuous operation has been reported.[72]

1.5.1.2 Supercritical Fluid – Water Biphasic System

One very elegant way of circumventing the pressure swings required in the CESS process whilst still using a CO_2 soluble catalyst is to work with reactions that give water-soluble products. Water is only poorly soluble in $scCO_2$. Such processes resemble coffee decaffeination because the product can be removed in the water phase without the need for decompression of the $scCO_2$ and hence, very significant savings are obtained in energy utilisation.

Leitner and co-workers[68, 69] have used water-CO_2 systems to facilitate the separation of the catalyst from the product in homogeneous catalytic systems. By careful choice of the catalyst and the product, it is possible to have the catalyst dissolved in the $scCO_2$, with the product being preferentially soluble in water. Such reactions can be carried out in continuous flow mode with the substrate, reacting gases and water being continuous flowed into the reactor and the aqueous solution of the product being continuously removed. As for caffeine recovery, large pressure swings are not required so the process costs are reduced, but the number of products that fulfil the required criterion of preferential solubility in water is small.

One such reaction that has been demonstrated is the hydroformylation of itaconic acid or methyl-2-acetamido acrylate using a cationic rhodium complex of a BINAPHOS ligand bearing fluorous ponytails with BARF {$B[3,5-C_6H_3(CF_3)_2]_4$}

anions to render the catalyst completely CO_2 soluble (Scheme 1.3).[68, 69] Excellent

conversion and selectivity (ee = 93.6 % *(S)* and 98.4 % *(R)* respectively) were

obtained. Using batch operation and removing the water phase after each run

before adding more substrate and gases, the catalyst survived five repeat runs

apparently unscathed.
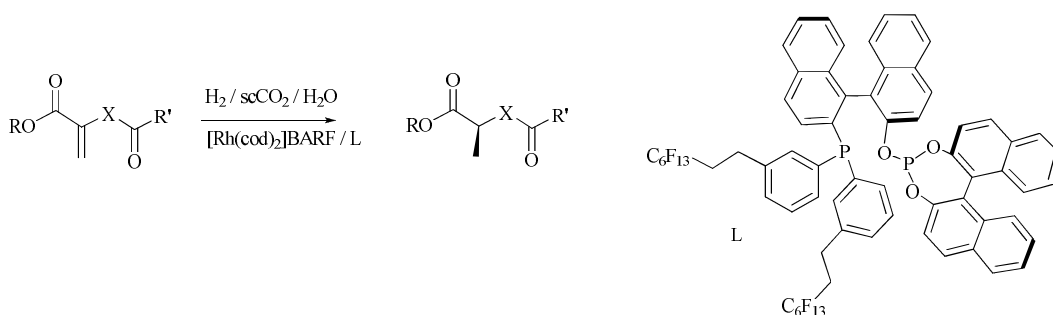
Scheme 1.3 Asymmetric hydrogenation of itaconic acid (R = H, R' = OH, X = CH_2) or of

methyl-2-acetamido acrylate (R = R' = Me, X = NH), a reverse phase CO_2/H_2O system

catalysed by a cationic rhodium complex of fluorinated BINAPHOS.[68]

Hancu and Beckman have applied similar methodology in the homogeneous

catalytic synthesis of hydrogen peroxide from H_2 and O_2 in CO_2.[73] This is a one

step reaction catalysed by a CO_2-soluble palladium complex and is an alternative

to its most popular commercial process, the anthraquinone or AQ process (Figure

1.13).
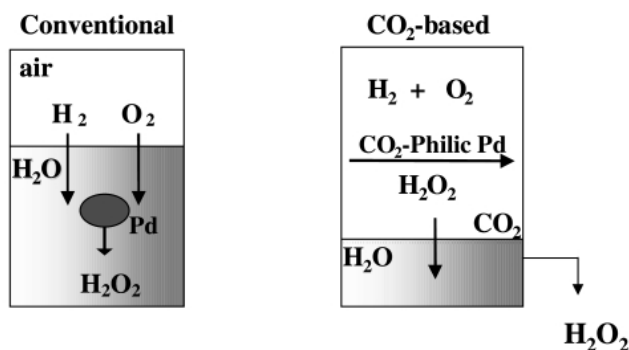
Figure 1.13 The AQ process *vs.* the direct reaction of hydrogen and oxygen for the production of hydrogen peroxide.[73]

Although hydrogen peroxide is widely known as a green oxidant, the AQ process has quite a few drawbacks, including the large energy input, the generation of waste and the number of unit operations along the process. Preliminary results have demonstrated the synthesis of hydrogen peroxide using both CO_2-soluble Pd(II) and Pd(0) catalysts bearing fluorinated phosphines, although the latter revealed better catalytic results. The product can be easily recovered from the reaction medium without any large drops of pressure because it can be extracted into water, which is only poorly soluble in $scCO_2$ (as previously said). An added benefit is that the inert (non-oxidisable) nature of CO_2 means that handling oxygen is much safer than in conventional systems, where organic solvents and other material quickly exceed their explosion limits and severe risks are encountered at anything but very low oxygen partial pressures.

1.5.1.3 Polymerisation in Supercritical Fluids

One other area where $scCO_2$ soluble catalysts are important is when the product is insoluble in $scCO_2$ and precipitates during the reaction. A significant application of this concept is in polymerisation reactions, although the first examples made CO_2 soluble polymers. A partnership between DuPont and the University of North Carolina - Chapel Hill resulted on the first commercial example of fluoropolymer resin synthesis using carbon dioxide as a solvent, the Teflon[TM] polymerisation process.[74, 75] C_2F_4 is polymerised in $scCO_2$ using radicals derived from C_4F_9I as the initiator in a truly homogeneous process so that long chain polymers can form. The use of CO_2 greatly increases the safety of the process[76] and the lifetime of the initiating radicals since, unlike almost all organic solvents, it is resistant to radical attack.[77]

Reactions where the polymeric product such as cross-linked poly(divinylbenzene) is insoluble in $scCO_2$ and precipitates during the reaction have been developed,[78, 79] but continuous flow operation has not yet been demonstrated.

1.5.1.4 Biphasic Systems involving a Supercritical Fluid

The majority of flow processes involving supercritical fluids as the transporting media that have been reported have the substrate, reacting gases and products dissolved in $scCO_2$ and the catalyst immobilised in some way so that it is insoluble. The immobilisation can be on a solid support or in a separate phase, the solvent for which has low solubility in $scCO_2$. In the biphasic systems, the catalyst is often rendered insoluble in $scCO_2$ by virtue of its being ionic, although sometimes high molecular mass is enough to immobilise the catalyst, for example, in a system where a rhodium hydroformylation catalyst is immobilised in excess "polygard" - a mixture of tris(4-nonylphenyl)phosphites[80] - or in a hydrogenation reaction using $[RhCl(PPh_3)_3]$ in polyethylene glycol.[81]

1.5.1.5 Supported Catalysis with Supercritical Flow

Figure 1.14 Thomas Swan plant for the use of supercritical fluids as solvents.[82]

Early in 2002, Thomas Swan started operating a multi-purposed flow plant using supercritical fluids (Figure 1.14). This plant has the potential for using $scCO_2$ as a solvent in various chemical processes, such as, hydrogenations, Friedel-Crafts alkylations, hydroformylations, etherifications and acylations. With the capacity of producing 1000 tonnes of products per year, this facility can easily work both commercially and as a pilot plant to continue testing the use supercritical fluids as solvents. This plant was constructed to develop the work initiated by Poliakoff and co-workers on catalytic reactions in supercritical fluids.[83-87] The selective hydrogenation of the C=C double bond in isopherone to give trimethylcyclohexanone (Scheme 1.4) was carried out with selectivities as high as those obtained in conventional solvents, but with higher rates, using a supported palladium catalyst and CO_2 as the transport medium.[86, 87] Although this process no longer works on a commercial scale, key parameters of the reaction are listed in Table 1.3 but of particular interest is the overall pressure of 40 - 60 bar, which greatly reduces the engineering and recycling costs compared with those required when using $scCO_2$ (100-150 bar). The reaction is carried out in the expanded liquid phase, which has a number of important advantages in addition to the lower pressure of operation. Diffusion constants are higher, gases are more soluble and catalyst leaching is reduced compared with those for the liquid phase, whilst the substrate concentration is higher than for the gas phase reactions.
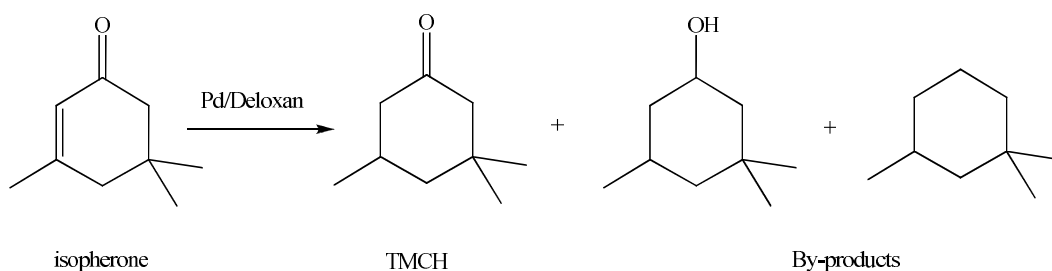
Scheme 1.4 Hydrogenation of isopherone to 3,3,5-trimethylcyclohexane (TMCH).[86, 87]

Table 1.3 Comparison of optimised conditions for isopherone production in a supercritical plant in the laboratory and on the plant.[86, 87]

	Laboratory Scale	**Plant**
Reactor Size	0.85 cm (i. d.), 25 cm	
Catalyst	2 % Pd (supported)	2 % Pd (supported)
T (^{o}C)	56 (inlet) 100 (outlet)	104-116 (isothermal)
Pressure (bar)	40 - 60	40 - 60
Hydrogen (equivalents)	1.7 - 2.75	1.7
Substrate feed (wt %)	2 - 48	9 - 17
Rate (kg h^{-1})	0.25	100
Selectivity to TMCH (%)	100	99.7

This process involved a heterogeneous catalyst, but Poliakoff and co-workers were also the first to introduce scCO$_2$ flow systems with supported homogeneous catalysts.[88] Using a ligand that had been developed by van Leewen and co-workers[89-91] (see Figure 1.15), which had been shown to be highly robust for a variety of hydroformylation reactions in the liquid phase, Poliakoff and co-

workers transported alkene, CO and hydrogen all dissolved in scCO$_2$ over the catalyst in a simple flow tube reactor. The overall pressure was 170 bar and the catalyst proved to be very robust in the continuous hydroformylation of 1-octene with very low rhodium leaching [< 1.2 mg (mole product)$^{-1}$]. The activity (TOF = 160 h^{-1})[88] was somewhat reduced compared with the liquid phase system (TOF = 287 h^{-1})[89], but the selectivity to linear aldehyde remained high (94 %, *cf.* 95 % for the liquid phase system). The activity is expected to be lower because the substrate, being dissolved in the mobile phase, is distributed throughout the reactor whereas in the liquid phase, the substrate concentration at the catalytic sites is higher. This effect may be ameliorated somewhat by the better contact of the gases with the catalyst in the CO$_2$ based system, but only if the transport of gases across the gas-liquid interface is rate determining in the liquid phase system. The supported catalyst shown in Figure 1.15 is a very rare example where leaching in the liquid phase is undetectable and the lifetime is very long (one sample was used on and off for 1 year for different hydroformylation reactions without loss of activity or selectivity),[89] so it is difficult to improve on its performance.

Figure 1.15 Ligand used for the hydroformylation of octane in a continuously flowing supercritical phase.[88, 89, 2]

Using supercritical flow would be beneficial in cases where catalyst leaching into the liquid phase is significant, but reactivity is high. The lower solubilising power of the supercritical fluid should reduce the leaching to acceptable levels whilst retaining catalytic activity. Results from one example are shown in Table 1.4 (although not in a flow system), involving the methyl iodide (MeI) promoted carbonylation of methanol using $[Rh(CO)_2I_2]^-$ supported on polyvinylpyrrolidone (PVP).

Table 1.4 Comparison of methanol carbonylation using Rh/PVP with substrate in the liquid[92], gas[93] or supercritical phases[94].

Phase	[MeI] (mol dm^{-3})	T (^{o}C)	P (bar)	TOF (h^{-1})	Rh leaching
Liquid[b]	1.07	150	40	280	40 %[c]
Gas[d]	1.37×10^{-3}	180	80[e] (40)[f]	280	< 1 %[g]
scCO$_2$[b]	0.107	150	200 (40)[f]	500	<0.08 %

[a] MeOH/MeI = 5, absolute concentrations vary enormously;
[b] Batch reactions;
[c] In t = 7.5 h;
[d] Continuous flow;
[e] 1:1 CO:H$_2$;
[f] CO pressure;
[g] No losses detected by analysis of the solid.

Kinetic studies of liquid phase reactions show that the catalyst leaching is very high (40 % over a period of 7.5 h) and that most of the catalytic activity arises from dissolved (*i.e.* leached) catalyst, but not all.[92] Using scCO$_2$ as the solvent, the activity was almost doubled, but the catalyst could be reused 6 times without significant loss of activity. Rhodium in the recovered products was below the detection limit (0.3 ppm).[94] The same catalyst was used for all gas phase reactions, with the disadvantage that the space time yield was much reduced.[93]

In principle, any catalyst that can be immobilised on a solid support can be used for continuous flow catalytic reactions with supercritical transport, provided that the product is soluble in a supercritical fluid or can be transported as a CO$_2$ expanded liquid. We can thus expect to see major developments in this area, including commercialisation, over the next few years.

1.5.1.6 "Solventless" Systems with Supercritical Flow

In addition to the supercritical fluid – ionic liquid biphasic systems (Section 1.4.2.3) and other biphasic systems where the catalyst is dissolved in water (Section 1.5.1.2) or another liquid solvent (Section 1.5.1.4), described above, it is possible to carry out homogenous reactions where no solvent is added but the substrates and products are carried through the reactor dissolved in $scCO_2$. Such continuous flow processes have been dubbed "solventless" (Figure 1.16).[11]
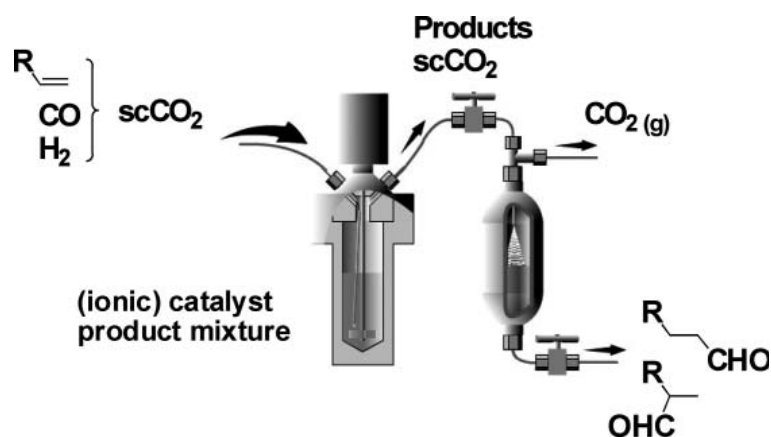
Figure 1.16 Schematic diagram for the continuous flow hydroformylation of alkenes, in which the catalyst is dissolved in the substrate/product mixture and the mobile phase is $scCO_2$.[11]

Frisch *et al.* have described[11] such a system for the hydroformylation of 1-octene catalysed by a rhodium complex prepared *in situ* from [Rh(acac)(CO)$_2$] and [OctMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)], which was chosen for its favourable solubility properties in the reaction product, nonanal, leading to high reaction rates.[60] The principle of these systems is quite similar to that used in the ionic liquid-

supercritical fluid biphasic systems previously described in this Chapter. However, instead of using an ionic liquid as solvent, the catalyst is dissolved in the substrate-product mixture that develops during the reaction. The mobile phase used to extract the product from the reaction medium is $scCO_2$, which can, in principle, be recycled. These systems, besides being the most simple catalyst system possible, due to the absence of "outsiders" except for the catalyst and the CO_2, have the potential to be run at lower pressure than the $scCO_2$ – ionic liquid biphasic systems because the product does not require extraction from the ionic liquid, in which it is soluble.

The reactions are started by dissolving the product in a mixture of the starting material (1-octene) and product (nonanal) and the flows of substrate, gases (CO/H_2) and $scCO_2$ started. Care must be taken to balance the flow of substrate into the reactor, with the rate of extraction of the product from the reactor so that the level in the reactor remains constant. To help with this, a Jorgensen gauge was incorporated into the reactor. Care must also be taken with the overall pressure because $scCO_2$ swells the liquid phase. If the ratio of CO_2 to CO/H_2 is too high, the liquid expands so much that it is forced out of the reactor taking the substrate, product *and catalyst* with it. Careful optimisation allowed suitable flow rates to be adopted (Figure 1.17) so that the reaction could be run continuously for at least 8 h with minimal rhodium leaching (0.3 ppm at the steady state), good activity (TOF = 180 h^{-1}), constant ratio of linear : branched aldehyde and a stable liquid level in the reactor (Figure 1.18).[11]
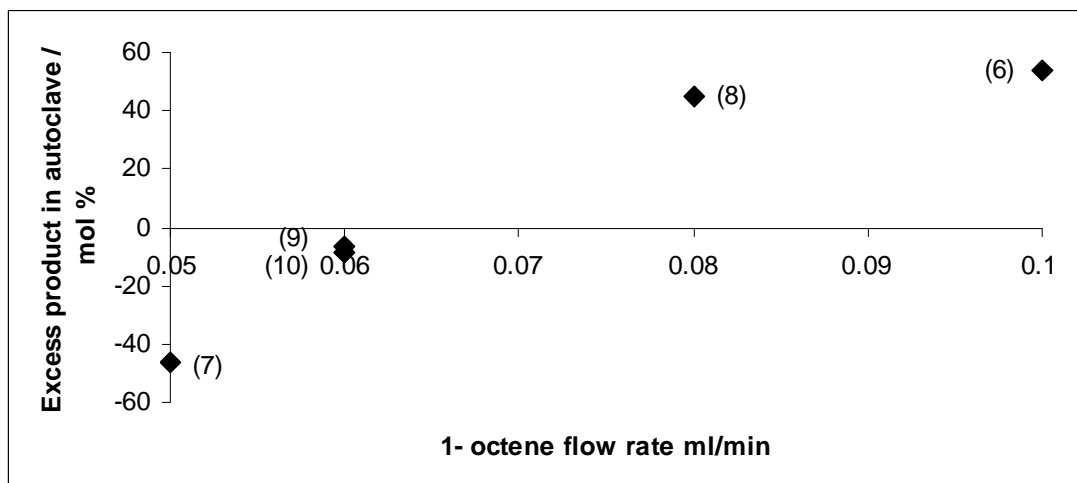
Figure 1.17 Plot showing the build-up or loss of material in the autoclave (mol of material recovered from the reactor – mol of material introduced at the beginning) as a function of 1-octene flow rate. CO_2 (2.0 nL/min), CO = H_2 (0.4 cm^3/min), T = 100 ^{o}C, p = 140 bar. Normalised to a t = 10 h reaction time. Numbers in parenthesis are run numbers.[11]
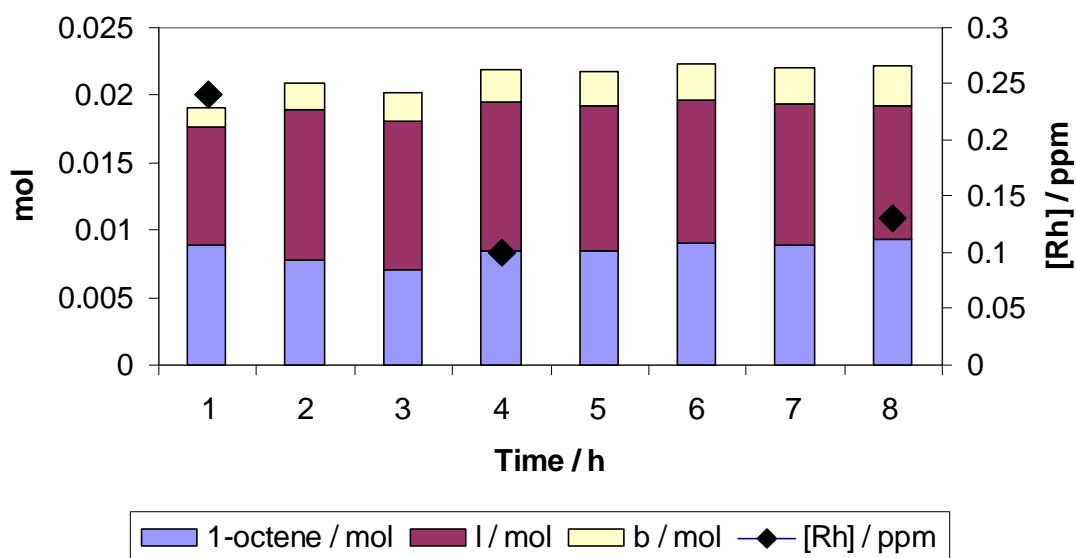
Figure 1.18 Composition of the fractions collected under conditions of balanced flow from the "solventless" hydroformylation of 1-octene (l = linear product; b = branched product). Conditions as for Run 10 shown in Figure 1.17.[11]

1.5.2 Recycling CO_2

One other issue that needs to be addressed in systems employing $scCO_2$ is CO_2 recycling. As already suggested, decompressing and recompressing CO_2 to allow for the separation of the products is an energy intensive process. Extraction of the product at pressure with a solvent that is insoluble in $scCO_2$ is an option,[68, 69] but then means that a further separation will be required. Often such solvents are not obvious. In principle, in the absence of a suitable extraction strategy, either recompression or cooling can be used before returning the CO_2 in the liquid phase to the reactor. Generally speaking, cooling below the critical temperature of 31.1 ^oC is the less energy intensive option. However, there is a further problem in reactions that employ permanent gases, especially as they are often used in excess over the amount of substrate. Either cooling or compressing a mixture of CO_2 containing permanent gases will lead to two phases. One is a liquid phase consisting predominantly of CO_2 but containing dissolved gases. This can be pumped back to the reactor, although outgassing on the way may constitute a problem. The second, more problematic phase is a gaseous phase consisting of CO_2 and permanent gases. If this is to be recycled, it must be compressed and if compression is carried out below the critical temperature, it will phase separate giving liquid and gaseous components which are difficult to pump. A design concept has been developed[58] in order to try to get around this problem (Figure 1.19). Here, the output from the continuous flow reactor passes through a heat

exchanger, giving up some heat to the incoming gaseous fraction, to a separator where the product is collected by partial decompression. The gaseous phase (CO_2 and permanent gases) then passes to a chiller or compressor where the majority of the CO_2 condenses. The gas phase then passes through the heat exchanger, where it is heated above its critical temperature and can then be compressed as a gas without condensation back into the reactor. The alternative, which completely circumvents the recompression issue, would be to vent the CO_2 coming out of the separator to atmosphere. It would be necessary to oxidise any unreacted permanent gases (CO, H_2) to CO_2 and water before venting. This may be a cheaper solution, but it is somewhat inelegant, does not hold up the CO_2 for long between production and loss to the atmosphere, wastes permanent gases and can generate small amounts of extra CO_2 (from CO oxidation).
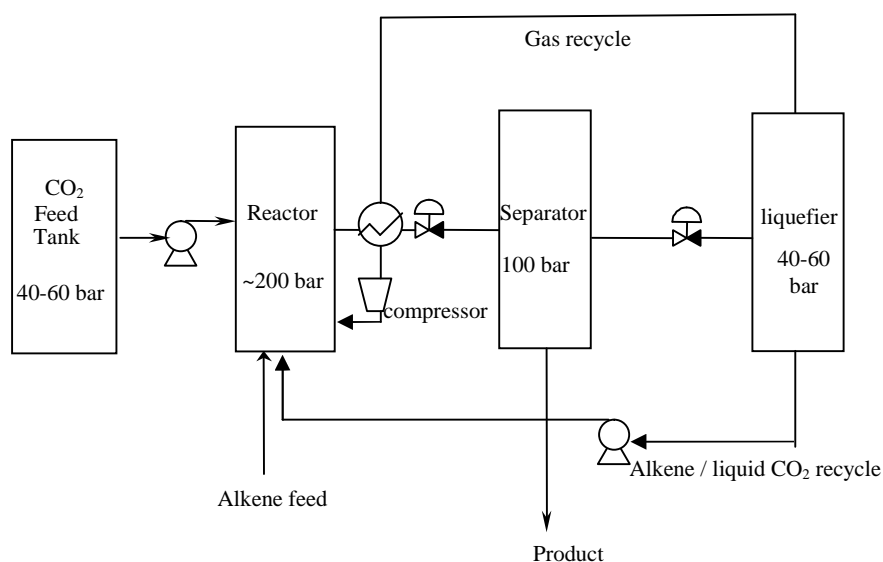
Figure 1.19 Process design for continuous operation with full recycling.[58]

1.6 Final Remarks

Concepts such as "green chemistry", "environmental chemistry", "green solvents" or "sustainability" are buzz words that have developed over the last few years. However, beneath their appealing exterior there lurk very serious concerns about the development of modern ways of living. Every day, scientists from all research fields are being challenged by society to provide processes which make the products that make life so much safer and more comfortable, but in ways that will leave our planet with no adverse affects for future generations. The chemical industry is charged with developing "perfect chemical processes" in which the raw materials can be regenerated on the appropriate timescale and the process uses no energy, produces only the desired material, generates no waste and produces no pollution. Our goal must be to redesign already existing chemical processes or design new processes to minimise the, until recently, normal formation of waste (often toxic and dangerous) and the use of hazard substances, which require special disposal at the end of the process. In other words, all this means that it is necessary to develop processes with minimised E-factors,[95] with high atom economy and which fit with the twelve principles of green chemistry introduced by Anastas and Warner.[96]

Catalysis provides an important step along the pathway to these ideals and homogeneous catalysis with its high reaction selectivity and mild operating conditions is particularly attractive.

Taking in account the main problems concerning homogeneous catalysis:

- the separation of the reaction products from the catalyst and any solvent used in the reaction;

- the emission of volatile organic solvents as a result of solvent use;

- the requirement for batch or batch continuous processing;

this Chapter tried to outline several different processes being studied or already being commercialised to overcome these problems.

Here have been described and highlighted flow systems which automatically build in the catalyst/product separation and often use supercritical carbon dioxide as the transport medium. Although CO_2 is a greenhouse gas, making the most significant contribution to global warming, it is not generated in the processes here described, but is simply held up on its way from being generated to being released into the atmosphere. In all other ways – non-toxic, non-flammable, effective anti-explosion diluent – it is entirely benign in the environment. Its transport properties (high diffusivity), solubilising power (totally miscible with gases, good solvent for many organic compounds when pressurised) and low cost, make it a highly suitable solvent for flow processes. Its one disadvantage is the high pressures that are required to reach the critical condition. However, recent developments in the use of subcritical CO_2 and expanded liquids may go a long way towards addressing this potential problem. These types of systems work best if the catalyst is in the solid state either covalently attached to a support or dissolved in a thin

film of a solvent, which is insoluble in $scCO_2$, supported in the inside of a porous solid.

The other type of solvent here examined is ionic liquids. Having non-measurable vapour pressure, most ionic liquids do not pollute the atmosphere and in many cases, they appear to have low toxicity. Full lifetime analyses are lacking, but no major issues appear to be being thrown up. Ionic liquids can be designed to have all kinds of polarity and be miscible with different types of liquid, making them ideal for biphasic reactions, although continuous flow is best served by using them in tandem with supercritical fluids, either as biphasic systems or as the thin film for supported ionic liquid phase catalysts with or without supercritical flow.

The development of the use of these alternative solvents for catalytic processes is in its infancy. There is very much to be done, but they have the potential for creating a major revolution not only in the chemical industry, but also in society as a whole.

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Chapter 2

Continuous Flow Hydroformylation of 1-octene Using an Ionic Liquid/scCO$_2$ Liquid – Liquid Biphasic System

2. Continuous Flow Hydroformylation of 1-octene Using an Ionic Liquid/scCO$_2$ Liquid – Liquid Biphasic System

This Chapter describes the developments achieved on the continuous flow hydroformylation of 1-octene carried out in an ionic liquid/scCO$_2$ biphasic system previously developed by Webb *et al.*.[1]

2.1 Introduction

2.1.1 The Hydroformylation Reaction

The hydroformylation of alkenes, also known as the oxo reaction, is one of the most important industrial chemical processes in use, producing about 8 million tonnes (1995) of aldehydes per annum.[2, 3] This reaction consists of the addition of an atom of hydrogen and a formyl group (CHO) derived from H$_2$ and CO to a terminal alkene in the presence of a Co or Rh catalyst in order to produce the aldehyde products.[4] After hydrogenation, the aldehyde group can be transformed into an alcohol for use as plasticizers or in the creation of detergents and soaps.[5] They can also be oxidized into carboxylic acids.
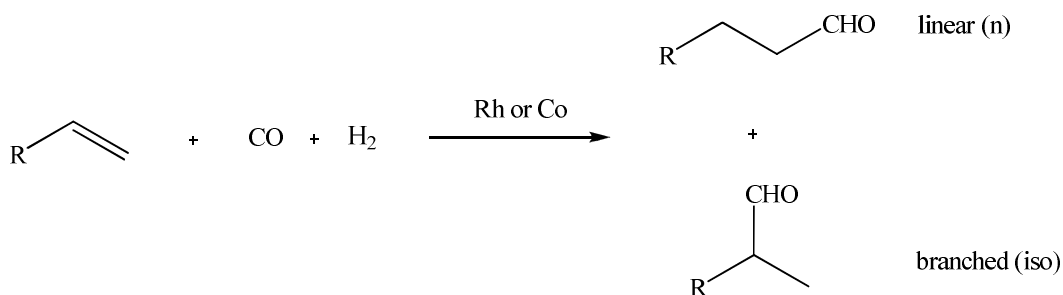
Figure 2.1 The hydroformylation reaction.

Otto Roelen discovered this very important chemical process in 1938[6, 7], while he was investigating the origin of oxygenated products from cobalt-catalysed Fischer-Tropsch reactions. The hydroformylation catalysis began when Roelen realized that ethene, H_2 and CO were converted into propanal, and also into diethyl ketone if the reaction was carried out at higher pressures.

Nowadays, the hydroformylation reaction is the most important homogeneous process being carried out in industry. Its commercial applications go from the manufacture of soaps, detergents and perfumes to plasticizers.[2, 6]

2.1.1.1 The Hydroformylation Process and Catalysts

Nowadays, there are three commercial processes involving either cobalt or rhodium catalysts being used for the hydroformylation process.

For the two hydroformylation processes involving the use of cobalt catalysts, one concerns the old known unmodified cobalt process and the other concerns the process where a cobalt salt is used with a tertiary phosphine to form a catalyst complex. The unmodified cobalt process is not very easy to run, since $[HCo(CO)_4]$ is volatile and so, has to be separated from the alcohol products so

that the cobalt can be recovered and recycled.[4] It also requires very high pressures (300 bar) because of the instability of the intermediate [HCo(CO)$_4$].

As for the hydroformylation process involving the use of rhodium catalysts, it also involves the use of a tertiary phosphine to form the catalyst complex.

Table 2.1 compares the reaction parameters for the three commercial hydroformylation processes described above.

Table 2.1 Process parameters for some commercial hydroformylation processes.[8]

Process parameters	Cobalt	Cobalt + phosphine	Rhodium + phosphine
Temperature (ºC)	140 – 180	160 – 200	90 – 100
Pressure (bar)	200 – 300	50 – 100	10 – 20
Alkane formation	Low	Considerable	Low
Main product	Aldehyde	Alcohol	Aldehyde
Selectivity (%)	75 – 80	85 – 90	92 – 95
Isolation of catalyst	Difficult; [HCo(CO)$_4$] is volatile	Less difficult	Very difficult if chain length > C$_7$; water-soluble phosphine a major advance

It is a fact that by using the rhodium catalyst, it is possible to achieve better results in terms of selectivity to the desired linear aldehyde product and better catalyst activity, carrying the reaction out under milder conditions than when using cobalt catalysts. However, in commercial processes, rhodium is still not as much used as

cobalt. This is due to the fact that rhodium is a very expensive metal and that it is very difficult to separate the products from the catalyst. On the other hand, cobalt catalysts are less selective and need harsher experimental conditions but they have a much better performance in terms of catalyst separation, especially in the hydroformylation of long chain alkenes.

New approaches have been made to overcome the catalyst separation problem, such as, the introduction of water-soluble phosphines to form the catalyst complex used as a reaction precursor, known as the Ruhrchemie/Rhône-Poulenc process (Figure 2.2).[2, 9, 10] Here, the rhodium complex is rendered water-soluble by using trisulphonatedtriphenylphospine as its sodium salt and the product, being hydrophobic is decanted from the aqueous solution containing the catalyst in a gravity separator. However, this process is not still appropriate for long chain alkenes because the poor mass transport of the longer chain alkenes into the aqueous phase reduces the reaction rates to unacceptably low levels.
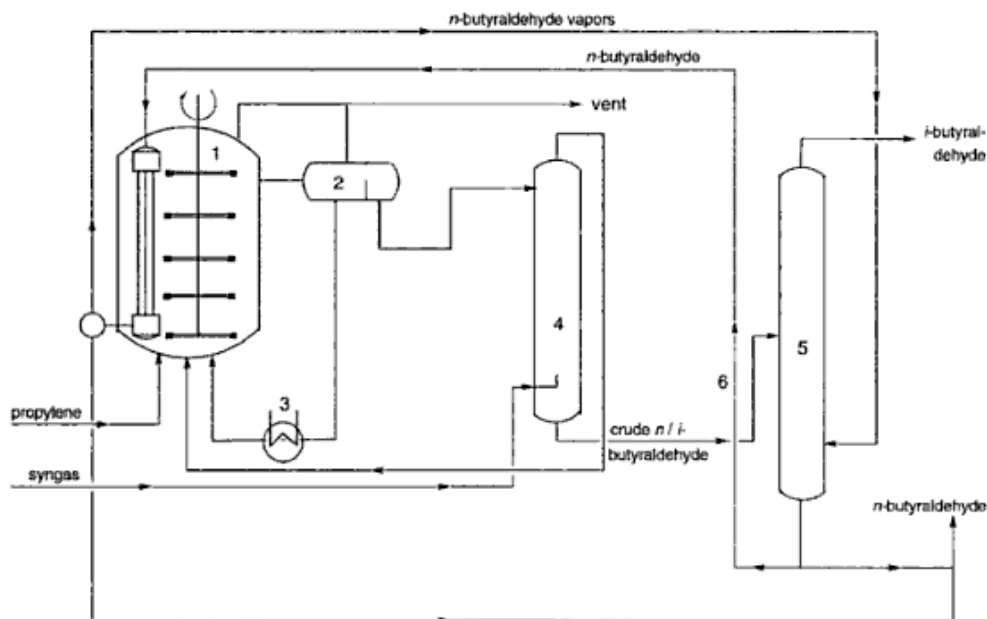
Figure 2.2 Flow diagram of the Ruhrchemie/Rhône-Poulenc process.[9]

The interest in these rhodium catalytic complexes started with the work of Osborn, Young and Wilkinson when they described that [Rh(I)-PPh$_3$] could be a very active and selective catalyst complex in the hydroformylation process, even under ambient conditions.[11] Wilkinson's catalyst,[RhCl(PPh$_3$)$_3$], was also tried in the system but soon they found out that rhodium starting complexes containing halides worked as reaction inhibitors.[12, 13] However, this problem was solved with the addition of hydrogen halide acceptors, which formed the new complex [RhH(CO)(PPh$_3$)$_3$].[12]

At the moment, some of the most common starting complexes that are being used in the hydroformylation process are [RhH(CO)(PPh$_3$)$_3$] and the [Rh(acac)(CO)$_2$] with added PPh$_3$.[14]

The well-known and accepted mechanism for the hydroformylation process catalysed by rhodium complexes is shown Scheme 2.1.
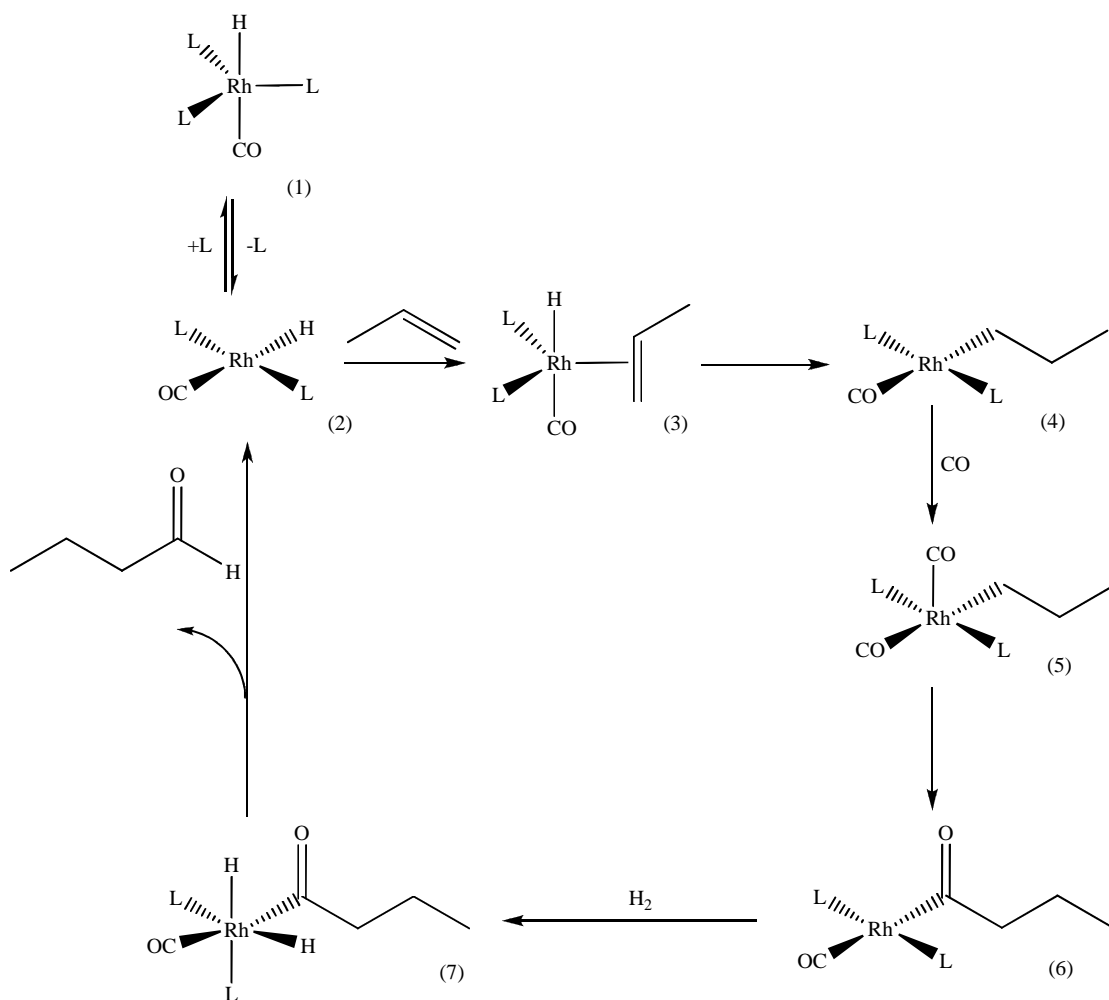
Scheme 2.1 Mechanism for the hydroformylation of propene using a Rh/PPh$_3$ based catalyst. Only the cycle leading to the linear product is shown. For the branched product, migration of H occurs onto the internal C atom of the double bond in intermediate (3). (L = PPh$_3$)

Reaction of (1) to give (2) corresponds to the ligand dissociation. The selectivity is determined from (3) to (4) when an anti-Markovnikov addition takes place, if

the linear product is to be formed. It is important to notice that, although it is possible to run the process in order to obtain a bigger percentage of n-aldehydes or iso-aldehydes, we will always obtain both aldehydes since during this stage both linear and branched alkyl-Rh complexes are formed.

From (5) to (6) the CO is added and the alkene migrates onto it to form an acyl complex. H_2 is added by oxidative addition, forming the complex represented in (7). The aldehyde is separated from the Rh complex by reductive elimination to regenerate (2).

This mechanism works well and it is possible to obtain good linear to branched selectivities, under mild experimental conditions.

Nevertheless, one of the biggest and still remaining problems involving the industrial homogeneous processes and, in this case, the hydroformylation reaction, concerns the separation of the catalyst from the aldehyde products.

2.1.1.2 The Use of Ionic Ligands

Many water-soluble phosphines, such as the ones shown in Figure 2.3, have been synthesized over the years. These sodium salts are often of low solubility in ionic liquids and so, a cation exchange is performed in which the small sodium cation is replaced by a larger cation, which normally resembles the cation of the ionic liquid to be used.

These ionic ligands can then form catalyst complexes with the rhodium catalysts, allowing the retention of the catalyst in an ionic liquid reaction medium.
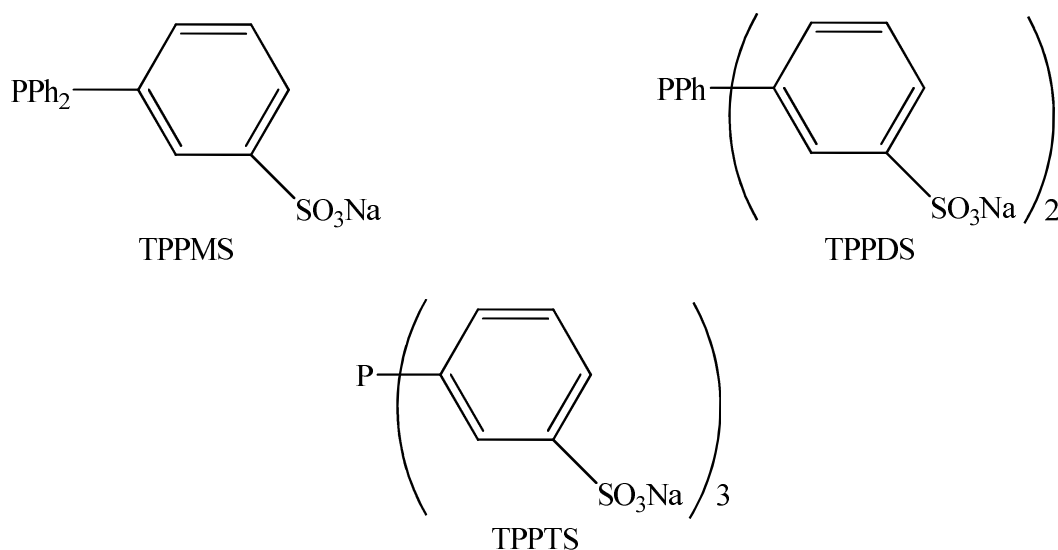
Figure 2.3 Water-soluble phosphines.

In aqueous biphasic reactions, tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) is the most common phosphine used to perform this exchange reaction since the presence of three sulfonated groups increases the catalyst retention, decreasing its leaching from water. As indicated above, TPPTS is already being successfully employed in a commercial process (the Ruhrchemie/Rhône-Poulenc process), which uses water as solvent.[2, 6, 9, 10]

In 1995, Chauvin *et. al.* reported the use of TPPTS as ligand to retain the rhodium catalyst in an ionic liquid reaction medium.[15] The results were not too impressive because of the low solubility of the sodium salt in [BMIM]PF$_6$. Since then, many different ligands have been tested in order to improve the catalyst solubility and retention.[1, 16, 17] Previous work in our laboratories as well as in that of Mehnert[18] showed that [RMIM][TPPMS] (R = Pr, Bu, pent, octyl)[19] all promoted greater solubility of the rhodium complexes in a variety of imidazolium based ionic

liquids, so these cations were also used in our studies. Apart from NMR studies, which suggest that the major species present in solution before and after hydroformylation reactions using [RMIM][TPPMS] in imidazoilium based ionic liquids are of the form [RhH(CO)(TPPMS)$_3$][RMIM]$_3$,[19] little is known about the nature of the catalytic species present, so we were interested to study the catalyst solutions by X-ray photoelectron spectroscopy (XPS).

2.1.2 The Ionic Liquid/scCO$_2$ Biphasic Systems

As previously described in Chapter 1 (Section 1.4.2.3), Cole-Hamilton and co-workers were the first to carry out continuous flow hydroformylation reactions of long chain alkenes in ionic liquid/scCO$_2$ biphasic systems.[19-21] The IL/scCO$_2$ biphasic systems are amongst the most recent and promising alternatives to deal with the catalyst/product separation problem. These systems are based on the separation of the product and the retention of the catalyst in the solvent. The scCO$_2$ transports the products from the reactor and they can then be precipitated from the solution after the decompression of the gas.

Webb *et al.* were the first to report a successful continuous flow homogeneous catalytic system for relatively low volatility products.[1] They ran several continuous flow hydroformylation reactions testing several ionic liquids and ionic ligands, in order to obtain better rhodium catalyst performances in terms of activity, selectivity and retention. Also, they have demonstrated that by using the correct ionic liquid as solvent, and reaction parameters and helped by "reactor

design" it is possible to use biphasic systems for the continuous flow hydroformylation of long chain alkenes.

In order to optimise the reaction conditions, several ionic liquids were investigated. Although [BMIM]PF$_6$ is the most commonly studied ionic liquid for catalytic reactions, its results are not brilliant in terms of the solubility of the alkenes, which decreases the mass transport and reduces the reaction rate. In addition, water generated from aldol condensation of the product aldehydes can react with [PF$_6$]$^-$ to give HF and [O$_2$PF$_2$]$^-$.[19]

Previous studies demonstrated that the solubility of the alkenes in the ionic liquids is influenced by the size of the alkyl chain.[22, 23]

Following these conclusions, Webb *et al.* not only increased the size of the alkyl chain of the ionic liquid, but also substituted the [PF$_6$]$^-$ anion by the [Tf$_2$N]$^-$ anion. This anion substitution was very successful since it also increased the reaction rate when using a given cation, possible by reducing the viscosity of the reaction medium.

Several hydroformylation reactions were then carried out continuously using [OctMIM]Tf$_2$N as an ionic solvent and [PrMIM][TPPMS] as an ionic ligand at p = 200 bar and T = 100 ºC for more than 40 hours.

In terms of results, Webb *et al.* obtained a catalyst activity (TOF) of over 500 h^{-1} and several weeks of catalyst stability. The rhodium leaching was as low as 12 ppb, which is equivalent to 1 g of rhodium in approximately every 40 tonnes of product. The resultant l:b ratio was 3:1.

These results were compared with the ones obtained by the commercial processes for the hydroformylation of alkenes. Although cobalt catalysts require higher temperatures, pressures and high concentrations (these conditions may be improved by the addition of tertiary phosphines) when compared with rhodium catalysts, they are still the first choice because of the well-known catalyst/product separation problem.

A comparison between Webb *et al.*'s results with the commercial systems is shown in Table 2.2.

Table 2.2 Comparison between IL/scCO$_2$ biphasic systems and commercial systems for the hydroformylation process.[1]

Substrate	System	[M] (mmol/dm^3)	[P] (mmol/dm^3)	T (°C)	p (bar)	space time yield[a] (h^{-1})	Rate (mol/dm^3/h)	TOF[b] (h^{-1})	linear aldehyde (%)
propene	Rh/PPh$_3$	2.7	286	95	18	0.19	2.1	770	89.5
propene	Rh/PPh$_3$	1.8	150	110	16	0.09	1.0	556	84
1-octene	Co	80		160	300	0.48	2.8	35	72
1-octene	Co/PR$_3$	90	270	170	60	0.31	1.8	20	87.5
1-octene	Rh/IL-scCO$_2$	15	225	100	200	1.37	8.0	517	76

[a] Space time yield is the volume of aldehyde produced per volume of catalyst per hour.
[b] Turnover frequency mol of product/(mol of catalyst h)$^{-1}$

It is possible to observe that only by the addition of tertiary phosphines in large quantities to the cobalt catalyst it is possible to highly decrease the reaction pressure, from 300 to 60 bar, while the rhodium catalysts still work below that pressure.

The IL/scCO$_2$ biphasic systems using rhodium catalyst gives good turnover frequency and space time rates under lower pressure and temperature conditions.

However, the use of these systems is still far away from perfection and plenty of work has to be done in order to improve them, especially in terms of selectivity to the desired linear aldehydes and catalyst retention. It would also be very appealing to work at lower pressure since commercial organisations prefer pressures very much lower than 200 bar.

The work presented in this Chapter was focused on improving the previous results obtained by Webb *et al.*, in terms of the rhodium catalyst's stability, activity and retention. Since the ionic liquid [OctMIM]Tf$_2$N presented good solubility results for the long chain alkenes, this ionic liquid was kept as a solvent for the continuous flow experiments.

Previously, the cation exchange reactions to prepare the ionic ligands were performed using TPPMS. This water-soluble phosphine reacts with, for example, [PrMIM]Cl forming [PrMIM][Ph$_2$P(3-C$_6$H$_4$SO$_3$)], which is easy to crystallize and is highly soluble in [OctMIM]Tf$_2$N.[1] However, small amounts of catalyst leaching do occur when using this system, so improved ligand design should be possible.

This Chapter discusses the results involving the substitution of TPPMS for TPPTS, the trisulfonated water-soluble phosphine. Despite both types of phosphines being commonly used to prepare ionic ligands, in terms of reaction performance and results, the TPPTS might lead to a better selectivity and catalyst retention because of the presence of the three sulfonated groups attached to the three phenyl groups.

2.2 Experimental

2.2.1 General Experimental

The synthesis of the ionic liquids and ionic ligands used in these experiments are described in Chapter 5 (Sections 5.4.1 and 5.4.2) of the present thesis.

2.2.2 Preparation of the Ionic Catalyst

The phosphines used in these studies were sticky gums.

The catalyst solutions were made by weighing an amount of the phosphine and then calculating the appropriate amount of rhodium for a P/Rh ratio of 15:1. This meant that the rhodium concentration was not constant for different reactions. The actual concentrations used are shown in the Tables presented in Section 2.3 of this Chapter (Results and Discussion).

An example of a reaction protocol was as follows:

The ionic ligand, for example [PentMIM][TPPTS] (0.93 g, 9.69×10^{-4} mol), and the precursor [Rh(acac)(CO)$_2$] (0.017 g, 6.46×10^{-5} mol) (in a ratio of 15:1), were dissolved under a N_2 atmosphere, in the previously dried and degassed ionic liquid [OctMIM]Tf$_2$N (12 cm^3) at T = 50 °C until forming a homogeneous pale yellow solution.

2.2.2.1 History of the Catalysts

For these experiments two ionic ligands were used, [PentMIM][TPPTS] and [OctMIM][TPPTS]. Several batches of each ionic ligand were synthesised and further used to prepare the ionic catalyst complexes. Some of these complexes were only used once while others stayed inside the reactor for several weeks, being tested constantly.

For a better understanding of some catalysts' behaviour under certain experimental conditions, Tables 2.3 and 2.4 describe the list of experiments in which the catalysts presented in Section 2.3 of this Chapter took part.

Table 2.3 History of the ionic catalysts prepared with [PentMIM][TPPTS].

Catalyst	[Rh(acac)(CO)$_2$] (mmol)	Reaction	p (bar)	T (C)	CO flow (mmol/min)	1-octene flow (mmol/min)	CO$_2$ flow (nL/min)
A	0.1007	TQ50	200	100	3.77	1.89	1.0
		TQ51	160	100	3.77	1.89	1.0
		TQ52	100	100	3.77	1.89	1.0
		TQ53	200	100	3.77	1.27	1.0
B	0.0814	TQ66	100	100	3.77	1.89	1.0
		TQ67	150	100	3.77	1.89	1.0
C	0.197	TQ69	150	100	3.77	1.06	1.0
		TQ70	150	100	3.77	1.89	1.0
		TQ71	150	100	6.6	1.89	0.8
D	0.0744	TQ78A	200	100	4.2	2.65	1.0
		TQ78B	200	100	4.2	1.89	1.0
		TQ78C	200	100	3.77	1.89	1.0
E	0.0646	TQ80A	200	100	4.2	2.65	1.0
		TQ80B	200	100	4.2	2.65	1.0
F	0.0775	TQ83A	200	100	3.77	1.89	1.0
		TQ83B	150	100	3.77	1.89	1.0
G	0.0973	TQ88A	150	100	3.77	1.89	1.0
H	0.112	TQ89A	150	100	3.77	1.89	1.0
		TQ89B	150	100	3.77	1.89	1.0
		TQ89C	150	100	3.77	1.89	1.0
I	0.0832	TQ90A	150	100	3.77	1.08	1.0
		TQ90B	150	100	3.77	1.08	1.0
		TQ90C	150	100	3.77	1.08	1.0

Table 2.4 History of the ionic catalysts prepared with [OctMIM][TPPTS].

Catalyst	[Rh(acac)(CO)$_2$] (mmol)	Reaction	p (bar)	T (C)	CO flow (mmol/min)	1-octene flow (mmol/min)	CO$_2$ flow (nL/min)
K	0.0976	**TQ94A**	200	100	3.77	1.89	1.0
		TQ94B	150	100	3.77	1.89	1.0
L	0.1000	**TQ96A**	200	100	3.77	1.89	1.0
		TQ96B	150	100	3.77	1.89	1.0
M	0.1124	**TQ97A**	150	100	3.30	1.89	1.0
N	0.0701	**TQ99A**	200	100	3.77	1.89	1.0
		TQ99B	150	100	3.30	1.89	1.0

2.2.3 Continuous Flow Hydroformylation of 1-octene using an Ionic Liquid/scCO$_2$ Biphasic System
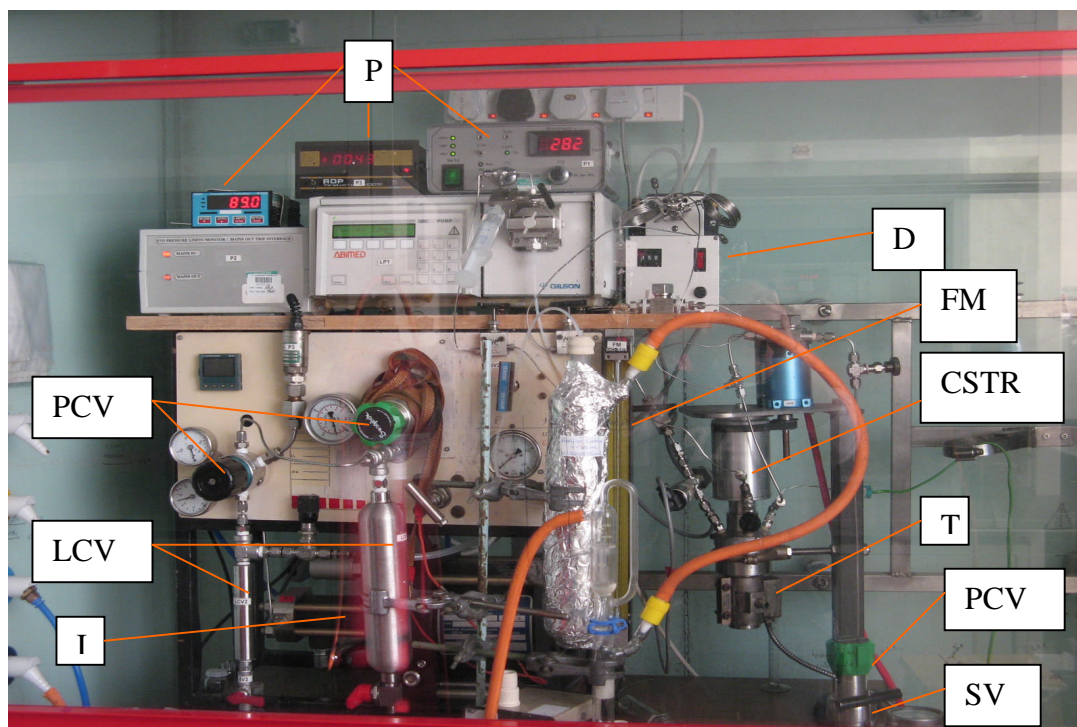
Figure 2.4 Continuous flow rig used to carry out the hydroformylation reactions.

CSTR Continuously stirred tank reactor; **SV** Shut-off valve; **PCV** Pressure control valve; **T** Thermocouple; **FM** Flow meter; **D** Dosimeter; **P** Pressure transducer; **LCV** Liquid collection vessel; **I** Intensifier.

In a typical hydroformylation experiment, the ionic catalyst solution was injected into the reactor previously purged with N$_2$. The reactor was then sealed, purged and pressurized with *syn* gas (CO/H$_2$ in 1:1) until reaching a p = 40 bar. To allow the pre-formation of the catalyst solution, the system was slowly heated to T = 100 ºC and rapidly stirred (20 V, 1059 rpm) for about t = 8 h.

CO_2 (grade N5.5, BOC) was slowly added to the system to the pre-defined reaction pressure (e.g. 200 bar) and the gas mixture allowed to expand through the system until the first decompression stage. The total gas flow was obtained by adjusting the gas expansion valves and shown in the flow meter (43 mm = 1.0 nL/min of CO_2 flow) and a pressure of about 4 – 5 bar was shown at the inlet of the 2nd expansion valve. The *syn* gas was then delivered into the system with a booster pressure of about 270 bar and at a switch rate predefined for the input booster pressure. Maintaining the 1st expansion valve at room temperature, the 1-octene was continuously pumped into the system at a constant rate using a HPLC. The system was left to stabilize between 2 – 3 h and after that, the product stream was collected every hour from the liquid collection vessel until the end of the reaction (12 to 24 h). The reaction mass balance was verified by weighing the collection vials before and after every fraction collection. All the fractions were then analysed by GC and ICPMS. The ionic solution was also collected by venting it under pressure at the end of the reaction.

2.3 Results and Discussion

The ionic catalysts presented in this Chapter were prepared using [PentMIM][TPPTS] and [OctMIM][TPPTS] ionic ligands, according to the procedure previously described in the Experimental section (Section 2.2.2). Each ionic catalyst solution was tested for a determined period of time for the study of

the hydroformylation of 1-octene, during which several parameters were changed. The reaction was always carried out on a continuous flow mode.

When not in use, the ionic catalyst solution was kept sealed inside the autoclave at a certain pressure (CO_2) and temperature and constant stirring.

2.3.1 Brief Discussion on the Probable Effects of the Concentrations of P and Rh on the Kinetics of the Hydroformylation Reaction

Since problems associated with weighing the ionic ligand mean that the concentrations of catalyst [Rh] and ligand [P] varies between the different reactions, although not usually their ratio, we should consider how this might affect the results.

Usually, under similar experimental conditions to those used in these experiments, the rate of the hydroformylation reaction under a given set of conditions is first order in [Rh] and negative order in [P].[2] The negative order in [P] has been experimentally confirmed in the very similar continuous flow system using [PrMIM][TPPMS].[1]

If we increase both the concentrations of catalyst and ligand, but keeping the P/Rh ratio constant, the rate of formation of product or of gas uptake (measured in mol dm^{-3} s^{-1}), may or may not change, depending upon the relative orders with the respect to [Rh] and [P]. If these are + 1 and – 1, the rate should not change. Assuming that the reaction is first order in [Rh], the turnover frequency (TOF) should be independent of [Rh] at a given [P].

$$TOF = Rate / [Rh]$$

This means that plots of TOF against [P], or even more easily, log (TOF) against log [P] can be used to determine the reaction order in [P].

We, therefore discuss the following results using TOF as a measure of rate, so that effects of changing [Rh] do not affect the results, providing that the hydroformylation reaction IS first order in [Rh].

2.3.2 Continuous Flow Hydroformylation of 1-octene Using Rh/[PentMIM][TPPTS] as Catalyst

Continuous flow hydroformylation reactions of 1-octene catalysed by Rh/[PentMIM]$_3$[P-(3-C$_6$H$_4$SO$_3$)$_3$] were carried in the [OctMIM]Tf$_2$N/CO$_2$ homogeneous biphasic system.

The [OctMIM]Tf$_2$N/CO$_2$ biphasic system was tested at pressures of 200, 150 and 100 bar. The flow rates of the reactants (CO, H$_2$ and 1-octene) were varied in order to study their influence in terms of activity, stability and rhodium catalyst leaching.

The overall CO$_2$ flow was kept constant at a flow rate of 1.0 nL/min (1 nL = 1 litre at NTP).

During the continuous flow reactions, carried out using different batches of Rh/[PentMIM][TPPTS] catalyst, fractions were collected every hour (and in some cases, every thirty minutes) for GC analysis.

The most relevant general results are shown in Table 2.5.

Table 2.5 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] (P/Rh ratio = 15:1) at p = 200, 150 and 100 bar and T = 100 ℃.

Reaction	[Rh]	p	CO flow	1-octene flow	Reaction time	Conversion to aldehyde	l:b ratio	TOF
	(mmol)	(bar)	(mmol/min)	(mmol/min)	(h)	(%)		(h⁻¹)
TQ50[a]	0.1007	200	3.77	1.89	8.0	33	2.3	371
TQ83A	0.0775	200	3.77	1.89	9.0	37	2.5	534
TQ78A	0.0744	200	4.20	2.65	9.0	26	2.6	552
TQ80	0.0646	200	4.20	2.65	10	23	2.4	544
TQ67	0.0814	150	3.77	1.89	5.0	33	3.2	460
TQ83B	0.0775	150	3.77	1.89	5.5	13	2.0	185
TQ88A	0.0973	150	3.77	1.89	10	13	2.0	146
TQ89A-C	0.112	150	3.77	1.89	20	32	2.0	313
TQ90A-B	0.0832	150	3.77	1.08	18	58	2.3	452
TQ71[b]	0.1970	150	6.60	1.89	6.0	46	3.1	263
TQ66	0.0814	100	3.77	1.89	9.0	30	3.3	424

[a] P/Rh ratio = 12:1
[b] CO_2 flow rate = 0.8 nL/min

2.3.2.1 *Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 200 bar*

Figures 2.5 and 2.6 represent the results in terms of catalyst activity and stability for the hydroformylation reactions carried out at a system pressure of 200 bar, starting from steady state.

We note that, as indicated in the catalysts' history presented in Table 2.3, all the catalysts presented in these reactions were fresh and had not been used previously.
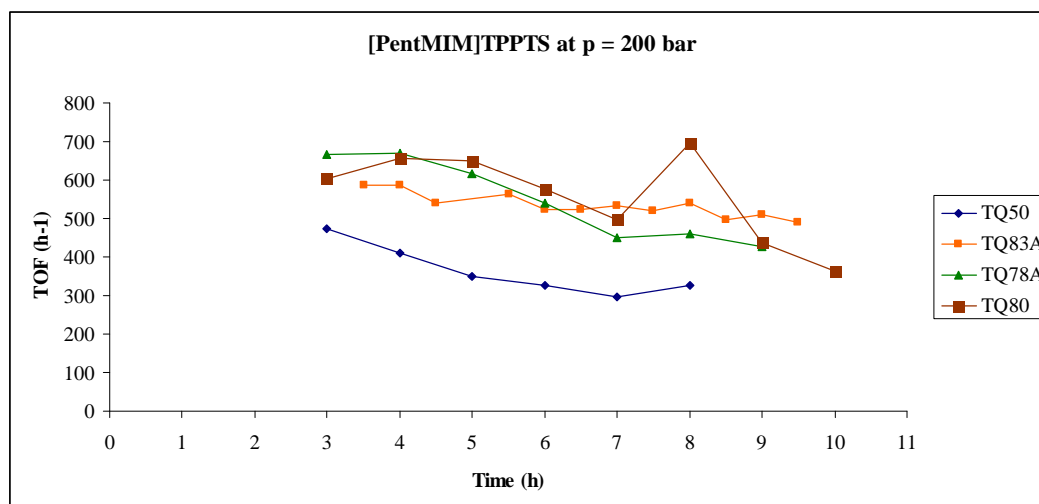
Figure 2.5 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 200 bar and T = 100 ºC. CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min (TQ50 and TQ83A); CO flow rate = 4.20 mmol/min, 1-octene flow rate = 2.65 mmol/min (TQ78A and TQ80).
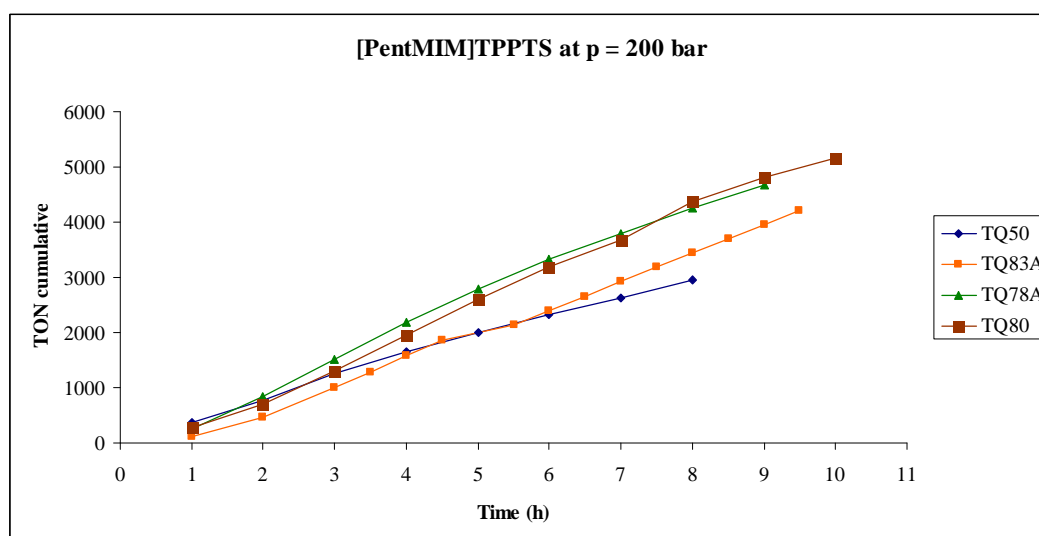
Figure 2.6 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 200 bar and T = 100 ºC. CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min (TQ50 and TQ83A); CO flow rate = 4.20 mmol/min, 1-octene flow rate = 2.65 mmol/min (TQ78A and TQ80).

For the first set of conditions imposed at 200 bar, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min, both catalysts presented a high activity, although the one with the lower P/Rh ratio (12:1) which was used to carry out TQ50, decreased its activity during the reaction time. The same behaviour did not appear to happen in the catalyst used to carry out TQ83A with a higher phosphine loading (P/Rh = 15:1). Generally, loss of phosphine, e.g. as a result of oxidation, would be expected to lead to an increase in the reaction rate because the reaction is negative order in phosphine.[1] A comparison of the average turnover frequency (slope of the graphs in Figure 2.6) for P/Rh ratios of 12:1 and 15:1 (TQ50 and TQ83A respectively) shows that the rate is higher at the higher catalyst loading (700 h^{-1} compared with 400 h^{-1} at the lower loading). This drop off in activity observed for TQ50 may be because the catalyst leaching was greater for the lower P loading. This suggestion is supported to some extent by the ICPMS analysis of the collected fractions (see Figure 2.7, below), which show higher catalyst leaching for TQ50 (P/Rh = 12:1) than for TQ83A (P/Ph = 15:1), although only in the early part of the reaction. However, in both cases, the obtained turnover frequency is higher than the one presented by Webb *et al.* under the same experimental conditions (TOF ~ 360 h^{-1}).[1]

The alkene consumption was not very high in both cases and both catalysts presented a low selectivity to the desired linear aldehyde product. Nevertheless, the TQ83A obtained a higher selectivity, with a l:b ratio of 2.5:1, as expected when using a higher phosphine loading.

Still working at a system pressure of 200 bar, a second set of experimental conditions were imposed, CO flow rate = 4.22 mmol/min, 1-octene flow rate = 2.65 mmol/min. The flows of all the reaction's reactants were changed at the same time to equal the experimental conditions tested by Webb *et al.*.[1]

From looking at Table 2.5, it is possible to observe that the conversion into the aldehyde product decreased when compared to the first set of experimental conditions imposed at 200 bar. Although this is an expected result when the *syn* gas/substrate ratio is decreased (TQ78A and TQ80), we must take in consideration that both flows were changed.

Both catalysts presented a high activity at the beginning of their reactions, which showed a tendency to drop during the reaction time. However, in both cases, the obtained turnover frequency is still higher than the one presented by Webb *et al.* under the same experimental conditions (TOF ~ 400 h^{-1}).[1]

The alkene consumption was not very high in both cases and both catalysts presented a low selectivity to the desired linear aldehyde product. Nevertheless, TQ78A obtained a higher selectivity, with a l:b ratio of 2.6:1.

In general, the ICPMS analysis for the OctMIM]Tf_2N/CO_2 biphasic system tested at a system pressure of 200 bar, revealed a decrease on the rhodium concentration over the reaction time.

The first fractions collected from all the carried out reactions presented a pale yellow colour (Fractions 1 and 2; for TQ80 also Fractions 3 and 8) and after that, all the other fractions collected were absolutely colourless. These last collected fractions presented rhodium concentration values below 1 ppm (Figure 2.7).
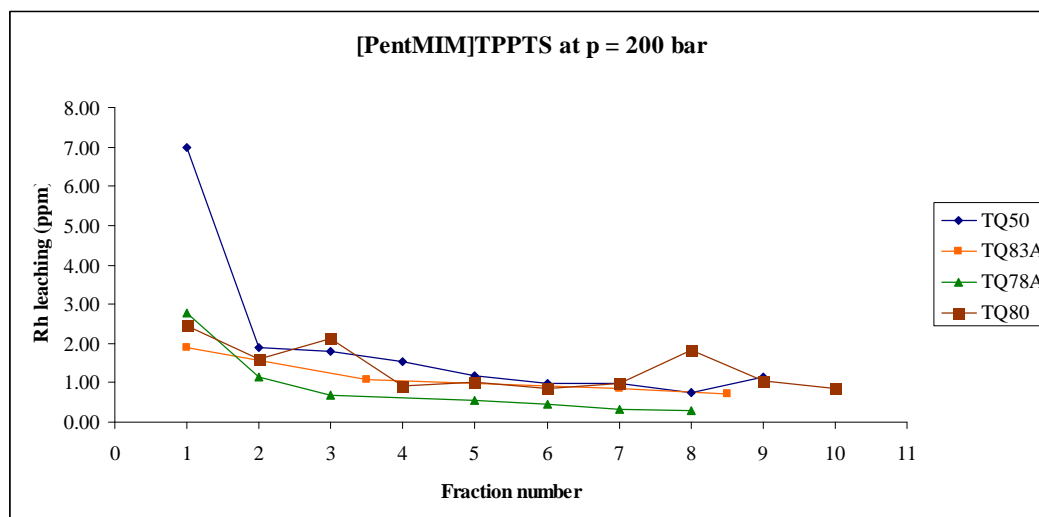
Figure 2.7 Rhodium loss during the continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 200 bar and T = 100 ºC.

Reactions carried out using a higher CO/H_2 pressure would be expected to present lower rhodium leaching.[1] However, this is only observed in one of the two reactions carried out under those conditions, TQ78A. As for TQ80, a justification for the fact that the rhodium leaching did not decrease more, is the fact that the reaction was stopped at t = 7 h and afterwards restarted, explaining the new increase in rhodium concentration present in the collected fractions and the higher apparent turnover frequency in the eighth hour (Figure 2.5).

2.3.2.2 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar

To help simplifying the results analysis, Table 2.6 below is a repetition of the results presented in the above Table 2.5, but only regarding the results obtained at a system pressure of 150 bar.

Table 2.6 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] (P/Rh ratio = 15:1) at p = 150 bar and T = 100 ºC.

Reaction	[Rh]	p	CO flow	1-octene flow	Reaction time	Conversion to aldehyde	l:b ratio	TOF
	(mmol)	(bar)	(mmol/min)	(mmol/min)	(h)	(%)		(h^{-1})
TQ67	0.0814	150	3.77	1.89	5.0	33	3.2	460
TQ83B	0.0775	150	3.77	1.89	5.5	13	2.0	185
TQ88A	0.0973	150	3.77	1.89	10	13	2.0	146
TQ89A-C	0.112	150	3.77	1.89	20	32	2.0	313
TQ90A-B	0.0832	150	3.77	1.08	18	58	2.3	452
TQ71[a]	0.1970	150	6.60	1.89	6.0	46	3.1	263

[a] CO_2 flow rate = 0.8 nL/min

Since the experimental conditions were mostly the same when running the system at this pressure, we thought of analysing the catalysts' performances in terms of their reproducibility. This is due to the fact that, at 150 bar, most of the batches of catalysts are not new and have been previously tested under different experimental conditions (Table 2.3).

Figures 2.8 and 2.9 represent the results in terms of catalyst activity and stability for the hydroformylation reactions carried out at a system pressure of 150 bar, starting from steady state. Not only were both reactions carried out under the same experimental conditions, but also, both batches of catalyst have been previously used.
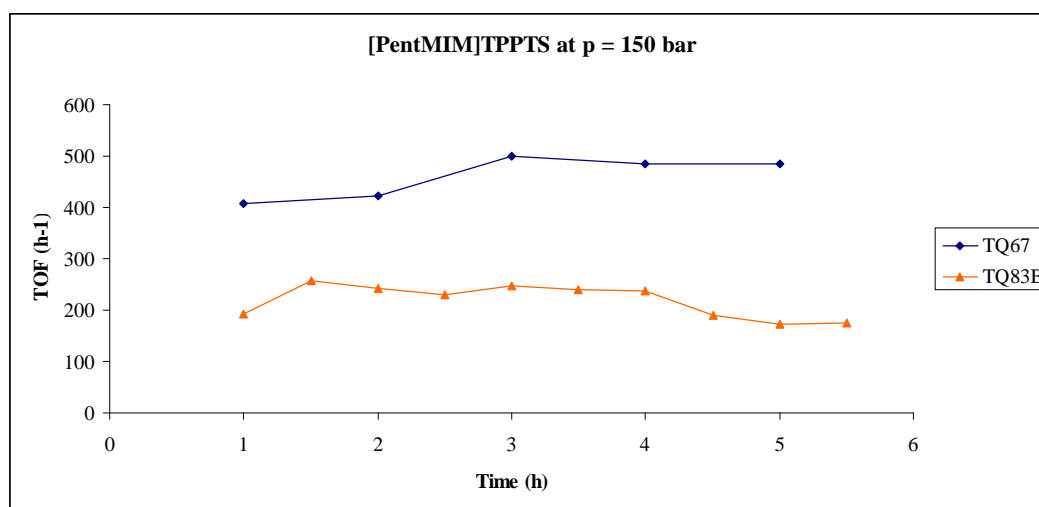
Figure 2.8 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar, T = 100 ℃, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min, overall flow = 1.0 nL/min. Both batches of catalyst had been previously used.
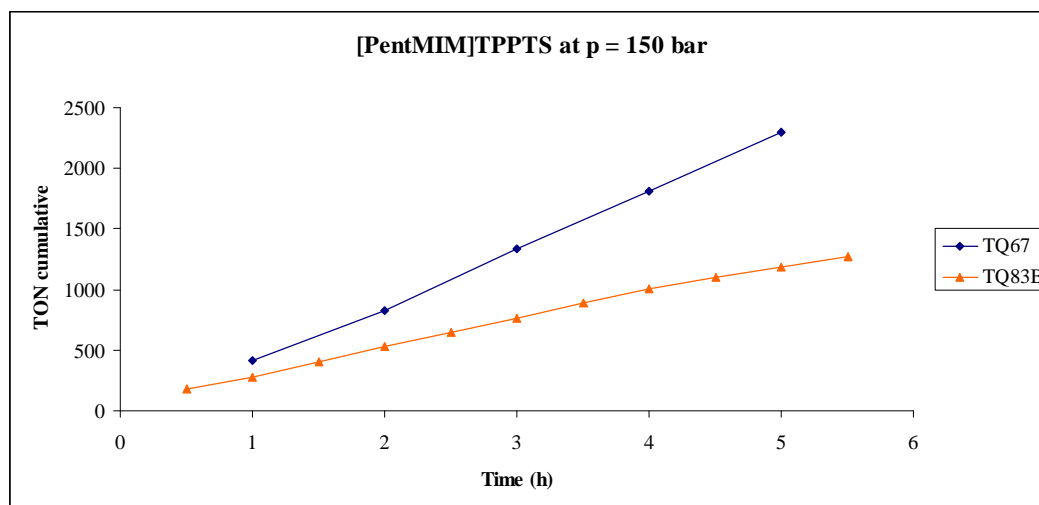
Figure 2.9 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar, T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min, overall flow = 1.0 nL/min. Both batches of catalyst had been previously used.

Although these hydroformylation reactions were carried out under the same experimental conditions, the history of the catalyst (Table 2.3) used in each one of them is very important and is reflected in the reactions' final results. TQ67 was carried out after another hydroformylation reaction, which took place at 100 bar (TQ66), and so, when the system pressure was increased to 150 bar, the catalyst's performance improved. Contrarily, in TQ83B the system pressure was decreased from 200 bar (TQ83A) to 150 bar, leading to a decrease in the catalyst's performance.

The alkene consumption was not very high in both cases and both catalysts presented a low selectivity to the desired linear aldehyde product. Nevertheless, the TQ67 obtained a higher selectivity, with a l:b ratio of 3.2:1.

As a good example of the importance of changing variables in these kind of reactions, Figure 2.10 shows a direct comparison of the behaviour of the catalysts described above during their use.
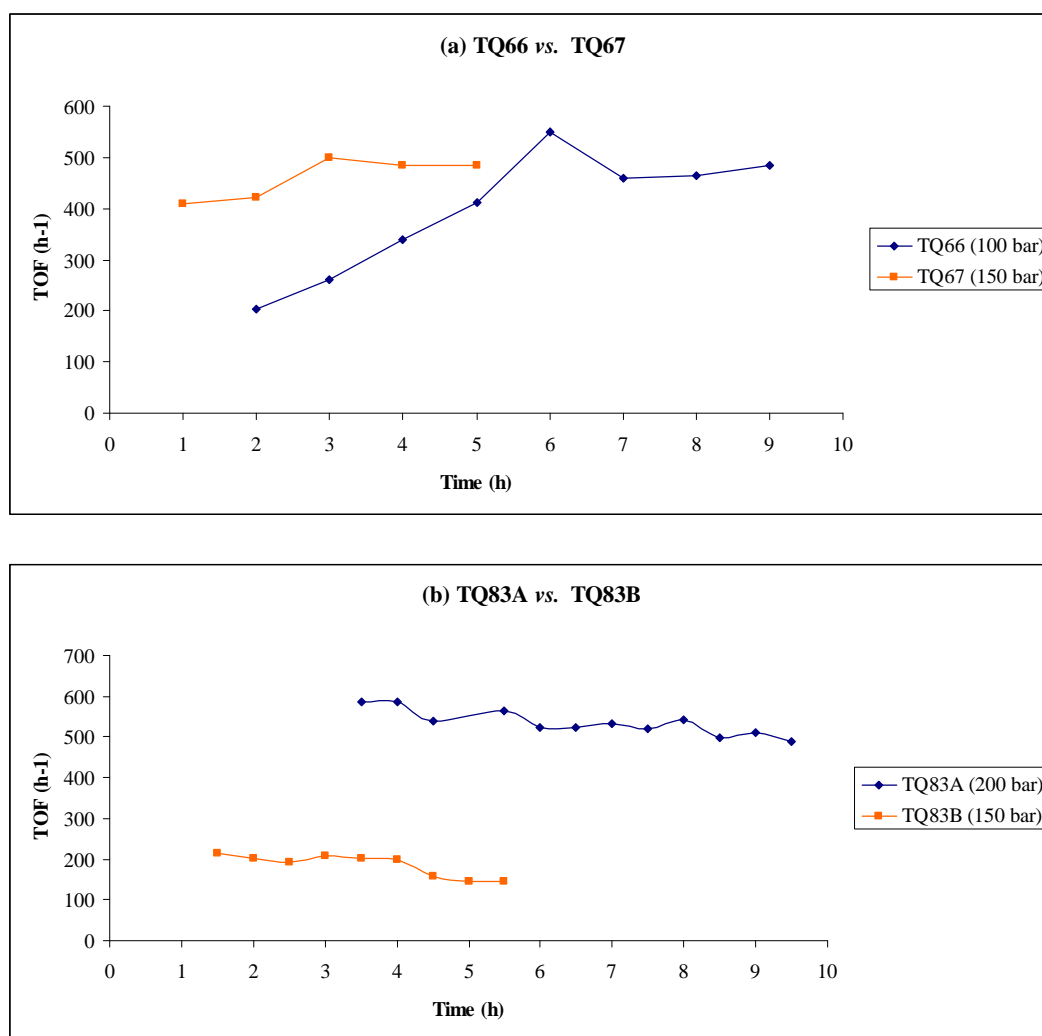
Figure 2.10 Variation of the catalysts' activity with the experimental conditions.

From Figure 2.10, it is possible to observe that in (a) the reaction rate increased due to an increase of the system pressure whilst for (b), the reaction rate decreased when the system pressure decreased from 200 to 150 bar. The results show that the rate increases as the system pressure is increased; this is expected because the residence time of the substrate within the reactor also increases. It seems that the increased residence time dominates over the better partitioning of the substrate into the ionic liquid phase, which is higher at lower pressure and would give an increase in rate as the pressure is reduced.

There is no ICPMS analysis for TQ67. From the observation when collecting the samples, it was noticed that the first samples collected (Fractions 1 and 2) presented a pale yellow colour, which is indicative of the presence of rhodium catalyst. All the other samples collected were absolutely colourless to the human eye.

As for TQ83A, the ICPMS analysis revealed a decrease on the rhodium concentration over the reaction time. The first fractions collected presented a pale yellow colour (Fractions 1 and 2) and after that, all the other fractions collected were absolutely colourless. The last collected fractions presented rhodium concentration values below 1 ppm (Figure 2.11).

[PentMIM]TPPTS at p = 150 bar
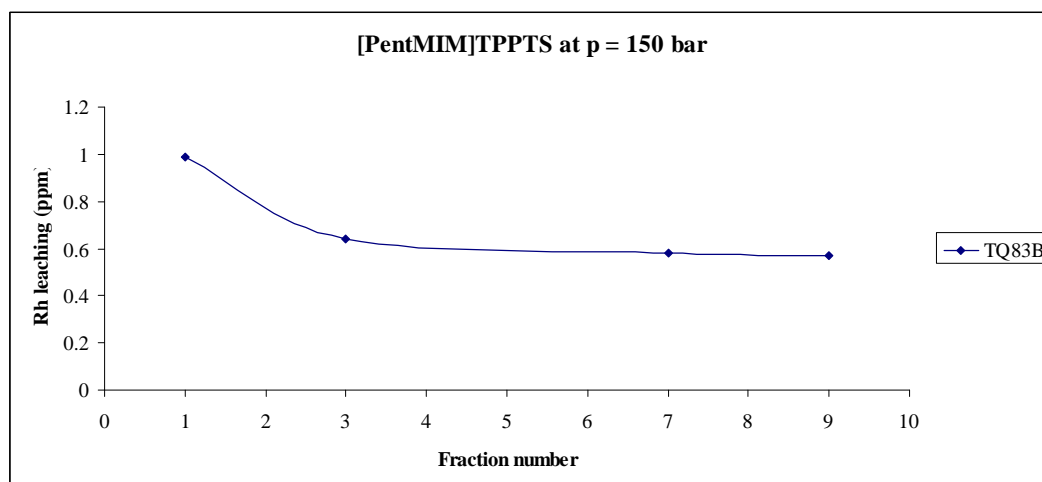
Figure 2.11 Rhodium loss during the continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar and T = 100 ºC (TQ83B).

Still working at a system pressure of 150 bar, two new batches of ionic catalyst were used to carry out consecutive continuous flow runs, this time without changing the experimental conditions set-up since the injection of each catalyst solution The two sets of runs differed only in the substrate flow rate with that for TQ89 being almost double that for TQ90. The results are shown in Figures 2.12 and 2.13.
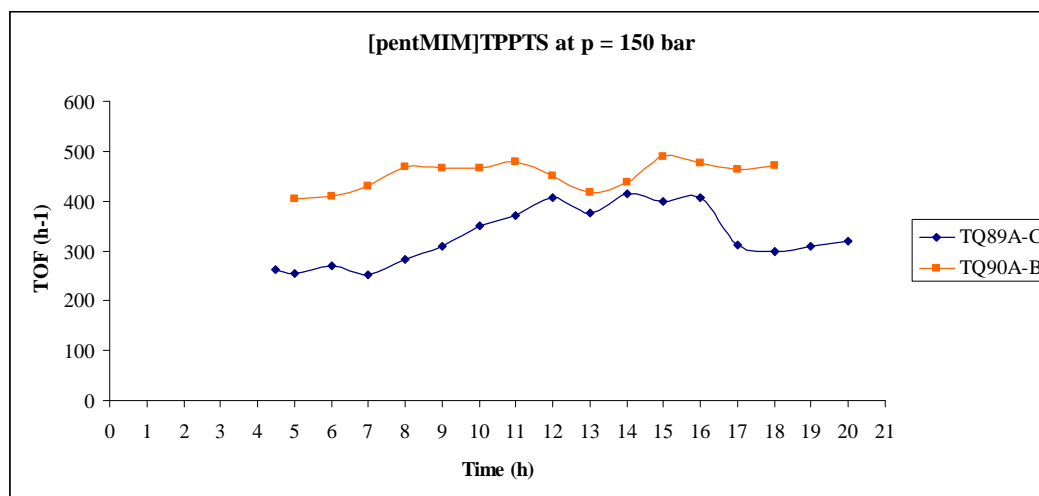
Figure 2.12 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar and T = 100 ºC. CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min (TQ89); CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.08 mmol/min (TQ90). Overall flow = 1.0 nL/min.
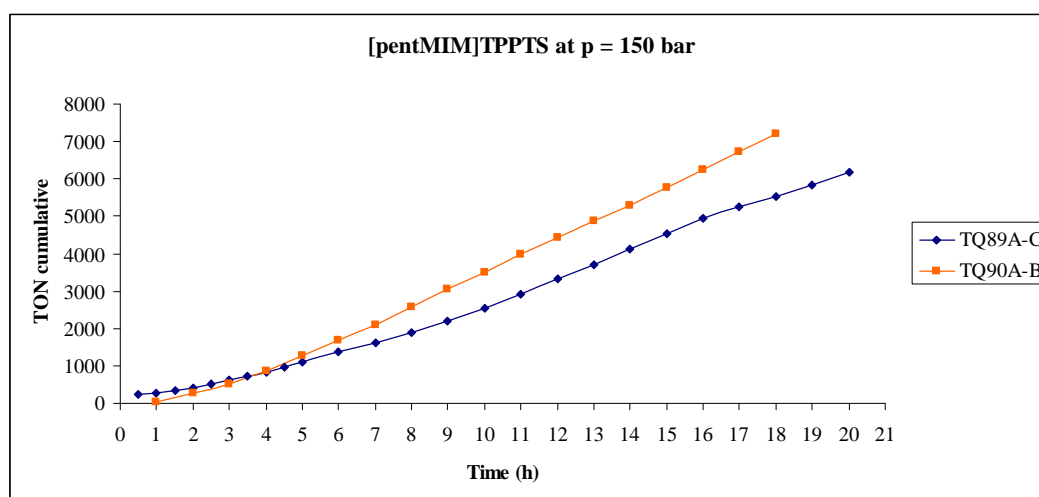
Figure 2.13 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar and T = 100 ºC. CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min (TQ89); CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.08 mmol/min (TQ90). Overall flow = 1.0 nL/min.

For the system running at pressure of 150 bar, the catalyst used to carry out the TQ89 consecutive runs continued after reaching the steady state, to increase its turnover frequency until the end of TQ89A (t =11 h). During TQ89B, the catalyst kept a constant turnover frequency, which only dropped from about 400 h^{-1} to 300 h^{-1} when the system was restarted to carry out TQ89C.

The alkene consumption was not very high in TQ89 and the catalyst presented a low selectivity to the desired linear aldehyde product, with a l:b ratio of 2:1.

As for TQ90A-B, with the lower substrate flow rate, the catalyst activity increased and so did the conversion into the aldehyde products.

Even though working at a lower pressure than the one used by Webb *et al.* in his work[1], the turnover frequency here obtained is clearly superior to his, using the same flow rates (TOF ~ 250 h^{-1}).

Under this set of conditions, the mass balance was only of about 70 %. This may mean that these are not the best flow rates to be used at this system pressure. Either there is a significant loss in terms of reactants or the flowing medium may not now be a sufficiently good solvent to remove all the product and unreacted substrate at a rate equivalent to that of the introduction of the substrate and so the product accumulates inside the reactor. Eventually, a mixture of ionic liquid, catalyst, unreacted substrate and products overflows the reactor and the catalyst is removed from it. The latter explanation is favoured because of the dramatic increase in rhodium leaching at the end of the reaction (see Figure 2.14, below).

Although the alkene consumption in TQ90A-B is higher than in many other cases (55 % conversion to aldehyde), the catalyst did present a low selectivity to the desired linear aldehyde product, with a l:b ratio of 2.3:1.

In terms of stability (Figure 2.13), both catalyst solutions used presented a very linear behaviour, suggesting that the catalysts are quite stable under these conditions, although TQ90A-B presented a more stable behaviour over time, since TQ89A-C tended to stabilise after t = 16 h.

There is no ICPMS analysis for the TQ90A-B consecutive reactions. Nevertheless, and except for fractions 1, 2 and 3 which presented a pale yellow colour, all the other fractions collected during the reactions were absolutely colourless.

As for TQ89A-C, the results of the ICPMS analysis are shown in Figure 2.14.
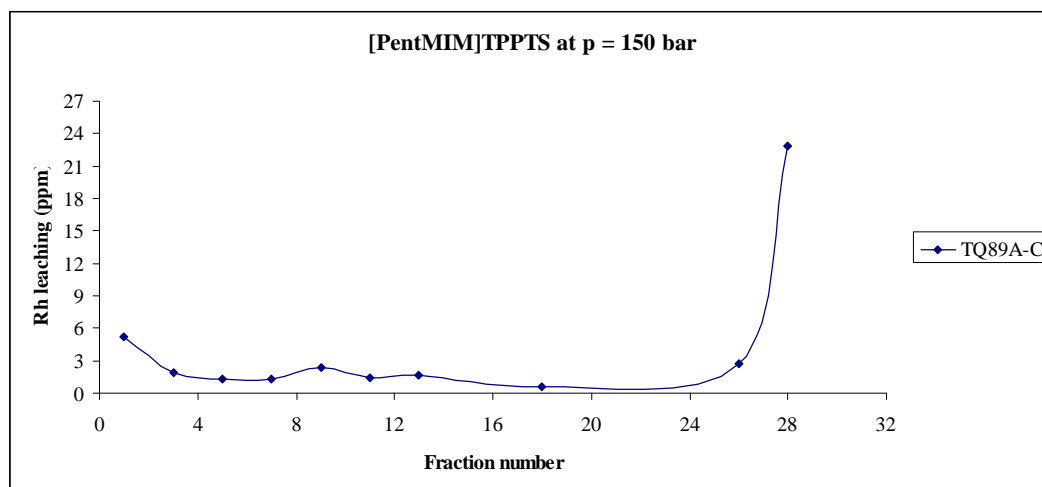
Figure 2.14 Rhodium loss during the continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar and T = 100 ºC (TQ89A-C).

During the sample collection, it was possible to observe that the first four samples collected (Fractions 1, 2, 3 and 4) presented a pale yellow colour, which was indicative of the presence of the rhodium catalyst. With the continuing of the runs, the fractions became colourless, indicating a decrease in leaching of the rhodium catalyst, as expected. However, at t = 16 h of catalyst testing (beginning of TQ89C), the fractions collected started to present a very strong yellow colour, indicating severe rhodium leaching.

NMR analysis of the catalyst solution after it was taken off the reactor confirmed that most of the phosphine had suffered decomposition.

Another hydroformylation reaction was carried out at p = 150 bar. However, this time, the CO_2 flow rate was decreased to 0.8 nL/min and the CO flow rate was increased to 6.60 mmol/min.

The results are shown in Table 2.5 and Figures 2.15 and 2.16.

Figure 2.15 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar, T = 100 ºC, CO flow rate = 6.60 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 0.8 nL/min.

[PentMIM]TPPTS at p = 150 bar
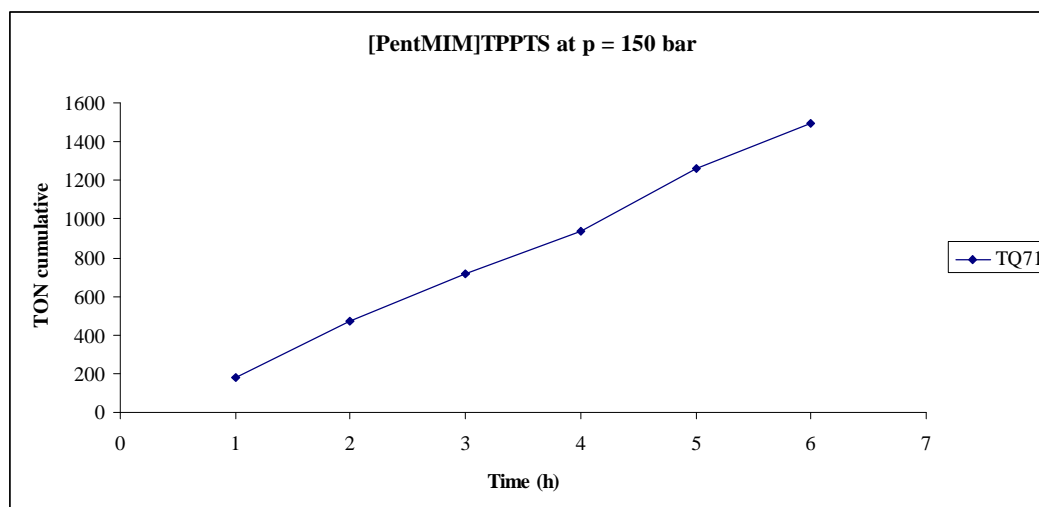
Figure 2.16 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 150 bar, T = 100 ºC, CO flow rate = 6.60 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 0.8 nL/min.

During the reaction, it was very difficult to maintain the CO_2 flow rate stable at 0.8 nL/min. This may explain the unstable turnover frequency of the catalyst during the reaction (Figure 2.15). As a consequence of the lower CO_2 partial pressure and higher *syn* gas flow rate, which lead to a poorer solubilising power of the flowing medium, the unreacted substrate and product were not fully extracted, so that reactor filled-up and some of the fractions collected presented a very bright yellow colour, indicating a high concentration of rhodium. NMR analysis confirmed the presence of ionic liquid in these samples.

2.3.1.3 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 100 bar

The results of carrying out the hydroformylation of 1-octene in continuous flow mode at a system pressure of 100 bar are shown in Table 2.5 and Figures 2.17 and 2.18.

Figure 2.17 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 100 bar, T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

[PentMIM]TPPTS at p = 100 bar
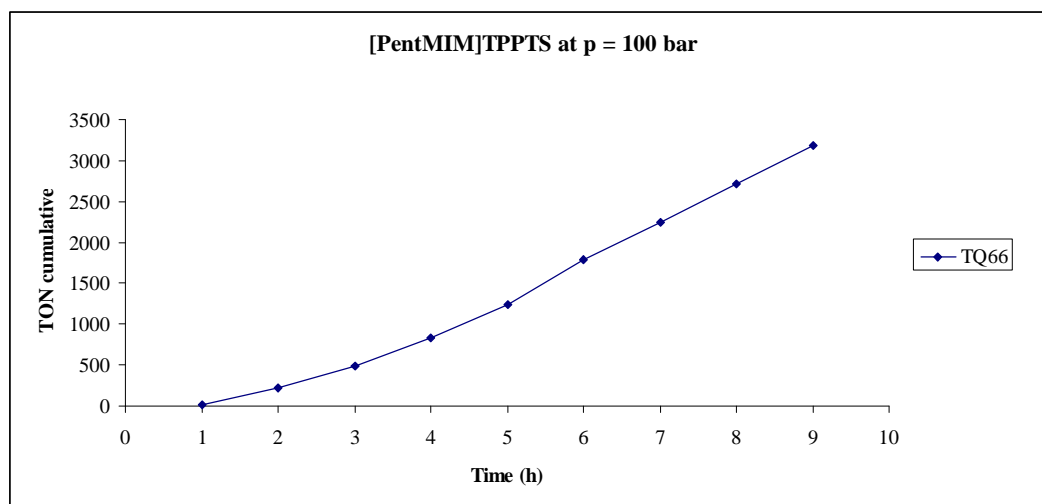
Figure 2.18 Continuous flow hydroformylation of 1-octene catalysed by Rh/[PentMIM][TPPTS] at p = 100 bar, T = 100 ℃, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

The system ran continuously for t = 9 h, during which the turnover frequency rose steadily from 200 to > 400 h^{-1}. At t = 6 h the TOF was even above 500 h^{-1}. At the lower CO_2 partial pressure, the substrate is expected to partition better into the ionic liquid so rates should increase, as observed. However, there is a danger that the flowing phase may not be a good enough solvent to extract all the product formed, so that the reactor will start to fill-up. However, the samples collected (apart from pale yellow fraction 1) were still colourless and their weight was very acceptable, so that the minimum working pressure may not have been reached. Overall, this reaction had an average mass balance of about 70 %. Although this may not be considered as a "brilliant" mass balance, it must be taken in account that the system was ran at 100 bar instead of the usual 200 bar.

The alkene consumption was not very high (29 %) and the catalyst presented a low selectivity to the desired linear aldehyde product, with a l:b ratio of 3.3:1.

2.3.3 Continuous Flow Hydroformylation of 1-octene Using Rh/[OctMIM][TPPTS] as Catalyst

As described in Section 2.3.2 for the Rh/[PentMIM][TPPTS] catalyst, continuous flow hydroformylation reactions of 1-octene catalysed by Rh/[OctMIM]$_3$[P-(3-C$_6$H$_4$SO$_3$)$_3$] were also carried in the [OctMIM]Tf$_2$N/CO$_2$ biphasic system. The reason for increasing the length of the cation of the ionic ligand to the same length as that of the cation of the reaction solvent was to check if it would increase the catalyst's solubilisation and therefore, its retention in the reaction medium.

Once again, different experimental parameters were changed at p = 200 and 150 bar. The most relevant results are shown in Table 2.7 and do note that, the history of the catalysts used to carry out these reactions was presented in Table 2.4.

Table 2.7 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] (P/Rh ratio = 15:1) at p = 200 and 150 bar and T = 100 ºC.

Reaction	[Rh]	p	CO flow	1-octene flow	Reaction time	Conversion to aldehyde	l:b ratio	TOF
	(mmol)	(bar)	(mmol/min)	(mmol/min)	(h)	(%)		(h^{-1})
TQ94A	0.0976	200	3.77	1.89	12	41	3.0	471
TQ96A	0.1000	200	3.77	1.89	12	63	3.0	714
TQ94B	0.1124	150	3.77	1.89	8.0	27	2.8	317
TQ96B	0.1000	150	3.77	1.89	9.0	50	3.0	583
TQ97A	0.0701	150	3.30	1.89	12	48	3.0	486

Figures 2.19 and 2.20 represent the results obtained for the hydroformylation reactions carried out at a system pressure of 200 bar.
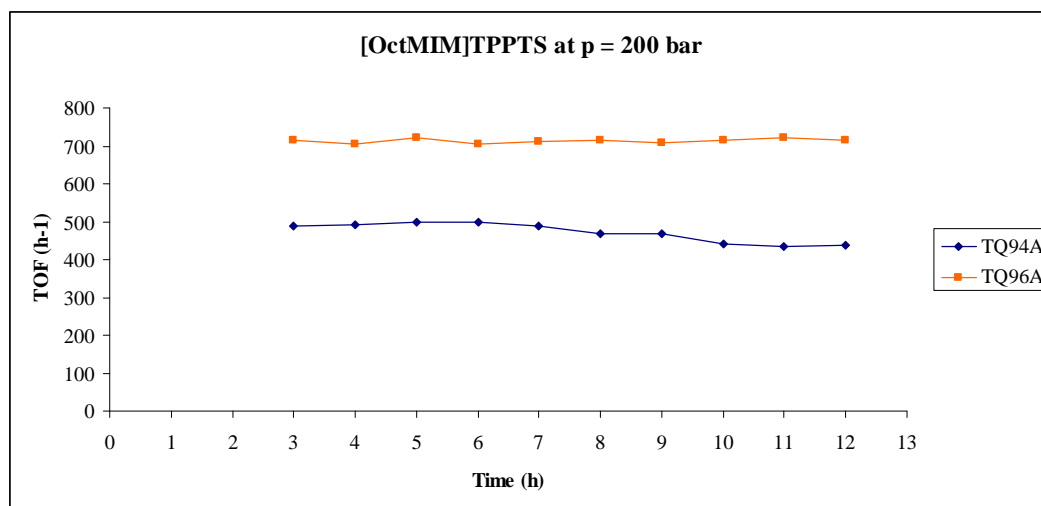
Figure 2.19 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 200 bar, T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

Figure 2.20 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 200 bar, T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

Both systems ran continuously for t = 12 h, during which the turnover frequency reached values above 500 h^{-1} (TQ94A) and 700 h^{-1} (TQ96A). Although both batches of catalyst presented a similar behaviour, the difference in the turnover frequency is surprising since the only difference between the two runs is a lightly higher catalyst loading in TQ96A. This should not affect the TOF if the reaction is first order in Rh. Nevertheless, the rates are clearly above the ones obtained by Webb *et al.* under the same experimental conditions (TOF ~ 360 h^{-1}).[1] Also, in terms of mass balance, the obtained results were very good. TQ94A presented an average mass balance of 85 % while TQ96A presented an average mass balance of 91 %.

In terms of stability (Figure 2.20), both catalysts presented a very linear behaviour, suggesting good catalyst stability.

Although the alkene consumption was significant (45-63 %), the catalysts did present a low selectivity to the desired linear aldehyde product. Both presented a l:b ratio of 3:1.

Preliminary ICPMS analysis for the OctMIM]Tf$_2$N/CO$_2$ biphasic system tested at a system pressure of 200 bar, revealed a decrease on the rhodium concentration over the reaction time. The first fractions collected presented a pale yellow colour (7.5 ppm Rh in Fraction 1 of TQ94A) but after that, the other fractions collected

were absolutely colourless. The last collected fraction for TQ94A had a rhodium concentration of 0.1 ppm.

While in use, both batches of catalyst were kept inside the reactor isolated under constant pressure, temperature and stirring. After sometime new hydroformylation reactions were again performed, this time at a system pressure of 150 bar. The results are shown in Figures 2.21 and 2.22.
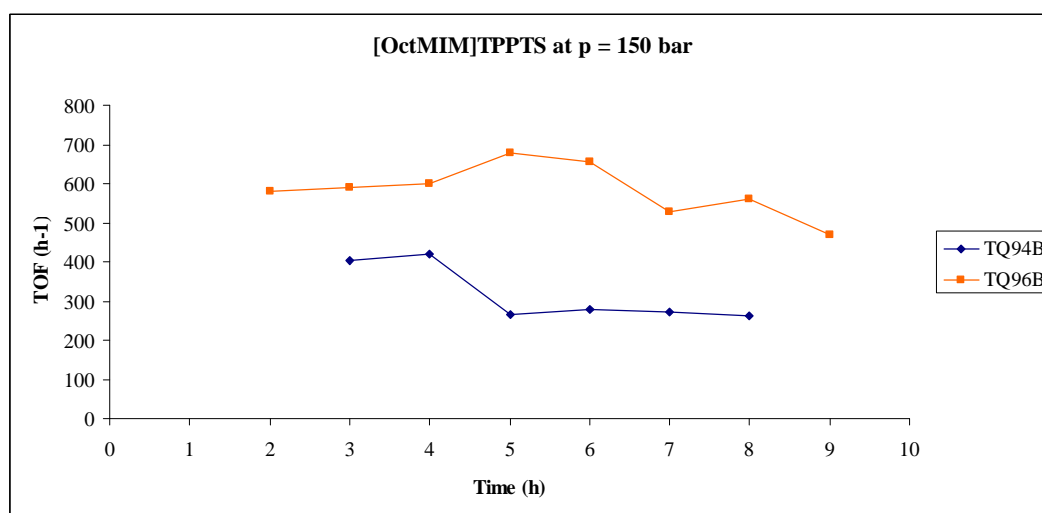
Figure 2.21 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 150 bar and T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.
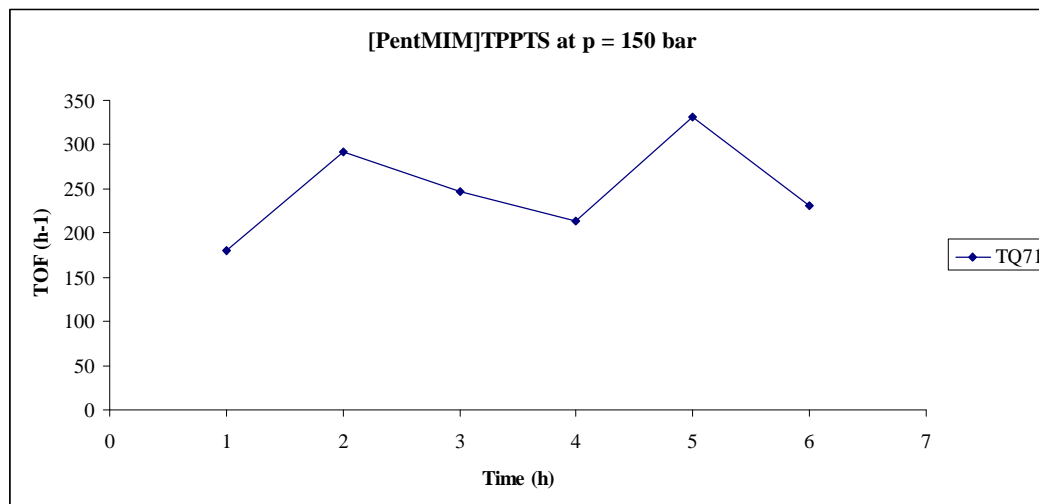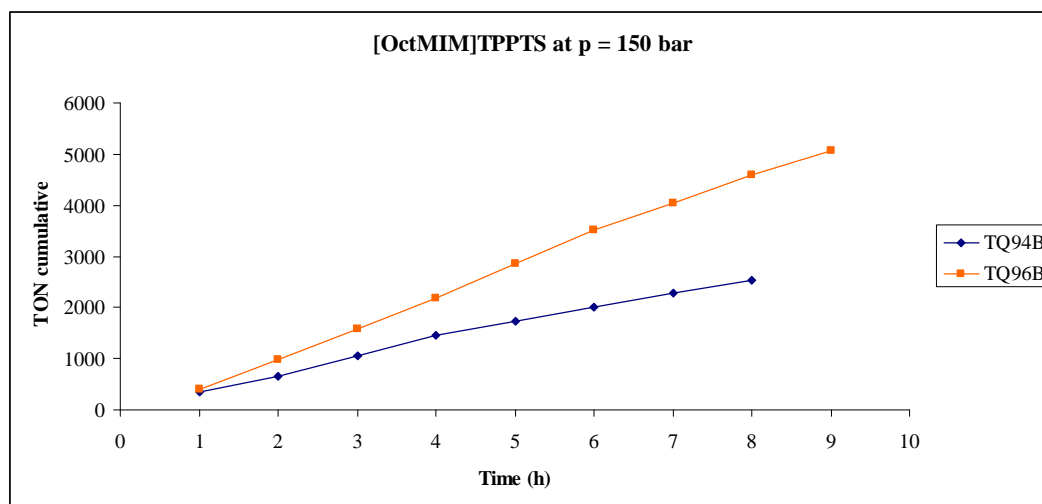
Figure 2.22 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 150 bar and T = 100 ºC, CO flow rate = 3.77 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

TQ94B started by presenting an unstable behaviour at the beginning of the reaction and ended up by stabilising at a much lower turnover frequency (TOF ~300 h^{-1}) than the one this same catalyst presented at 200 bar. As a consequence, the aldehyde conversion also dropped from an average of 41 % at 200 bar to 27 % at 150 bar. Considering the obtained results, this catalyst solution was taken off from the reactor and analysed by NMR, which shown signs of phosphine decomposition.

As for the continuous flow reaction TQ96B, although the turnover frequency here represented can be considered high, the colour of some of the fractions collected added to the fact that this catalyst was used for several different tests, made us take the catalyst solution out from the reactor at the end of this run. NMR analysis also shown signs of phosphine decomposition.

Figures 2.23 and 2.24 show the results for another hydroformylation reaction carried out at 150 bar. In TQ97A a totally new catalyst solution was injected.
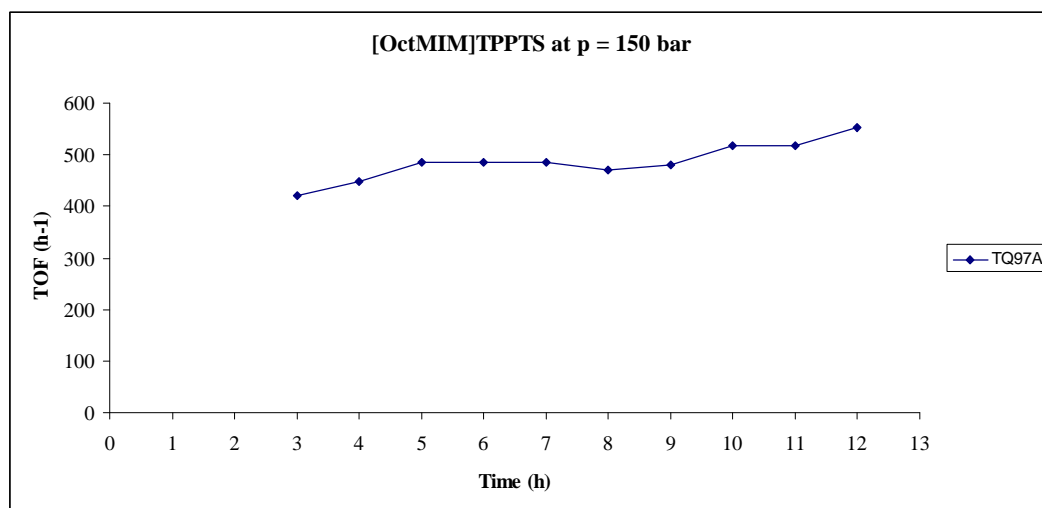
Figure 2.23 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM]TPPTS at p = 150 bar and T = 100 °C, CO flow rate = 3.30 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.
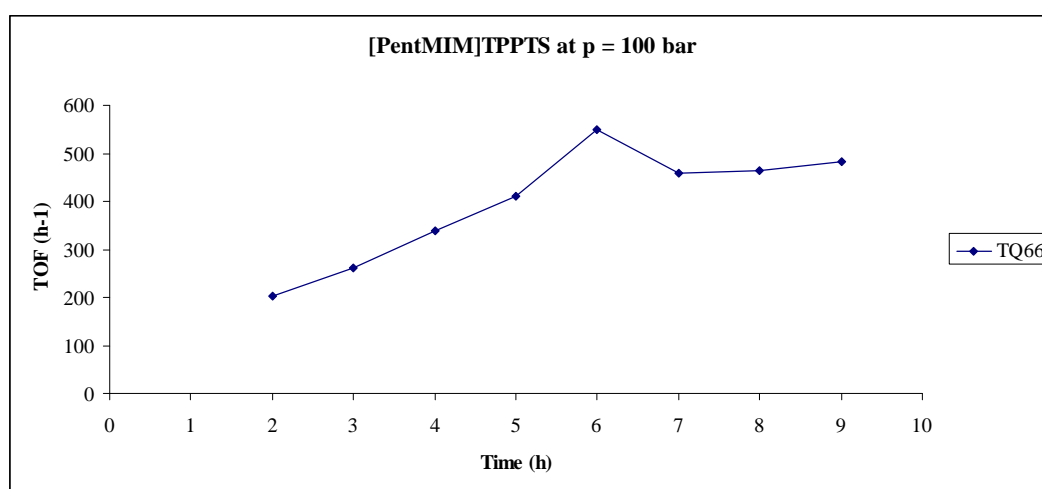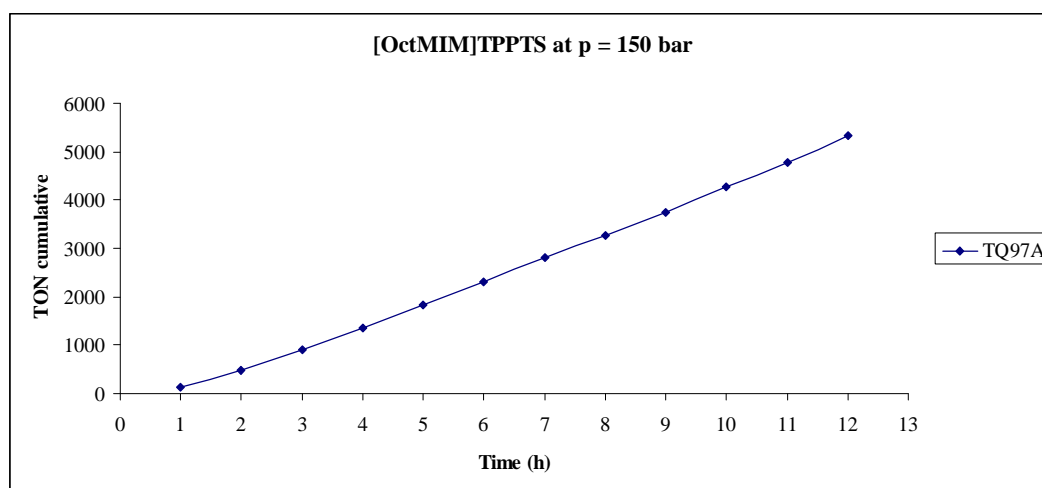

Figure 2.24 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM]TPPTS at p = 150 bar and T = 100 °C, CO flow rate = 3.30 mmol/min, 1-octene flow rate = 1.89 mmol/min. Overall flow = 1.0 nL/min.

Here, the CO flow rate was decreased to check its interference in the CO_2 flow rate. Normally, when the flow rate of the *syn* gas is lower, the partitioning of the substrates and products into the CO_2 increases so the rate of reaction decreases. It also increases the rhodium leaching. In result, its turnover frequency was above 400 h^{-1} in the steady state. Although there is not a direct comparable reaction carried out by Webb *et al.* to compare this TOF result, the idea was to check if the a decrease in the *syn* gas flow, would affect the solubility of the products in the CO_2 and avoid the catalyst leaching.

In terms of stability (Figures 2.22 and 2.24), reactions TQ96B and TQ97A show considerable variations of the rate as the reaction goes on, perhaps with a loss of rate later in the run. Reaction TQ94B, shows a much more stable behaviour, although the increase in rate towards the end of the run may represent phosphine loss through oxidation.

Although the alkene consumption was moderate (especially for TQ96B), the catalysts presented a low selectivity to the desired linear aldehyde product. Nevertheless, TQ96B and TQ97A presented a l:b ratio of 3:1.

There are no ICPMS analysis results for any of these reactions.

For the TQ97A reaction, except for Fraction 1 (Fraction 1 corresponds to the first sample collected on each reaction), which presented a very slightly pale yellow

colour, all the other fractions collected during the reactions were absolutely colourless.

2.3.3.1 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] using the same sample for sequential reactions at at p = 200 and 150 bar

A single sample of Rh/[OctMIM][TPPTS] in the [OctMIM]Tf_2N/CO_2 biphasic system was tested in continuous sequential reactions at pressures of 200 and 150 bar in order to ensure that all other parameters remained constant.

The overall flow was kept constant at a flow rate of 1.0 nL/min (1 nL = 1 litre at NTP).

During the continuous flow reaction, fractions were collected every hour for GC analysis.

The results are shown in Table 2.5 and Figures 2.25 and 2.26.

Table 2.8 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] (P/Rh = 15:1) at p = 200 and 150 bar and T = 100 °C.

Reaction	[Rh]	Pressure	CO flow	1-octene flow	Reaction time	TOF
	(mmol)	(bar)	(mmol/min)	(mmol/min)	(h)	(h^{-1})
TQ99	0.0701	200	3.77	1.89	12	981
		150	3.30	1.89	12	468
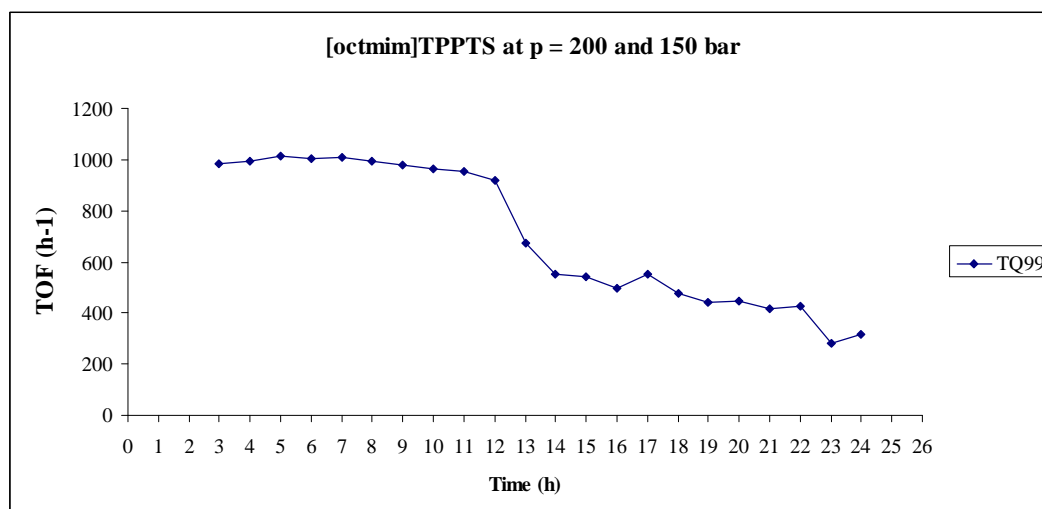
Figure 2.25 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 200 and 150 bar and T = 100 ºC. Overall flow = 1.0 nL/min.
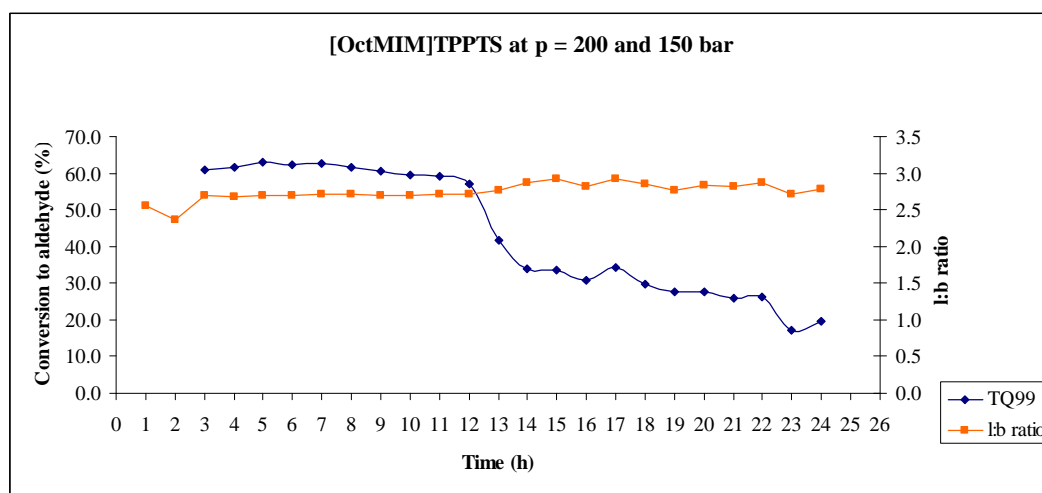
Figure 2.26 Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 200 and 150 bar and T = 100 ºC. Overall flow = 1.0 nL/min.

The system ran continuously (non-stop) for t = 24 h. For the first 12 h, the system pressure was 200 bar and for the second half of the 24 h, the system pressure was reduced to 150 bar.

When performing at 200 bar, the catalyst reached a very stable and impressive turnover frequency of 1000 h^{-1}. Although the TOF decreased to about 400 h^{-1} when the overall pressure was reduced to 150 bar, this is consistent with the result described above (using different batches of catalyst) under the same experimental conditions. Several experimental parameters may contribute to this reduction in rate:

- The reduced pressure will reduce the residence time, thus reducing the conversion;
- The reduction in total pressure would be expected to lead to an increase in reaction rate because of better partitioning of the substrate into the ionic liquid.

In terms of mass balance, the obtained results were very good. TQ99 presented an average mass balance of 92 %.

The catalyst showed a low selectivity to the desired linear aldehyde product, with the l:b. ratio remaining at 3:1 throughout the reaction, despite the change in overall pressure, flow rates and reaction rates.

[OctMIM]TPPTS at p = 200 and 150 bar

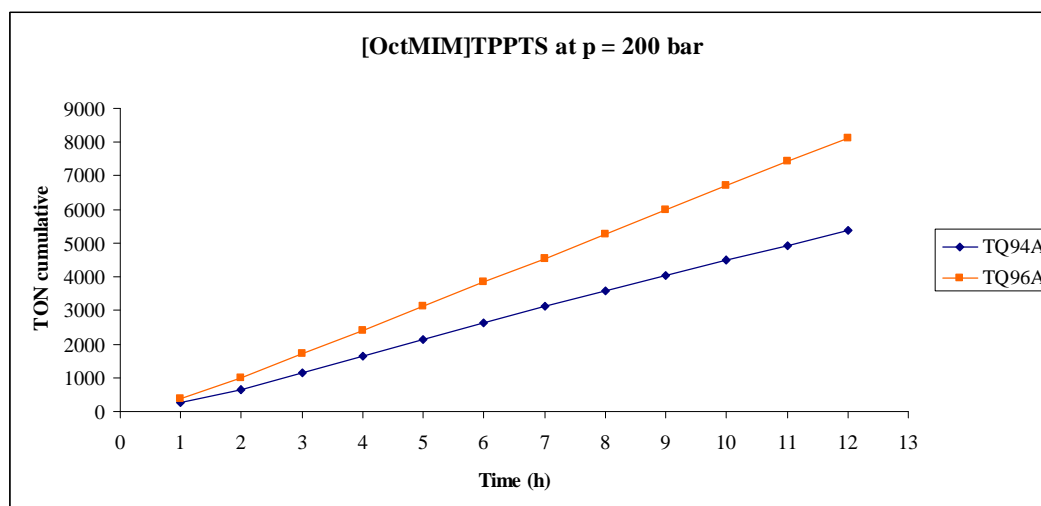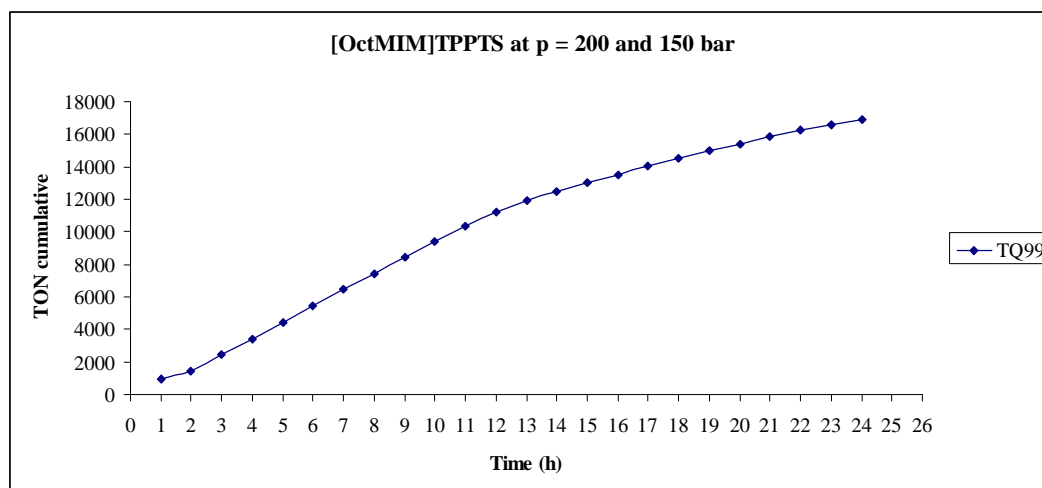**Figure 2.27** Continuous flow hydroformylation of 1-octene catalysed by Rh/[OctMIM][TPPTS] at p = 200 and 150 bar and T = 100 ºC. Overall flow = 1.0 nL/min.

In terms of stability (Figure 2.27), reaction TQ99 presented two linear portions representing stable but different rates under the two different pressure regimes.

There are no ICPMS analysis results for this reaction. Nevertheless, and except for Fraction 1 (Fraction 1 corresponds to the first sample collected on each reaction), which presented a very slightly pale yellow colour, all the other fractions collected during the reactions were absolutely colourless.

2.3.4 XPS Studies

Licence and co-workers have demonstrated that it is possible to apply XPS, a semi-quantitative spectroscopic technique, to analyse liquid samples dissolved in room temperature ionic liquids.[24, 25] This is possible because, although samples analysed through XPS are put inside an ultra high vacuum (UHV) chamber, ionic liquids have almost no measurable vapour pressure, meaning that they do not evaporate under vacuum like normal liquids and so, can be a suitable media for XPS studies.

Taking this in account, the two ionic ligands, [PentMIM][TPPTS] and [OctMIM][TPPTS] were used together with the precursor [Rh(acac)(CO)$_2$] to form the ionic catalyst complexes for XPS analysis *in vacuo*. The samples were irradiated with a beam of x-rays and the energy of the resulting photoelectrons was measured.

XPS studies confirmed that the rhodium coordination to either [PentMIM][TPPTS] or [OctMIM][TPPTS] (Figure 2.28) ligands results in a lower binding energy for the 3d electrons on rhodium, suggesting a higher electron density on the metal, expected when the phosphine ligand replaces the better π-accepting CO ligand in the formation of [Rh(acac)(CO)(L)] (L = [PentMIM][TPPTS] or [OctMIM][TPPTS]).[26] The binding energies are very similar for [PentMIM][TPPTS] and for [OctMIM][TPPTS], as expected when the sulphonate is in the 3-position, and they are very similar for solid [Rh(acac)(CO)$_2$] and for [Rh(acac)(CO)$_2$] in the ionic liquid, suggesting that there is no reaction between [Rh(acac)(CO)$_2$] and ionic ligands.
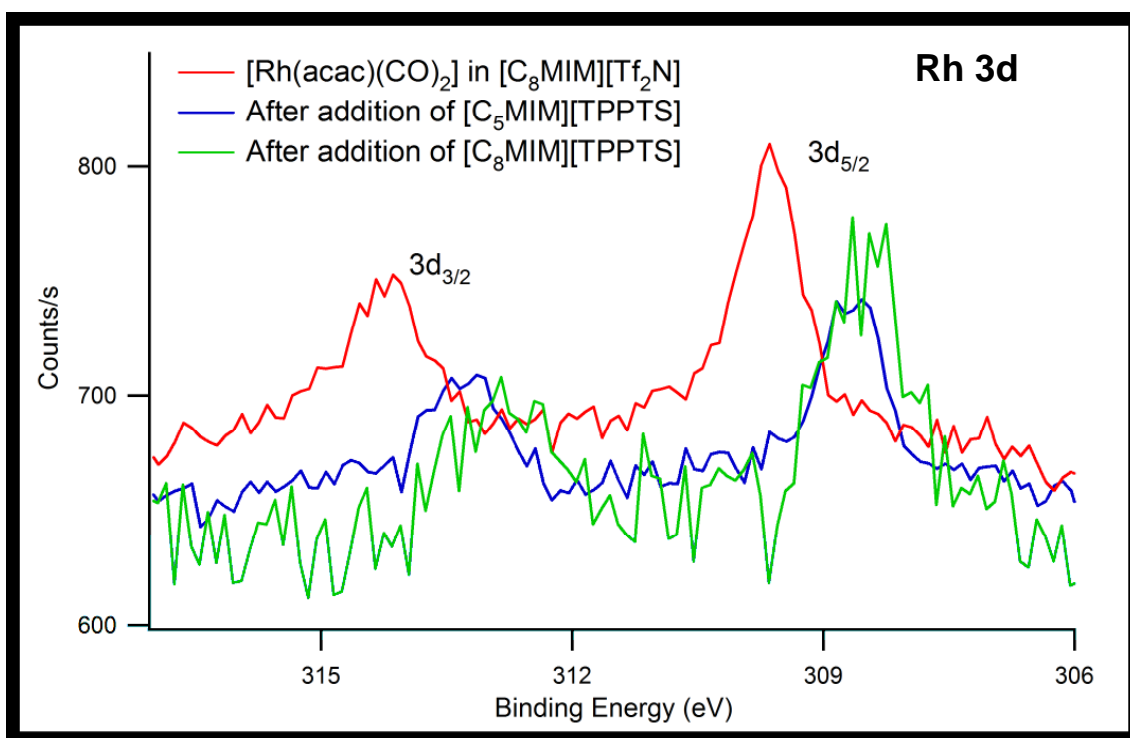
Figure 2.28 High resolution XPS spectra of [Rh(acac)(CO)$_2$] in [OctMIM]Tf$_2$N (red), [Rh(acac)(CO)$_2$] and [PentMIM][TPPTS] in [OctMIM]Tf$_2$N (blue) and [Rh(acac)(CO)$_2$] and [OctMIM][TPPTS] in [OctMIM]Tf$_2$N (green), highlighting the Rh 3d photoemission.[26]

2.4 Conclusions

The work described in this Chapter was focused on improving the previous results obtained by Webb *et al.*.[1] His work was especially focused on the optimisation of continuous flow hydroformylation reactions of long chain alkenes catalysed by Rh/[PrMIM][TPPMS] at p = 200 bar and 100 $^{\circ}$C carried out in a IL/scCO$_2$ biphasic system. Since the ionic liquid [OctMIM]Tf$_2$N presented good solubility

results for the long chain alkenes, this was kept as a solvent for the continuous flow experiments.

The [PentMIM][TPPTS] and the [OctMIM][TPPTS] ionic ligands were tested in the hydroformylation of 1-octene. Several batches of both ligands were prepared and tested; some were only used for one specific reaction while others were continuously used for some weeks.

Results show that both catalysts performed very well in terms of activity and stability, when running under different sets of experimental conditions. In most of the cases presented, the turnover frequencies of the catalysts were higher than the catalyst turnover frequencies presented by Webb *et al.* for the same set of experimental conditions. However, the biggest improvement was being able of keep obtaining higher turnover frequencies, when running the [OctMIM]Tf$_2$N/scCO$_2$ biphasic system at pressures below 200 bar.

These results obtained at lower pressures are very interesting and a more exhaustive study should be done on the experimental conditions (lower pressures), in order to achieve an even better optimisation of the system, in terms of l:b ratio and catalyst loss.

Also, it would be interesting to change the ionic solvent for another one, which would be capable of dissolving the TPPTS directly, without needing to perform the cation exchange (Na$^+$ for [RMIM]$^+$) reaction first.[27, 28]

2.5 References

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Chapter 3

Continuous Flow Hydroformylation of 1-octene "Without Gases" – A Supported Ionic Liquid Phase Homogeneous System

3. Continuous Flow Hydroformylation of 1-octene "Without Gases" – A Supported Ionic Liquid Phase Homogeneous System

The experiments included in this Chapter were performed at the University of Nottingham as part of a partnership integrated in the SuperGreenChem Marie Curie Training Network.

3.1 Introduction

Continuous flow hydroformylation of long chain alkenes (1-octene) has been carried out using a SILP (**S**upported **I**onic **L**iquid **P**hase) catalyst, where a thin layer of ionic liquid catalyst is immobilized at the surface of an inert solid support like, for instance, silica gel.

Poliakoff and the Clean Technology Group have been developing a new supported homogeneous system where the synthesis gas is obtained *in situ* by decomposing formaldehyde at T = 450 ºC.

3.1.1 The Supported Ionic Liquid Phase concept

Ordinarily known as SILP, the Supported Ionic Liquid Phase catalysts has been largely studied over the last few years, as a reliable alternative to heterogeneous catalysts.[1, 2]

SILP catalysts, which have already been previously described in Chapter 1 (Section 1.4.2.2), are included in a group of new approaches to overcome the well known problems related to homogeneous catalysis[3, 4], like for example, aqueous biphasic systems or reactions using supercritical fluids. By immobilising the ionic liquid using a solid support, like silica gel, two main advantages easily appear:

- the homogeneous catalyst becomes a solid, which means that it can be used in fixed-bed reactors, behaving like a normal heterogeneous catalyst and facilitating the catalyst/product separation;

- when compared with other alternative processes, this can be very economically reliable due to the small quantities of ionic liquids involved (larger interface areas).
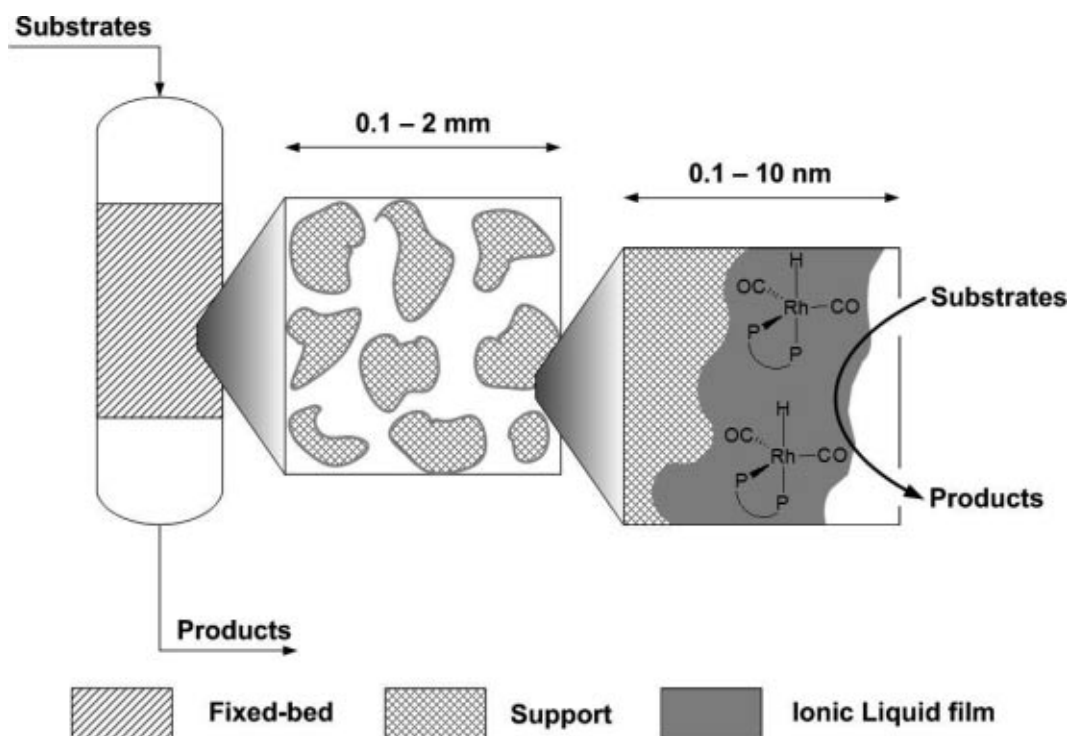
Figure 3.1 Supported ionic liquid phase catalysts applied to fixed-bed reactors.[5]

Inspired by the work of Davis *et al.*[6] on the support of aqueous biphasic systems, Mehnert and co-workers successfully reported the concept of supported ionic liquid catalysis applied to the hydroformylation of 1-hexene.[7] The ionic liquid [BMIM]PF$_6$ was immobilised in pre-treated silica gel and two phosphine ligands, TPPTS (tri(*m*-sulfonyl)triphenyl phosphine trisodium salt) and TPPTI (tri(*m*-sulfonyl)triphenyl phosphine tris(1-butyl-3-methylimidazolium) salt) (Figure 3.2), were used together with the rhodium precursor [Rh(acac)(CO)$_2$], forming the respectively active species, [HRh(CO)(tppts)$_3$] and [HRh(CO)(tppti)$_3$] (Figure 3.3). The reactions were carried out in a batch mode and although the results showed a high activity, this can be explained by the high concentration of rhodium in the autoclave. Also, the catalyst leaching was considerably high.

TPPTS   TPPTI
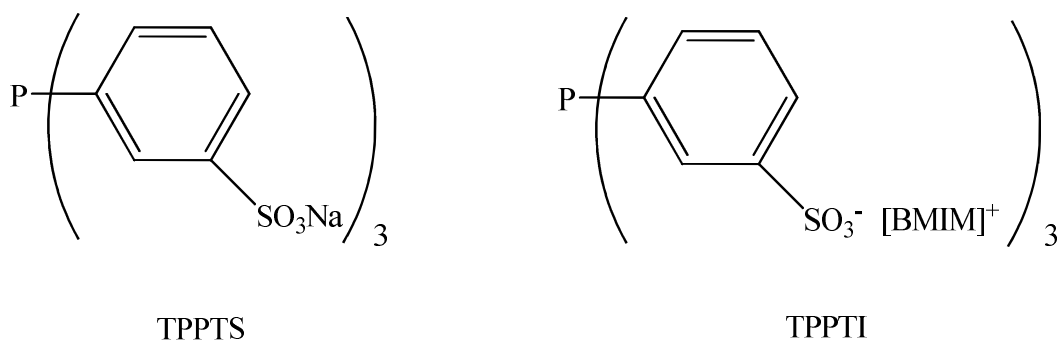
Figure 3.2 Structures of TPPTS and TPPTI.
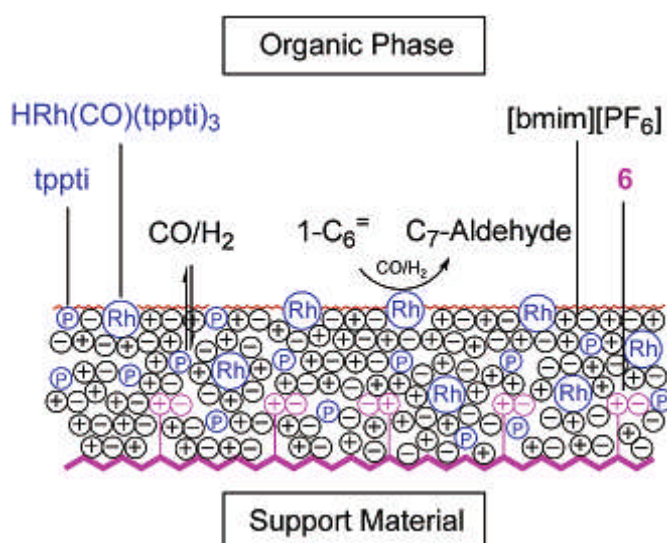
Figure 3.3 Supported ionic liquid catalysis used in the hydroformylation reaction of 1-hexene carried out by Mehnert and co-workers.[7]

Later on, Mehnert and co-workers were also the first to apply the same concept to the hydrogenation of olefins, with much better catalyst retention because the products are much less polar than those from hydroformylation and so, the ionic liquid is much less soluble in them.[8]

Although SILP catalysts can be used either in gas-phase or liquid-phase applications, its performance is much better when involved in gas-phase

catalysis.[5] This is mainly because the involatile ionic liquid and catalyst are not extracted by the gases. In long term continuous processes using, for example, a liquid-liquid biphasic system, it is possible to observe big losses of catalyst when carrying out the reaction. This can be reflected on a decreasing turnover frequency with time.

3.1.2 The Clean Technology Group "Without Gases" Approach

One problem with all reactions involving gaseous reagents or supercritical solvents is that they require specialised pressure vessels, which are not routinely available in all laboratories. To help the small scale continuous flow research, the Clean Technology Group, at the University of Nottingham, came up with the idea of overcoming the problems related with handling high-pressure gases. This is called the "without gases" or "gasless" approach.[9, 10]

Hyde *et al.* first presented this method applied to the hydrogenation reaction.[11] Here, both the CO_2, as a supercritical solvent, and the H_2 were synthesised *in situ* from the decomposition of formic acid, HCO_2H. This decomposition was obtained by passing cold formic acid through a 5% Pt catalyst pre-heated at T = 450 ºC, in a first reactor installed in the rig. The previously synthesised CO_2 and H_2 then passed into a second reactor where the main reaction occurred and finally, the products were collected at the back pressure regulator, by decompression/CO_2 phase separation. A scheme of the rig is shown in Figure 3.4.
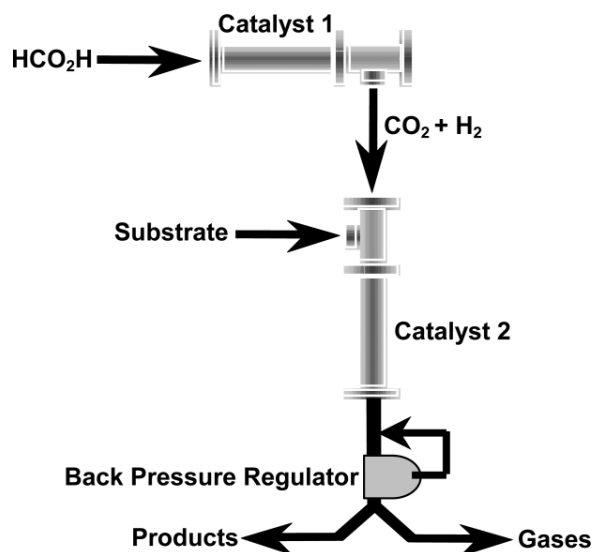
Figure 3.4 Scheme of the experimental set-up used on the "without gases" approach.[11, 12]

In the development of this work, other reactions were tested. The hydroformylation of long chain alkenes and/or cyclic alkenes has also been carried out by Poliakoff and co-workers, using either immobilised, Deloxan® (a polysiloxane material), or unsupported, ROPAC® (commercial name for the Rh(acac)(CO)(PPh$_3$) complex) catalysts.

Meehan *et al.* used immobilised Rh diphosphine catalysts to carry out hydroformylation reactions.[13] Cozier *et al.* continued his work by using the same immobilised Deloxan® catalyst in the "without gases" system.[14] On the hydroformylation of 1-decene, although the catalyst was stable in the system for over thirty days, low stability and activity (TOF ~ 80 h^{-1}) were obtained. The hydroformylation of cyclohexene for the production of cyclohexanecarboxadehyde was also carried out and better results were obtained in terms of conversion (~ 90 %) and catalyst activity (TOF ~ 240 h^{-1}).

The insoluble homogeneous ROPAC® catalyst was tested in the "without gases" system by Cozier *et al.*[14], following the results previously obtained by Sellin *et al.* concerning the catalyst/product separation problem, very common in the homogeneous processes.[15]

The hydroformylation of 1-decene with the unsupported ROPAC® catalyst was carried out in both batch and continuous flow mode. After an extensive use, the continuous flow system presented a high activity but a low selectivity to the desired linear aldehyde, with a l:b ratio of 2:1.

Surprisingly, no catalyst/product separation was necessary when using either the immobilised (Deloxan®) or unsupported (ROPAC®) catalysts. On both cases, the products were just obtained by simple decompression.

For the hydroformylation reaction, the CO and the H_2 were synthesised *in situ* by decomposing formaldehyde, HCOH. Similarly to the formic acid, cold formaldehyde is decomposed by passing it through a 2 % Pt catalyst pre-heated at $T = 450\ ^{\circ}C$ (Scheme 3.1), in the first reactor installed in the rig.
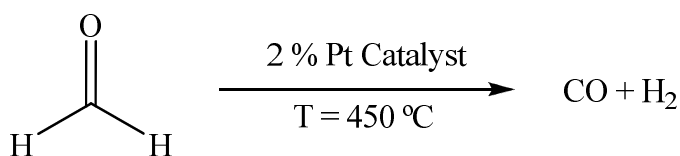
Scheme 3.1 Decomposition of formaldehyde to synthesise *syn* gas.[14]

The *syn* gas then flows into the second reactor where the hydroformylation reaction is carried out. The products can either be extracted using $scCO_2$ flow or

the reaction can be carried out in the liquid phase in a downwards flow reactor. In the latter case, the products are forced through the catalyst bed and into the collecting vessel using the *syn* gas pressure, meaning that no $scCO_2$ is used as a mobile phase.

3.1.2.1 The Use of DMC to produce CO_2

Dimethyl carbonate, or DMC as it is commonly known, has also been involved in the "without gases" study developed by the Clean Technology Group.

DMC can fully decompose at temperatures above *ca.* 175 ℃ in high pressure continuous flow systems under a pressure of 100 bar.[14] The catalyst used was γ-Al_2O_3.

The decomposition of DMC produces dimethyl ether (DME) and CO_2 (Scheme 3.2).
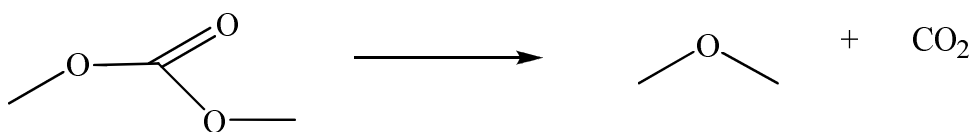
Scheme 3.2 Presumed pathway of the decomposition of DMC to DME and CO_2.[14]

This alternative way of producing CO_2 from a liquid precursor may be used as an alternative source of this gas, replacing the typical cylinder. Also, this can open a new research focus, which is running reactions in the "without gases" system

under supercritical conditions, with gases being produced inside the system only as and when they are needed.

3.1.3 The Purpose of This Work

As previously described in Chapter 1 (Section 1.4.2.2), Hintermair *et al.* obtained very good results on the continuous flow hydroformylation of 1-octene using a supercritical CO_2 flow system and the SILP based catalyst, Rh/[PrMIM]TPPMS with several [OctMIM]Tf_2N loadings.[16] Using a 44 wt % IL loading, he successfully achieved a TOF of 800 h^{-1}.

Considering these results, the main purpose of this partnership was not only to compare the IL/scCO_2 biphasic system with the SILP system, but to take a step further by having the chance to work directly with the "without gases" system.

Starting with a Rh/[PentMIM]TPPTS SILP based catalyst and carrying out continuous flow hydroformylation reactions under the same experimental conditions as Hintermair *et al.* in the "traditional" continuous flow SILP system, the aim if this work was to check the performance of a new ionic ligand in a (similar) new system. Most of the experiments were even performed without using CO_2 as a mobile phase.

3.2 Experimental

3.2.1 General Experimental

The Silica Gel was purchased from Merck (Silica Gel 100, grade 10184, 60-230 mesh). Prior to use it was pre-treated by heating over to T = 500 ºC for at least t = 16 h and then stored over P_2O_5 under N_2.

The methanol used as a solvent on the preparation of the SILP catalysts was purified prior to use following common techniques[17] and stored under N_2 when collected.

3.2.2 Preparation of the SILP based catalysts

The ionic ligand [PentMIM][TPPTS] (1.85 g, 1.93 x 10^{-3} mol) and the precursor [Rh(acac)(CO)$_2$] (0.049 g, 1.89 x 10^{-4} mol), in a ratio of 10:1, and the previously dried and degassed ionic liquid [OctMIM]Tf$_2$N were dissolved in pure methanol (50 cm^3) and stirred for about t = 1 h at room temperature. After this, the pre-treated silica gel (5.0 g) was added and the mixture stirred for two more hours, still at room temperature. The removal of the methanol was carried out by slowly drying the mixture under vacuum at T = 35 ºC.

Notes:

- The amount of ionic liquid was always previously calculated in order to give a w/w % related to the amount of silica gel.

- All the SILP catalysts tested were prepared just prior to use.

- Two SILP catalysts were prepared for these experiments. One had a 44 w/w % IL loading and the other had a 14 w/w % IL loading.

Figure 3.4 represents the "without gases" rig, which was used in this work. All its equipment was constructed from 318-SS (SwageLok®), Gilson 802 HPLC pumps and a Jasco 880 back pressure regulator.

In a typical hydroformylation reaction, the supported ionic liquid phase (SILP) based catalyst was put inside a fixed-bed reactor and sealed into the rig. The Pt 2 % (reactor 1) was heated to T = 450 ºC and the HCOH (Aldrich) would start flowing into reactor 1, delivered by one of the HPLC pumps at a pre-defined flow rate, until reaching the desired pressure in the system. When the system pressure was considered stable, the 1-octene (purified and degassed prior to use) was then injected (using another HPLC pump) directly into reactor 2 at a pre-defined flow rate. After each reaction hour, the products were collected directly downstream from the back pressure regulator and a sample was immediately prepared for GC-FID analysis.

When not in use, the SILP catalysts were kept inside the fixed-bed reactor at p = 100 bar (*syn* gas) and T = 100 ºC.

3.3 Results and Discussion

The SILP based catalysts presented in this Chapter were prepared with an IL loading of 14 and 44 w/w %, according to the procedure previously described in the Experimental section of the present Chapter (Section 3.2.2). Each SILP catalyst was tested for the hydroformylation of 1-octene over a period of three to four weeks, during which several parameters were changed. The reaction was always carried out on a continuous flow mode using the "without gases" process. When not in use, the SILP catalysts were kept inside the fixed-bed reactor at p = 100 bar (*syn* gas) and T = 100 ºC.

3.3.1 Stability of the SILP Catalysts

The lifetime of both SILP catalysts was tested by carrying out continuous flow hydroformylation reactions using 1-octene as substrate. For each SILP catalyst, two long runs were performed. The first long runs were carried out when the SILP catalysts were put inside the fixed-bed reactor and using the optimal experimental conditions from Hintermair *et al.*,[16] but in the absence of CO_2. The same catalyst samples were then used for reactions under different experimental conditions of temperature, pressure, flow rate, etc. Finally, the second long runs were carried out after these other tests to check whether the catalyst had maintained its activity. Basically, the difference between the two experiments with each IL loading here presented is that the first run was carried out at the beginning of its use and the second run was carried out after three or four weeks of extensive use and testing.

The system pressure was built up with the *syn* gas resulting from the HCOH decomposition and its flow was kept constant at flow rate of 0.1 mL/min. No scCO$_2$ was used as a mobile phase for product collection.

The obtained results are shown on Table 3.1 and Figure 3.5.

Table 3.1 Continuous flow hydroformylation of 1-octene using SILP based catalysts Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at p = 100 bar and T = 100 ℃.

IL Loading (w/w %)	Long run	CO flow (mL/min)	1-octene flow (mL/min)	Reaction time (h)	Conversion to aldehyde (%)	l:b ratio	TON cumulative
44	1st run	1.0	0.1	12	96	3.0	2326
	2nd run	1.0	0.1	12	94	3.0	2265
14	1st run	1.0	0.1	15	57	3.3	1594
	2nd run	1.0	0.1	15	43	2.4	1210
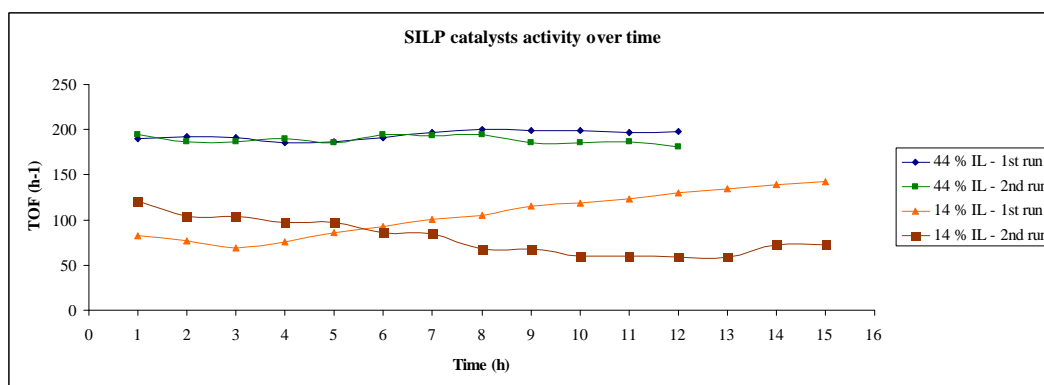
Figure 3.5 The activity of the catalysts over time for the reactions described on Table 3.1.

It appears at first sight, that the activity of the catalyst where the loading of IL is 44 % remains constant throughout its use over many days, but the conversion is almost 100 %, so comparisons are not valid. The approximately similar l:b ratio may suggest that the catalyst has not, for example, suffered from phosphine

oxidation. For the lower IL loading (14 %), the activity increased slightly throughout the first run, and the activity at the start of the second long run is almost the same as that at the end of the first long run, perhaps suggesting good catalyst stability. However, the activity in this case started to decrease over time.

The l:b selectivity is similar to that obtained by Hintermair *et al.*, in the first run at 14 % IL loading, but decreased in the second run. This may suggest that the phosphine is being oxidised or otherwise removed from the system.

Comparing the obtained TOF results (200 h^{-1} for 44 % IL loading; < 100 h^{-1} for 14 % IL loading) with the well known ones for the commercial hydroformylation of propene catalysed by rhodium (500 – 700 h^{-1})[3, 18], this could be considered low. Nevertheless, this is a new system, constantly being tested and the achieved conversion is high, so, for a beginning, the results are very promising. The TOF for the 44% IL loading is a lower limit because the reactions have gone to completion. Higher TOF's might have been obtained if lower catalyst loadings or higher flow rates had been used.

In terms of catalyst leaching, preliminary ICPMS analysis has shown a decrease in the rhodium leaching during the reaction time, reaching values below 1 ppm at the end of the reactions.[14] On all four performed reactions, the first two fractions collected presented a yellow colour. The leaching is much higher than that observed when using CO_2[14] as expected when carrying out the reaction in the liquid phase.

It had been previously established that the IL loading in the SILP catalyst can have an effect on the activity of the catalyst. At low loadings (film thicknesses), the mobility of the catalyst is reduced by interactions with the surface so rates are low. The rate increases as the loading is increased until a maximum is reached. The rate generally falls thereafter because transport of the substrate and or reacting gases into the ionic liquid becomes rate limiting (the catalytic centres being further from the interface).[5] In the work of Hintermair *et al.*[16] using CO_2 flow, the effect of the ionic liquid loading on the reaction rate was minimal with similar rates being observed at IL loadings of 14, 29 and 44 w/w %. It was proposed that mass transport is not rate determining partly because the ionic liquid [OctMIM]Tf$_2$N has been optimised to dissolve the substrate[19] 1-octene, and partly because the CO_2 assists in the transport of the substrate[20] and the reaction gases[21] into the ionic liquid by increasing their solubility. Surprisingly, this effect is not reproduced in the "without gases" approach, which also differs from the work of Hintermair *et al.*[14] because the substrates are in the liquid rather than the CO_2 expanded liquid phase. For the liquid phase reaction it appears that the catalyst with 44 % IL loading is much more active than that with 14 % IL loading. The reason for this is not clear.

3.3.2 The Influence of the Experimental Conditions on the Performance of the SILP Catalysts

Although having a starting point, which could also be used to compare experimental results[16], it is always important to optimise the system, in order to obtain the best results possible.

The results involving the variation of experimental parameters during the "without gases" SILP catalysed hydroformylation of 1-octene are described below.

3.3.2.1 Variation of the System Pressure

The system pressure was varied from 25 to 200 bar to check its influence on the SILP catalysts performances and rhodium leaching.

For each SILP catalyst, the system pressure was built up with the *syn* gas resultant from the HCOH decomposition and its flow was kept constant at a flow rate of 0.1 mL/min. No scCO$_2$ was used as a mobile phase for product collection.

The obtained results are shown on Table 3.2.

Table 3.2 Continuous flow hydroformylation of 1-octene using SILP based catalysts Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at T = 100 ℃ and 1-octene flow rate = 0.1 mL/min.

IL Loading (w/w %)	Pressure (bar)	CO flow (mL/min)	Conversion to aldehyde (%)	l:b ratio	TOF[a] (h^{-1})
44	50	1.0	85	3.0	172
	100	1.0	98	3.0	198
	150	1.0	98	3.0	198
	200	1.0	95	3.0	192
14	25	1.0	25	2.2	47
	50	1.0	80	1.3	148
	100	1.0	99	1.5	184
	150	1.0	96	2.3	177
	200	1.0	96	2.0	178

[a] Average catalyst turnover frequency over t = 3 h.

In each case, the system pressure was kept for t = 3 h and product samples were collected after every hour.

The results are not surprising in terms of conversion into the aldehyde product. Conversions above 80 % were achieved at p = 50 bar on both SILP catalysts, and even higher, to almost 100 %, when the system pressure increased to p = 100 bar. For both ionic liquid loadings (14 and 44 %), the rate increases with increasing pressure, although little can be said about the results above 100 bar where full conversion is achieved. Since all these reactions almost certainly occur in the liquid phase, this is perhaps a little surprising. Normally, Rh/triphenylphosphine catalysts hydroformylation reactions are first order in H_2 and negative order in CO, so the effect of overall pressure without changing the H_2/CO ratio is small.[3, 22] In the case of liquid phase SILP reactions, gas transport can be a major

problem. The liquid substrate fills the pores of the catalyst, which have a high aspect ratio. The gases dissolved in the substrate when it enters the pores react, but once that gas supply has been used up, diffusion of gas from the gas phase to replace it can be very slow. In this case, the reaction may be gas transport limited. Increasing the pressure will increase the amount of dissolved gas present initially, and will accelerate the rate of gas diffusion through the liquid to the catalytic centres. We propose that these two effects of higher initial gas concentration and faster gas diffusion may be responsible for the higher conversions observed at higher pressures. For the catalyst with 14 % IL loading, the effect of pressure is not observed above $p = 100$ bar. This may be because the available space for the liquid within the pores is greater so gas diffusion will be more efficient, and/or because gas diffusion within the ionic liquid is over much shorter distances so may not inhibit the reaction.

Although the alkene consumption was considerably high at higher pressure for both SILP catalysts, both of them presented a low selectivity to the desired linear aldehyde product. Nevertheless, the 44 % IL loading SILP catalyst presented a higher selectivity, with a l:b ratio of 3:1.

To notice that the l:b ratio here presented for the 14 % IL loading SILP catalyst is lower than the one presented in Table 3.1 under the same experimental conditions (i.e. $p = 100$ bar). This may be explained by the fact that the same catalyst was used for the initial runs as for changing the pressure, and so, maybe the phosphine is being oxidised. This may also justify lower l:b ratios in later runs, on both catalysts.

The first two collected samples of each IL loading presented a very pale yellow colour, indicating the presence of rhodium catalyst. During the rest of the pressure tests, the samples collected were colourless.
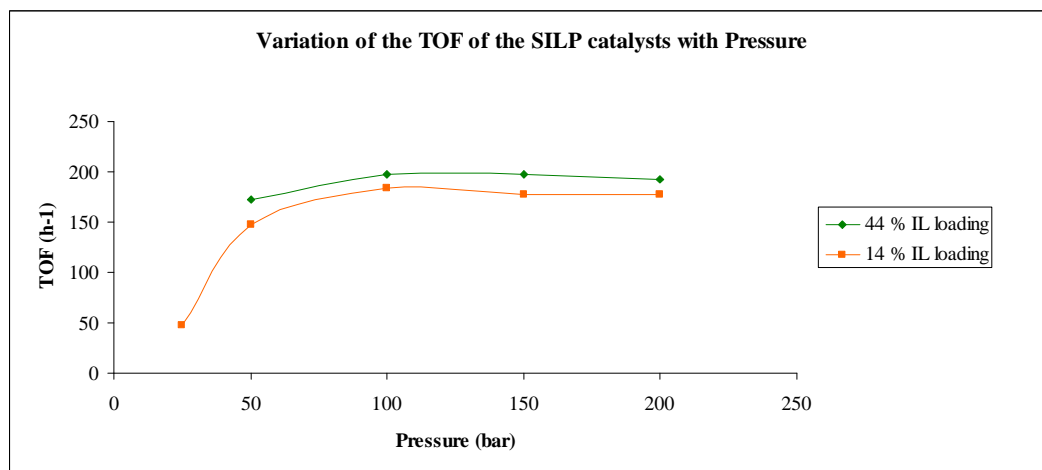
Figure 3.6 Variation of the turnover frequency with the variation of the system pressure.

Figure 3.6 represents the activity of both SILP catalysts under different system pressure conditions. It is difficult to draw any real comparative conclusions at pressures above 50 bar because the conversion to aldehyde is close to 100 %.

3.3.2.2 Variation of the System Temperature

The system temperature was varied from 40 to 100 ºC to check its influence on the SILP catalyst performance and rhodium leaching.

For the 14 % IL loading SILP catalyst, the system pressure was built up with the *syn* gas resultant from the HCOH decomposition and its flow was kept constant at

flow rate of 0.1 mL/min. No scCO$_2$ was used as a mobile phase for product collection.

The obtained results are shown on Table 3.3 and Figure 3.7.

Table 3.3 Continuous flow hydroformylation of 1-octene using a 14 % IL loading SILP based catalyst Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at p = 100 bar and 1-octene flow rate = 0.1 mL/min.

IL Loading (w/w %)	Temperature (ºC)	CO flow (mL/min)	Conversion to aldehyde (%)	l:b ratio	TOF^a (h^{-1})
	40	1.0	18	3.2	34
14	60	1.0	8.0	2.4	16
	80	1.0	76	2.6	141
	100	1.0	56	2.5	56

^{a} Average catalyst turnover frequency over t = 2 h.

For each case, the system temperature was kept for t = 2 h and product samples were collected after every hour.
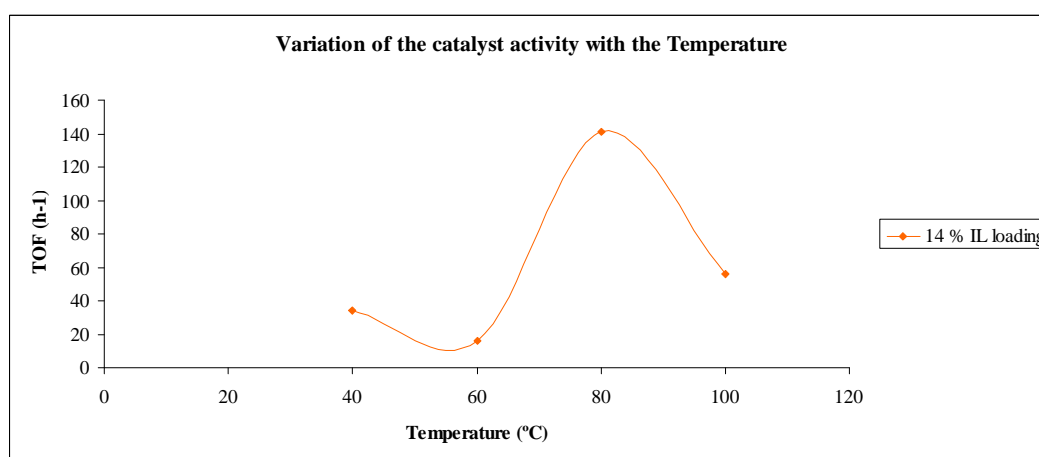
Figure 3.7 Variation of the turnover frequency with the variation of the system temperature.

The results above clearly show that at temperatures below 80 ℃, the hydroformylation reaction presents a very low conversion. Also, although the alkene consumption was high at higher temperature, a low selectivity to the linear aldehyde product was obtained. At its higher conversion rate, the 14 % IL loading SILP catalyst presented a l:b ratio to the desired linear aldehyde product of 2.6:1.

Despite the fact that a decrease in the activity and in the conversion were observed at T = 100 ℃, Table 3.3 and Figure 3.7 show that the hydroformylation reaction carried out in the "without gases", can achieve better conversion results when the system is running at higher temperatures.

Only the two samples collected at T = 40 ℃ presented a pale yellow colour, which is clearly indicative of the presence of rhodium catalyst. All the other samples collected were colourless.

3.3.2.3 Variation of the Substrate Flow Rate

Part of this study included testing the effect of the variation of the substrate flow rate over the SILP catalysts upon activity and conversion. Normally, the longer the residence time of the substrate inside the reactor, the higher should be its conversion into the expected product(s).

For each SILP catalyst, the system pressure was built up with the *syn* gas resultant from the HCOH decomposition and its flow was kept constant at a rate of 0.1 mL/min. No scCO$_2$ was used as a mobile phase for product collection.

The 1-octene flow rate was varied from 0.05 to 0.75 mL/min.

Each flow rate was tested for t = 3 h and product samples were collected after every hour.

The obtained results are shown on Table 3.4 and Figure 3.8.

Table 3.4 Continuous flow hydroformylation of 1-octene using SILP based catalysts Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at p = 100 bar and T = 100 ºC.

IL Loading (w/w %)	1-octene flow (mL/min)	CO flow (mL/min)	Conversion to aldehyde (%)	l:b ratio	TOF[a] (h^{-1})
	0.05	1.0	99	2.5	100
	0.10	1.0	98	2.6	198
44	0.25	1.0	56	2.8	282
	0.50	1.0	38	3.0	389
	0.75	1.0	21	3.0	322
	0.10	1.0	99	1.5	184
14	0.25	1.0	100	2.0	462
	0.50	1.0	97	1.8	903
	0.75	1.0	92	1.8	1283

[a] Average catalyst turnover frequency over t = 3 h.
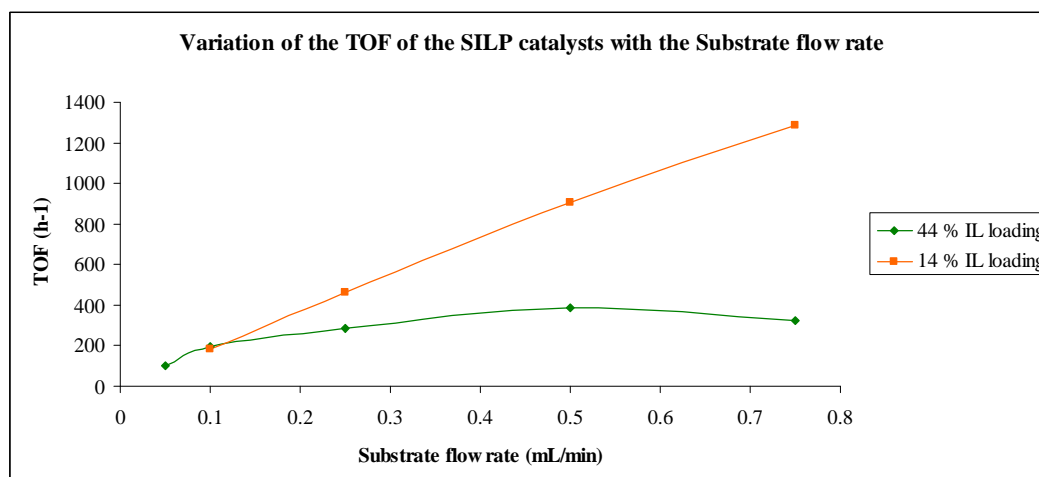
Figure 3.8 Variation of the turnover frequency with the variation of the 1-octene flow rate.

The results presented on Table 3.4 correspond to an average of the results achieved for the small continuous flow hydroformylation reactions of t = 3 h. After those three hours, the flow rate of the 1-octene was just changed and the reaction carried on, basically decreasing the *syn* gas/substrate ratio over time.

Because the conversion is close to 100 % for all flow rates when using the 14 % IL loading, it is not possible to draw conclusions about the effect of flow rate on catalyst activity. What is clear, however, is that the activity in this liquid phase SILP reaction is very high (> 1200 h^{-1}). This should be compared with a maximum of 800 h^{-1} observed in a liquid expanded by CO_2 (100 bar).[14]

For the 44 % IL loading, the conversion was close to 100 % at low flow rates, but dropped off markedly at high flow rates. The turnover frequency becomes almost constant above a flow rate of 0.25 $cm^3 min^{-1}$. This suggests that the reaction may become mass transfer limited, as might be expected for the more heavily loaded

catalyst as a result of flooding the pores of the catalyst with substrate and reducing the availability of *syn* gas.

Although the alkene consumption was high during the flow variation tests for both SILP catalysts, both of them presented a low selectivity to the desired linear aldehyde product. Nevertheless, the 44 % IL loading SILP catalyst presented a higher selectivity, with a l:b ratio of 3:1.

Interestingly, the catalyst with the lower IL loading (14 %) proved to be much more active at higher flow rates than the 44 % IL loaded one. This may be because the pore size is higher and there is less problem with accessing the catalyst as it is all near the liquid surface.

All the fractions collected were colourless, except the first fraction collected for each SILP catalyst (44 % and 14 % IL loading).

3.3.3 The "Without Gases" System Using CO_2

So far, none of the results presented include the use of CO_2 as a mobile phase to extract the products from the reaction medium. However, the "without gases" system was also used together with supercritical CO_2, either provided from BOC (the traditional cylinders source) or using another new approach being investigated by Cozier *et al.*, which is the production of CO_2 by the decomposition of DMC.[14] This process has already been described at the Introduction section of this Chapter (Section 3.1.2.1).

The results obtained for both cases are now discussed.

3.3.3.1 The "Without Gases" System Together with Traditional CO_2

In order to carry out the continuous flow hydroformylation reaction of 1-octene using traditional $scCO_2$ as a mobile phase to extract the products from the reaction medium, $scCO_2$ was passed through the system at a constant flow rate of 1.0 mL/min.

Contrary to the previous continuous flow hydroformylation reactions, *syn* gas (from the decomposition of formaldehyde) was delivered into the system by using a Rheodyne dosimeter, and the *syn* gas/substrate ratio was kept constant at 10:1.

When both SILP catalysts were not being used, they were kept inside the reactor, at T = 100 ºC and p = 100 bar.

The results obtained with the use of traditional $scCO_2$ are shown in Table 3.5 and Figures 3.9 and 3.10.

Table 3.5 Continuous flow hydroformylation of 1-octene using SILP based catalysts Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at p = 100 bar, T = 100 ºC and a *syn* gas/substrate ratio = 10:1.

IL Loading (w/w %)	Flow time (h)	CO_2 flow (mL/min)	Conversion to aldehyde (%)	l:b ratio	TON cumulative
44	3	1.0	29	2.4	173
14	2	1.0	6.0	2.2	23
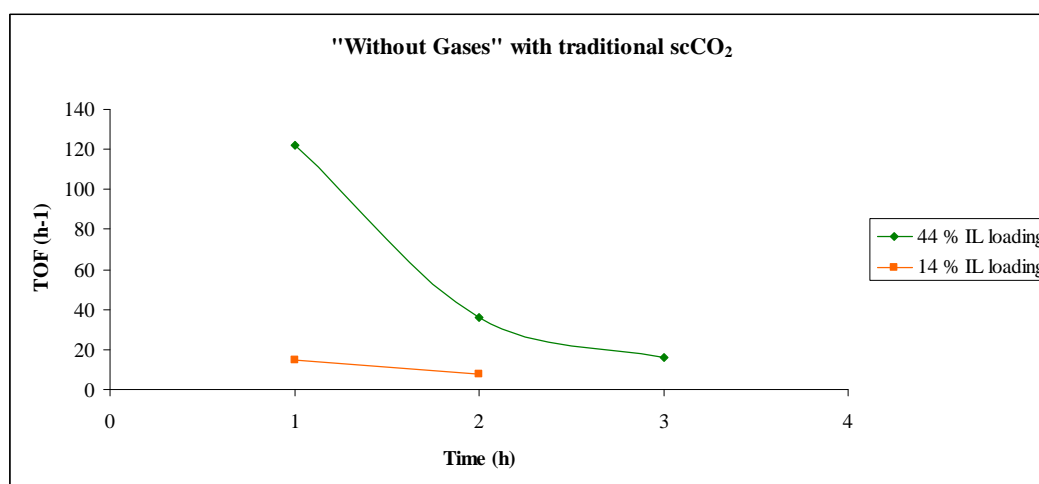
Figure 3.9 Turnover frequency for each SILP catalyst over time for the reactions described on Table 3.5.
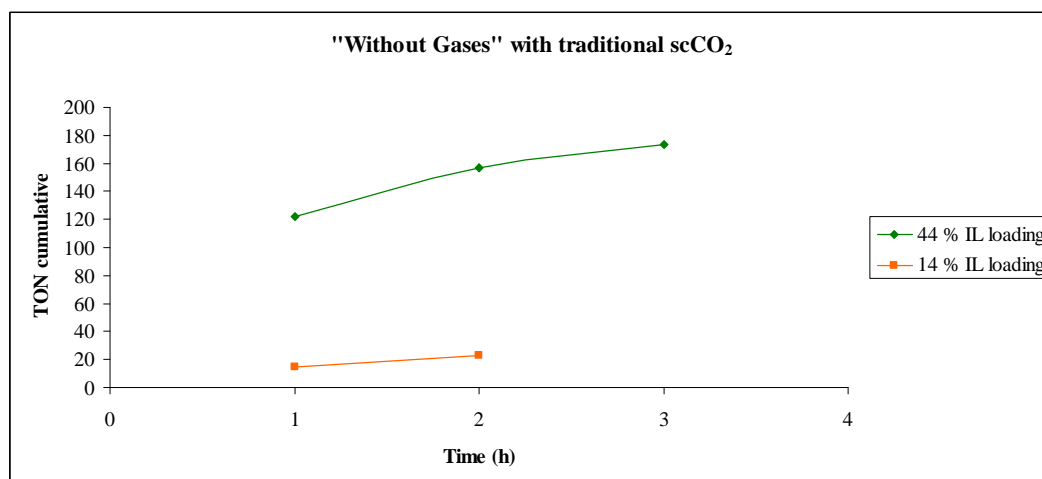
Figure 3.10 Stability of the SILP catalysts over time for the reactions described on Table 3.5.

From the results presented above, it can be easily observed that the catalyst activity and consequently, the conversion were very low, on both SILP catalysts. Also, and again on both SILP catalysts, there was a low alkene consumption, and not surprisingly, both of them presented a low selectivity to the desired linear aldehyde product.

These rather disappointing results do not mean that the "without gases" system does not work very well together with $scCO_2$. On the contrary, these results may only be a sign that the SILP catalysts are starting to "deactivate" after several weeks of intensive continuous flow hydroformylation reactions.

3.3.3.2 The "Without Gases" System Together with the DMC Decomposition as the Source of CO_2

Continuous flow hydroformylation of 1-octene was carried out using the "without gases" system together with the DMC decomposition in order to obtain $scCO_2$, to be used as a mobile phase.

The decomposition of DMC was carried out in series to the main hydroformylation reaction. A flow rate of 0.5 mL/min of DMC was passed over a 275 º C γ-Al_2O_3 catalyst bed at a 100 bar pressure.

For the 14 % IL loading SILP catalyst, the continuous flow hydroformylation reaction of 1-octene was carried out. The *syn* gas resulted from the HCOH decomposition and its flow was kept constant at flow rate of 0.1 mL/min.

The obtained results are shown on Table 3.6 and Figures 3.11 - 3.13.

Table 3.6 Continuous flow hydroformylation of 1-octene using a 14 % IL loading SILP based catalyst Rh/[PentMIM][TPPTS] (P/Rh = 10:1), at T = 100 ºC, p = 100 bar and 1-octene flow rate = 0.1 mL/min.

IL Loading (w/w %)	Flow time (h)	Conversion to aldehyde (%)	l:b ratio	TON cumulative
14	13	52	3.6	1254
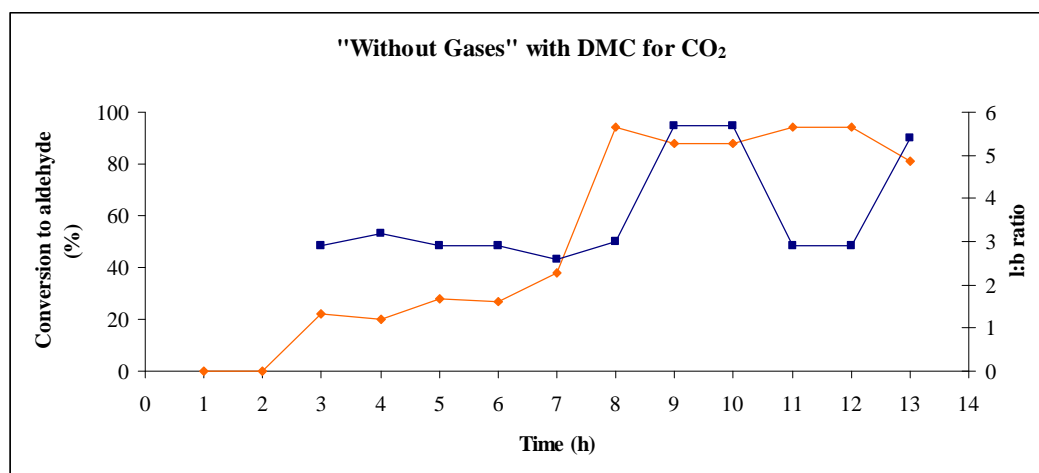
Figure 3.11 1-octene conversion (orange) and l:b ratio (blue) over time for the continuous flow hydroformylation reaction, using a 14 % IL loading SILP based catalyst.
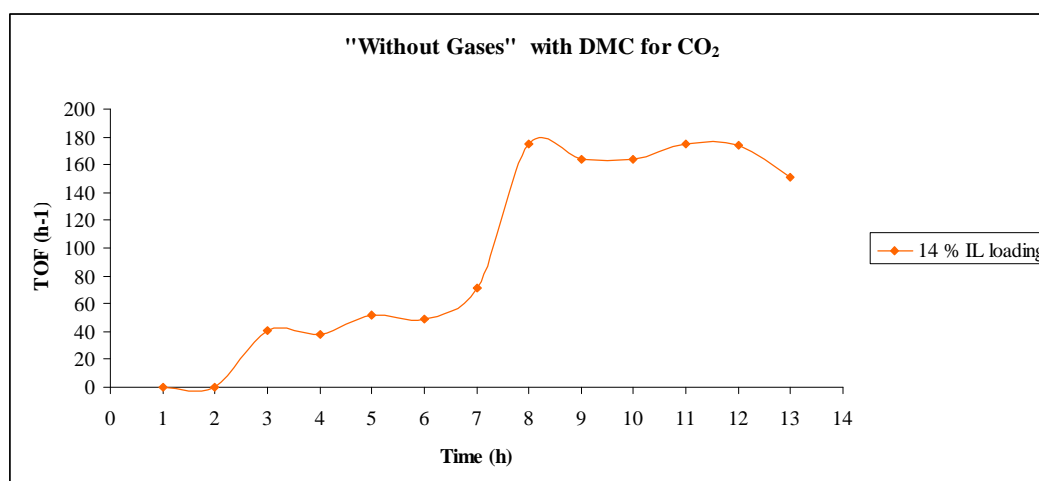
Figure 3.12 Activity for the 14 % IL loading SILP catalyst over time, for the reaction described on Table 3.6.

Figures 3.11 and 3.12 show that for the first two hours of reaction, there was absolutely no catalytic activity and therefore, no conversion.

As the reaction time increased, some catalytic activity appeared. Both TOF and TON (Figure 3.13) started to increase linearly but modestly.

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However, at t = 8 h, it is possible to observe a big twist in the reaction. There was a major increase in the catalyst activity and the conversion to aldehydes increased to about 90 %. This conversion rate was kept until the continuous flow was stopped. When this experiment was carried out, this sudden increase in the activity and in the conversion was justified by the possibility that the fixed-bed reactor was getting full, increasing the residence time.

From this point, although the alkene consumption was considerably high during the reaction time using the 14 % IL loading SILP catalyst, it usually presented a low selectivity to the desired linear aldehyde product. Nevertheless, on three of the product samples collected (fractions 9, 10 and 13) it did present a higher selectivity, with a l:b ratio of about 5.6:1.
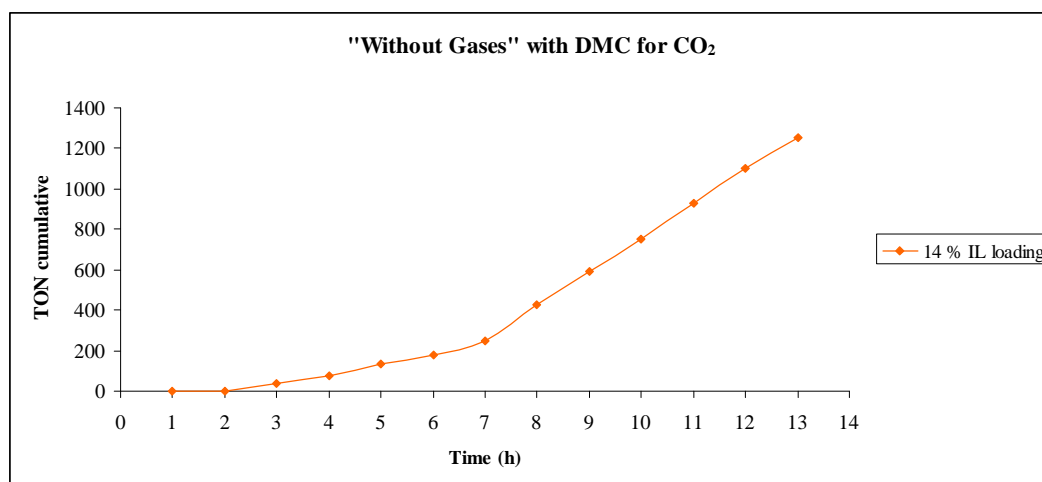
Figure 3.13 Cumulative turnover frequency for the 14 % IL loading SILP based catalyst over time, for the reaction described on Table 3.6.

Figure 3.13 represents the stability of the 14 % IL loading SILP catalyst during the reaction time. It started from an almost straight line, which is representative of

an almost deactivated catalyst to a very linear line (after t = 7 h), meaning that the catalyst started to behave in a very stable way.

The catalyst activation might be explained by the presence of $scCO_2$ produced from the DMC decomposition. The presence of $scCO_2$ is well known for increasing both the solubility and the mass transport of permanent gases.[2] This may lead to a better diffusion of the reaction substrate and the reactant gases into the pores of the SILP based catalyst, resulting into an increase on its activity.

Another common factor that leads to possible catalyst deactivation is the excess of high boiling side products, which start to accumulate in the ionic liquid layer of the SILP catalyst over time, blocking the access to the catalyst active centres. With the introduction of $scCO_2$ in the system, these side products can be easily extracted, and therefore, the catalyst reactivated. However, and in this case, this theory is not supported by the information collected through GC analysis.

3.4 Conclusions

The work presented in this Chapter was an extension to supported ionic liquid phase catalysis from all the other experimental work also presented in this thesis, which was carried out in a bulk continuous system. In addition, in an attempt to circumvent the problems associated with high pressure in reactions using gases, the new concept of "without gases" was investigated.

Two SILP based catalysts, each prepared with a different ionic liquid loading, were tested in several continuous flow reactions, carried out under different experimental conditions, for a long period of time (each SILP catalyst was used for up to three to four weeks). Results show that both SILP based catalysts presented a very efficient and stable behaviour, even when compared to commercial hydroformylation processes.

Taking into account these preliminary results, future work is highly recommended. A more exhaustive study could be done on the experimental conditions, in order to achieve an even better optimisation of the system, especially by working under conditions where full conversion is not achieved. Considering the obtained results for the hydroformylation reaction using DMC for the production of $scCO_2$, new experiments should be carried out, again using DMC for CO_2 and HCOH for *syn* gas productions. Once again, a study involving the variation of the experimental conditions on the "without gases" system, this time with the addition of DMC, is recommended.

In conclusion, all the results described in this Chapter show that the combination between the SILP concept and the "without gases" approach may potentially be very successful and that, in fact, it may even become a new method for carrying out the hydroformylation reaction on a continuous flow mode.

3.5 References

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Chapter 4

Continuous Flow Silver Catalysed Heterocyclisation using an Ionic Liquid/scCO$_2$ Biphasic System

4. Continuous Flow Silver Catalysed Heterocyclisation using an Ionic Liquid/scCO₂ Biphasic System

The work described in this Chapter resulted from a project developed together with Prof. David Knight's Group from Cardiff University.

4.1 Introduction

Knight and co-workers' main research topic has been especially focused on developing new synthetic routes for heterocyclic ring formation.[1-5] His research group has been involved on 5-endo cyclisations, which lead to the formation of heterocycles and heteroaromatics, like for instance, pyrroles, furans and indoles.[1, 6, 7]
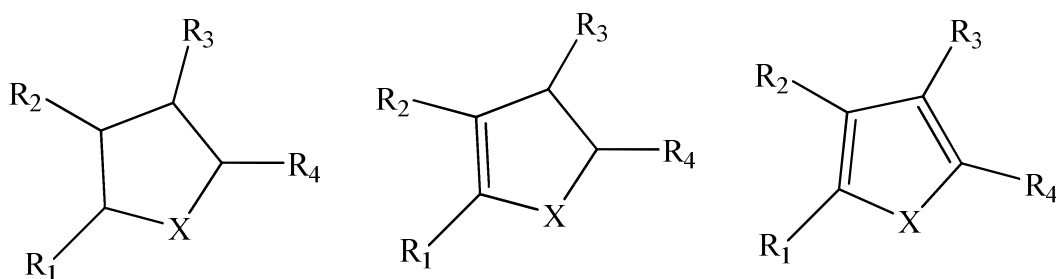
Figure 4.1 Typical heterocyclic compounds (X = *e.g.* O, N, S).[8]

In terms of practical applications, heterocycles are widely used. Their various applications go from their use as intermediates in synthetic chemistry to material science but their most important application is in the pharmaceutical industry, as therapeutic agents against diseases like cancer or Aids.

Since the project developed in this Chapter concerned the synthesis of furans, a brief explanation of their synthesis background will now be described.

4.1.1 The Synthesis of Furans

As mentioned above, the synthesis of furans is of great commercial interest due to their various therapeutic applications.

The most common industrial process to produce this colourless oil is the dicarbonylation of furfural, catalysed by nickel (Scheme 4.1). Furfural itself is previously obtained by the acidic dehydration of pentose sugars.[8]
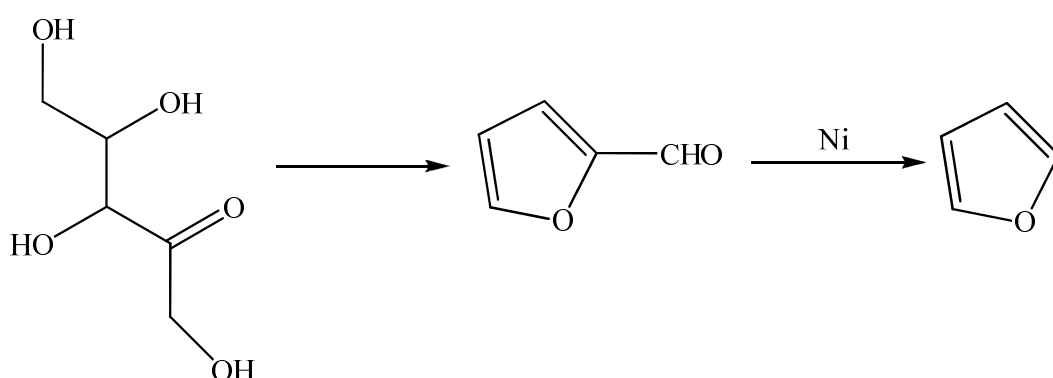
Scheme 4.1 Industrial process for the production of furans, catalysed by nickel.[8]

Although the heterocyclisation syntheses follow the three rules presented by Baldwin[9] for ring formation, many of the synthetic approaches investigated over the last years do come with several limitations, such as, the low yields obtained, the need for synthesising the starting materials and the harsh experimental conditions.[10]

Taking this into consideration, the work of Hayes *et al.* was focused on developing a new synthetic route for the formation of heterocycles (including furans), starting from commercially available starting materials.[8]

4.1.2 The Catalytic Synthesis of Furans

In terms of the catalytic synthesis of furans, several transition metal salts have been used with different results.

Some reports concern the use of mercury salts. Mercury triflate was successfully used by Nishizawa and co-workers[11] for the cyclisation of 1-alkyn-5-ones in order to obtain the corresponding furans in very good yields (> 70 %), under mild experimental conditions.
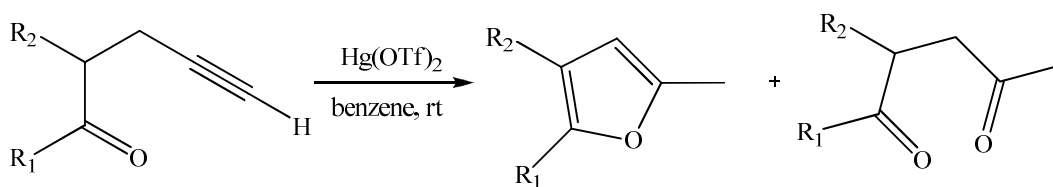
Scheme 4.2 Synthesis of furans catalysed by mercury triflate.[8, 11]

The main drawbacks faced by Nishizawa and co-workers were the observation of side-product formation (diones), the non-possibility of cyclisation of aldehydes or non-terminal alkynes and the fact that benzene was the most suitable solvent for this reaction.

Above all, mercury is not a desirable metal to work with due to its high toxicity level. Therefore, the chemical industry is not very keen on using it in any industrial process.

Palladium is another very popular example and many times reported in the field of the catalytic heterocyclic synthesis of furans.[12-15] However, and once again, these reports come with several associated drawbacks, not only because palladium is a very sensitive and extremely expensive metal, but also because harsh experimental conditions had to be applied and, in some cases, low yields were obtained.

Marshall and co-workers successfully reported the use of several silver salts to catalyse the ring closing of different substrates, obtaining their respective furans in very good yields (> 86 %). For instance, the cyclisations of alkynyl allylic alcohols[16, 17] (Scheme 4.3) and of allenones[18, 19] (Scheme 4.4) were successfully achieved by adding 10 w/w % silver nitrate on silica gel ($AgNO_3.SiO_2$) into a solution containing the heterocyclic precursor.
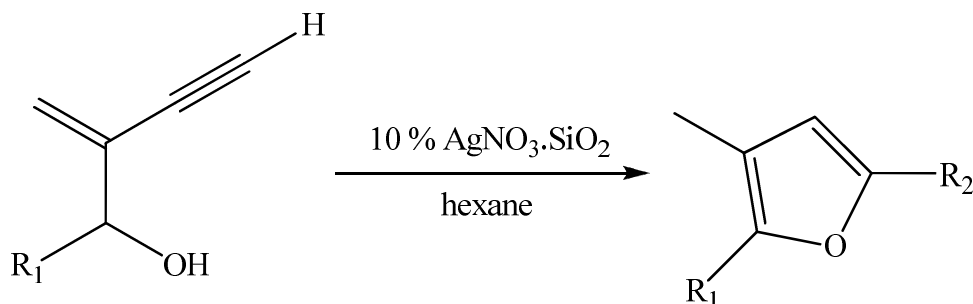
Scheme 4.3 Heterocyclisation of alkynyl allylic alcohols catalysed by silver nitrate on silica gel (AgNO$_3$.SiO$_2$).[8, 16]
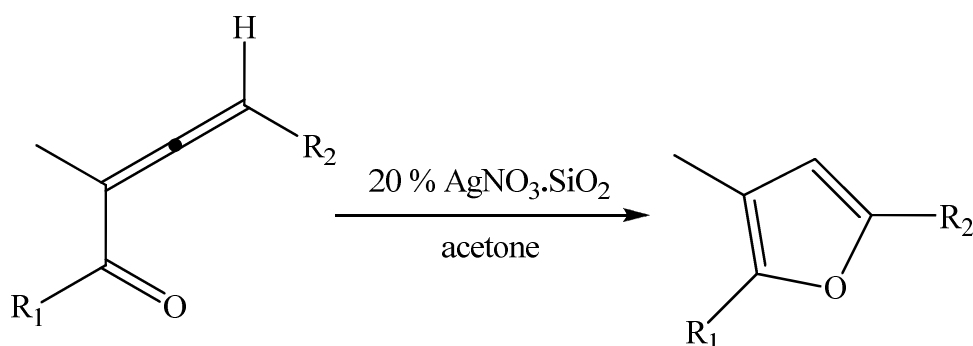
Scheme 4.4 Heterocyclisation of allenones catalysed by silver nitrate on silica gel (AgNO$_3$.SiO$_2$).[8, 16]

Taking into account the results obtained, a further optimisation was carried out, concluding that, for the alkynyl allylic alcohol precursors, the best yields (96 %) were obtained after 1 h of reaction when using 10 % AgNO$_3$.SiO$_2$ in hexane. For the allenones, 90 % yields were obtained after 1 h of reaction using 20 % AgNO$_3$.SiO$_2$ in acetone instead.[16]

More recently, there has been interest on using gold salt complexes. Hashmi and co-workers have used gold(III) chloride in the isomerisation of alkynyl epoxides into furans with relative success (the yields obtained were between 25 and 85

%).[20] Liu and co-workers have successfully reported the use of gold(III) chloride and the cationic gold(I) complex (PPh₃)AuCl/AgOTf for the cyclisation of both tertiary alcohols or (Z)-2-en-4-yn-1-ols to yield their respective dihydrofurans and furans.[21] They have also observed and reported that the addition of 1 mol % silver triflate to the catalyst improved immensely the initial experimental conditions (reflux in acetonitrile during five days) to a simple 3 h reaction carried out at room temperature (Scheme 4.5). The reaction yield also increased to 82 %.

These results reinforced the ones previously presented by Marshall and co-workers regarding their silver-catalysed work[16], and opened a new door in terms of combining the use of gold together with silver, in order to reduce the amount of catalyst needed.
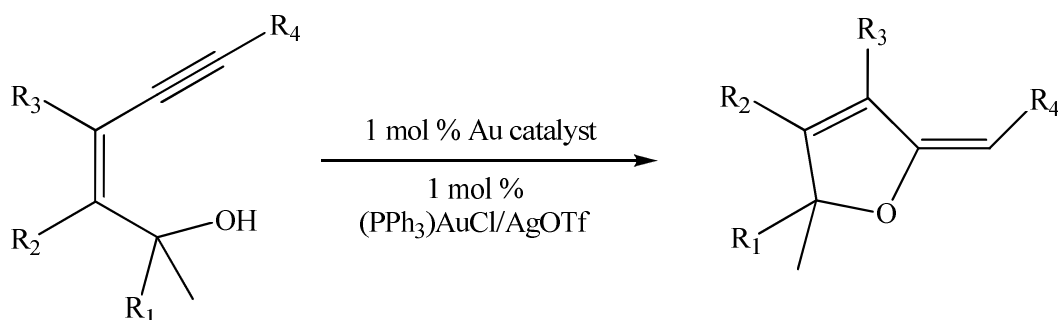
Scheme 4.5 Gold-catalysed synthesis of dihydrofurans starting from tertiary alcohols.[8, 21]

Marshall's results also inspired Knight's group to use silver in their heterocyclisation studies. Sharland, Menzies *et al.* used 10 % $AgNO_3.SiO_2$ to catalyse cyclisations to pyrroles and furans with very good yields (> 95 %) (Scheme 4.6)[8].
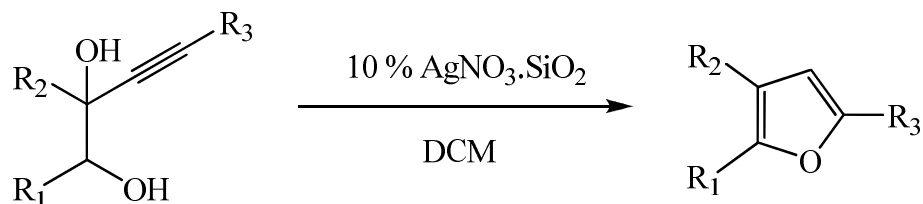
Scheme 4.6 Silver-catalysed heterocyclisation of furans.[8]

Although these results were not optimised at that time, it was possible to conclude that the silver-catalyst could stand as a "competitor" to the gold-catalyst. The major difference between these two catalysts is that, while the silver-catalyst performs in a heterogeneous system, the gold-catalyst performs in a homogeneous system. As expected, the advantages/disadvantages concerning both systems must be considered, which may mean an advantage for the silver-catalyst.

4.1.3 Silver-Catalysed Heterocyclisation of Furans

Hayes *et al.* proceeded with the work involving the silver-catalysed synthesis of heterocycles by 5-*endo*-dig cyclisation started by Sharland and Menzies. His intention was to create a flow system capable of increasing the range of synthesised pyrroles, pyrazole-*N*-oxides[22] and furans.[8]

2,4-disubstituted, 2,5-disubstituted and 2,3,5-trisubstituted furans were successfully synthesised using the α-hydroxycarbonyl pathway (Scheme 4.7).[8, 23]
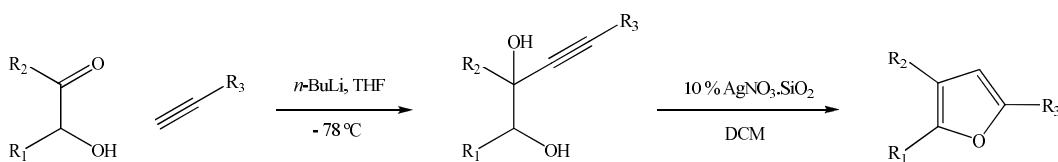
Scheme 4.7 The α-hydroxycarbonyl approach for the silver-catalysed synthesis of furans.[8]

The cyclisation was normally carried out by stirring a solution containing the diols in dichloromethane (DCM) with 10 % $AgNO_3.SiO_2$ for about 3 h at room temperature.

Highly pure furans were obtained in extremely good yields (> 95 %). There were only very few examples, like 5-butyl-2,3-dimethylfuran and 2-butyl-4-methylfuran, where lower yields were obtained (50 – 60 %). These may be explained due to product volatility. Also, apart from water, there were no reports of by-product formation during the cyclisations.

Nevertheless, and like almost all other processes, this one presents a few drawbacks, which are:

- It is not possible to obtain tetrasubstituted furans directly by silver-catalysed cyclisation;

- It is not possible to avoid the silver-catalyst leaching;

- Since it is necessary to filter the product through celite, in order to increase its purity level, it is not possible to re-use to catalyst.

4.1.3.1 Silver-Catalysed Heterocyclisation of Furans – A Heterogeneous Flow System

After the results obtained in the silver-catalysed cyclisation reactions carried out in batch mode, Hayes *et al.* decided to go a step further and create a flow system which could overcome the catalyst leaching and its problem of limited re-use.

In their first attempt, the silver nitrate was supported in silica gel inside a fixed-bed reactor and the flow was maintained by passing positive pressure straight from the air line into the solvent reservoir.[8] After evaporation of the filtrate, the yield of the desired furan product (Scheme 4.8) was very good (> 95 %).
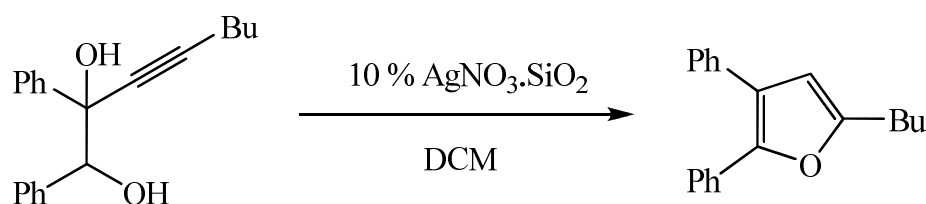
Scheme 4.8 Heterocyclisation of 5-butyl-2,3-diphenylfuran catalysed by AgNO$_3$.SiO$_2$.[8]

However, this result was associated with high silver leaching, which meant that, although the heterocyclisation of furans was achievable in a flow system, the system had to be redesigned.

To reduce or avoid the silver leaching from the system, Hayes *et al.* examined alternative supports, which would be able to immobilise the silver catalyst. The best support was amberlite 200C, in its sodium form. This ion exchange resin was tested in a column through which was passed an aqueous solution of silver nitrate followed by repeated washing from several solvents (Figure 4.2). What was

observed was that the Ag^+ exchanged with the Na^+, and so, there were almost no traces whatsoever of silver in any of the solvent washings.
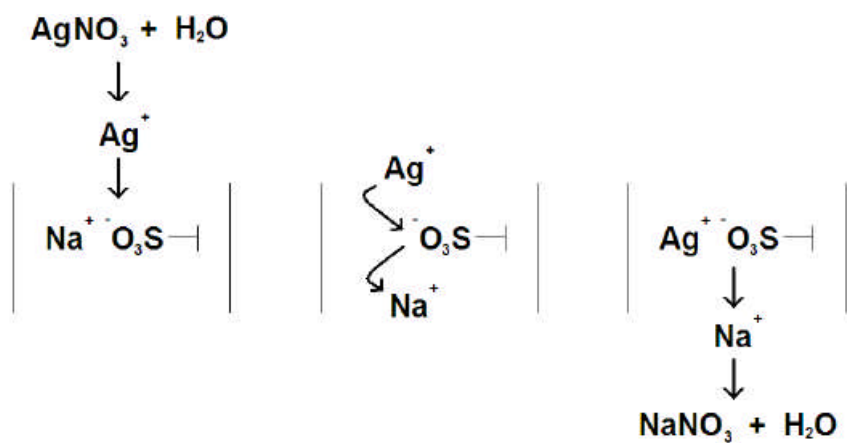
Figure 4.2 Silver exchange performed by amberlite 200C, an ion exchange resin.[8]

A heterogeneous flow system for heterocyclic synthesis[7] was then assembled (Figure 4.3).
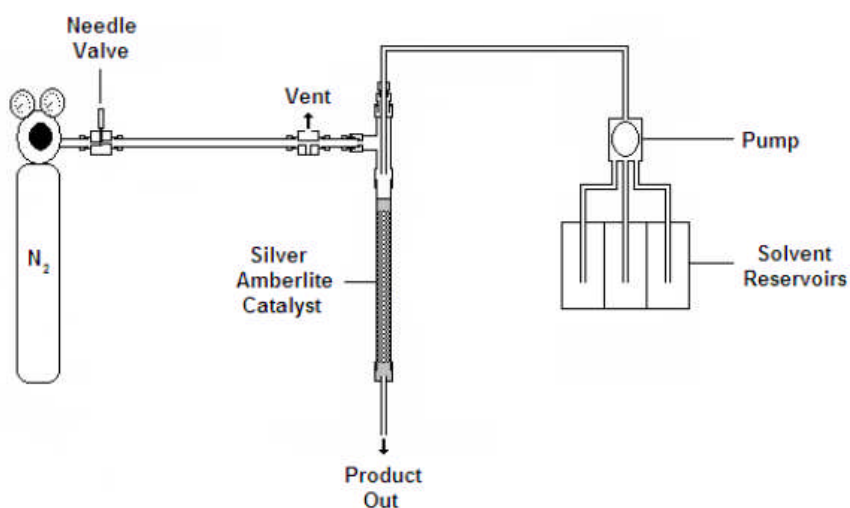
Figure 4.3 Heterogeneous flow system for the silver-catalysed heterocyclic synthesis.[8]

Once again, a 10 % solution of diol was passed through the column containing the immobilised silver-catalyst at constant flow rate of 1.0 mL/min. During the flow process, N_2 passed through the system at a pressure of 1 bar. The high purity furan product (Scheme 4.8) was always obtained at yields above 95 %.

ICPMS analysis of the collected product samples showed a silver leaching below 1 ppm.

In terms of system optimisation, Hayes *et al.* concluded that:

- Optimal flow rates are between 0.5 and 1.5 mL/min. Above 1.5 mL/min, the yields decrease substantially;

- The yields are not affected by a higher or lower substrate concentration. However, even though the reaction will take place without the presence of a solvent, this is useful to wash the column;

- All the experiments were carried out at room temperature. It was verified that an increase in the reaction temperature led to the formation of oxidation products.

4.1.3.2 Silver-Catalysed Heterocyclisation of Furans – A Homogeneous Flow System

Having an optimised heterogeneous flow system for the silver-catalysed heterocyclisation of furans, Hayes *et al.* came to St Andrews to work with us. Our idea was to verify if it was also possible to synthesise furans by silver-catalysed heterocyclisation, but this time, using a homogenous flow system, the ionic liquid/scCO$_2$ biphasic system and, in the end, compare the overall performance of both systems.

On changing from a heterogeneous system to a homogeneous system, a few experimental changes took place. These were:

- Although Hayes *et al.* had already been successful on the silver-catalysed heterocyclisation in ionic liquids[8], the ionic liquids chosen to use as solvents in the homogeneous system were our own home made [Octmim]Tf$_2$N and [Octmpyr]Tf$_2$N due to our previous knowledge regarding the ionic liquid/scCO$_2$ interaction.[24] During the experimental work, the [Octmpyr]Tf$_2$N ionic liquid was mostly used because we were concerned about some possible carbene formation;

- Normally, the silver-catalyst used was silver nitrate (AgNO$_3$). However, during this study, the silver nitrate was replaced for silver triflate (AgCF$_3$SO$_3$) because during our pre-experimental tests, we found out that silver triflate dissolved much better in the ionic liquid solvent.

4.2 Experimental

4.2.1 General Experimental

The ionic liquids here were synthesised according to the procedure described in the Experimental Chapter of the present thesis (Chapter 5, Section 5.4.1).

The substrates tested, 3-methylnon-4-yne-2,3-diol and 1-(hex-1-ynyl)cyclohexane-1,2-diol, were synthesised at the Cardiff University by Simon Hayes[8], prior to his visit to St Andrews.

Silver triflate was purchased from Alfa Aesar and used as received.

4.2.2 Batch and Continuous Experimental Procedure

All the batch and continuous flow experiments were performed in the rig described in the Experimental Chapter of the present thesis (Chapter 5, Section 5.5).

4.2.2.1 Batch Experimental Procedure

In a typical heterocyclisation experiment, carried out in batch mode, the reactor was filled with [Octmpyr]Tf$_2$N (12 cm^3) containing 10 w/w % of silver triflate

(related to the ionic liquid) and the substrate, 3-methylnon-4-yne-2,3-diol (6.4 x 10^{-3} mmol, 1.0 g).

The mixture was heated and pressurized (with CO_2) to pre-defined experimental parameters (e.g. p = 200 bar, T = 50 ºC) and stirred for t = 1 h. After that time, the CO_2 flow was introduced through the system (1.0 nL/min) in order to transport the products from the reactor and allow them to be collected by decompression.

4.2.2.2 Continuous Flow Experimental Procedure

In a typical heterocyclisation experiment, carried out in continuous flow mode, the reactor was filled with [Octmpyr]Tf$_2$N (12 cm^3) containing 10 w/w % of silver triflate (related to the ionic liquid) and sealed into the rig. The stirrer was started and the mixture heated to a pre-defined temperature (e.g. T = 50 ºC).

CO_2 (grade N5.5, BOC) was slowly added to the system to the pre-defined reaction pressure (e.g. p = 150 bar) and the gas allowed to expand through the system until the first decompression stage. The total gas flow (1.0 nL/min) was obtained by adjusting the gas expansion valves and shown in the flow meter. A pressure of about 4 – 5 bar was shown at the inlet of the 2nd expansion valve.

Maintaining the 1st expansion valve at room temperature, the substrate was continuously pumped into the system at a constant (and again, pre-defined) rate using a HPLC pump.

The reaction mass balance was verified by weighing the collection vials before and after every fraction collection. All the fractions were then analysed by ICPMS and GC.

Notes:

- A flow diagram of the system used to perform these experiments is included in the Experimental Chapter of the present thesis (Chapter 5, Section 5.5, Figure 5.1);

- After carrying out the first cyclisation reactions, we noticed that product amounts were most probably being swept away from the system due to its high volatility. To avoid this problem, we put heating tape all around the decompression valves and also attached a cold trap (dry ice + acetone) after the flow meter, through which the CO_2 is vented.

4.3 Results and Discussion

The silver-catalysed heterocyclic synthesis of 5-butyl-2,3-dimethylfuran (Scheme 4.9) was carried out in a ionic liquid/scCO$_2$ homogeneous biphasic system. The results obtained either in batch and continuous flow modes are presented and discussed below.
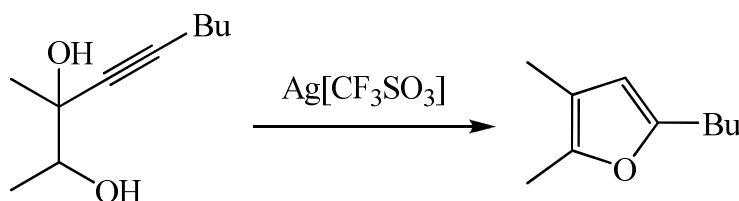
Scheme 4.9 Silver-catalysed cyclisation of 5-butyl-2,3-dimethylfuran.

4.3.1 Brief Discussion of Product Collection Efficiency

Although we have already spoken about mass balances in previous Chapters of this thesis, in the present Chapter, we think it would be helpful to give a brief explanation about the subject, in order to help interpreting the results here presented.

According to the law of conservation of mass (the mass of a closed system will remain constant over time), the definition of mass balance states that the mass that enters the system must be equal to either the mass that leaves the system or the mass that accumulates within it. For the chemical engineers, this is a very important tool used to optimise chemical processes.

The way to calculate the total mass balance is by using the equation

$$\text{Input} = \text{Output} + \text{Accumulation} \quad (4.1)$$

However, we normally tend to calculate the mass balance at the reactions' steady state, meaning that there will be no accumulation of mass within the process, and so, the equation is simplified to

$$\text{Input} = \text{Output} \quad (4.2)$$

When calculating the mass balance for any chemical process involving chemical reactions (carried out in either batch or continuous flow mode), it is important to remember that we should add all the masses of all the reactants that we feed in and the masses of all the products that we collect in the end, meaning that

$$\Sigma\text{Masses entering via feed streams} = \Sigma\text{Masses exiting via product streams} \quad (4.3)$$

We should also write a mass balance for each chemical used as a reactant and each chemical formed at the end of the reaction.

In the end, the final equation for calculating the mass balance of a chemical reaction is,

$$\text{Input} + \text{Formed} = \text{Output} + \text{Consumed} \quad (4.4)$$

As written at the beginning of this brief discussion, the mass balance is a very good tool for optimising an industrial chemical process in terms of, for example, profitability. Ideally, all the reactions should have a 100 % conversion together with a 100 % mass balance, meaning that not only all the reactants were converted into the desired products, but also, these products were totally collected. The reality is that in most of the cases that does not happen.

After this brief explanation, we will pass specifically to the heterocyclisation of furans. We already knew, from the work developed by Hayes *et al.* that this is a very fast reaction. Also, they have achieved very high yields of conversion, not

only assuming 100 % yields in most cases due to the high volatility of the furan products.

During this work, for which results are presented below, it will be possible to verify that due to the change of system from heterogeneous to homogeneous and also the fact that we used CO_2 flow to extract the products out from the reaction medium, the mass collection was affected *i.e.* the mass balance, and so were the overall reactions' yields. Although we assumed 100 % conversions because we never had the presence of the diol substrate present inside the reactor after the runs, all the calculations were only done with the mass of product we recovered. The mass missing was, as happened with Hayes *et al.*, swept away with the CO_2 due to its high volatility.

As a final note to this brief introduction to the results, we note that all the samples collected during this work were analysed by GC and none of them presented anything more than the desired product. No by-products or substrate was ever present.

4.3.2 Silver Catalysed Heterocyclisation in Batch Mode

The purpose of the batch reactions was to verify whether the $scCO_2$ was capable of extracting the heterocyclisation products from the reaction medium, and if so, what would be the best extraction conditions to use when running the system in continuous flow mode.

The catalyst mixture and the 3-methylnon-4-yne-2,3-diol substrate (1.0 g, 5.87 x 10^{-3} mol), which were put inside the reactor, were heated to T = 50 ºC with stirring and the system was pressurised, in three different experiments to 100, 130 and 200 bar. Each mixture was stirred for t = 1 h, followed by t = 30 min of CO_2 flow at a flow rate of 1.0 nL/min for supercritical extraction.

Table 4.1 shows the results obtained at 100 and 200 bar.

Table 4.1 Heterocyclic synthesis catalysed by $AgCF_3SO_3$ carried out in batch mode at 100 and 200 bar and T = 50 ºC.

Reaction	Procedure	Pressure (bar)	Temperature (ºC)	Ionic Liquid	Product (%)
1	Batch	100	50	[Octmpyr]Tf$_2$N	46
2	Batch	200	50	[Octmpyr]Tf$_2$N	95

GC analysis identified the resultant oil as the expected furan product, 5-butyl-2,3-dimethylfuran (Scheme 4.9), which was obtained with a very good yield when running the system at a pressure of 200 bar.

Also, NMR analysis shown no traces whatsoever of the [Octmpyr]Tf$_2$N ionic liquid in any of the collected fractions.

Although these are non-optimised reactions, they demonstrated that it is possible to extract the product resultant from silver catalysed heterocyclisation using CO_2.

4.3.3 Silver Catalysed Heterocyclisation in Continuous Flow Mode

For the continuous flow reactions, the reactor was filled with [Octmpyr]Tf$_2$N (12 cm^3) containing 10 w/w % of silver triflate (related to the ionic liquid). The CO$_2$ flow rate was 1.0 nL/min. The substrate (3-methylnon-4-yne-2,3-diol) flow rate varied between 0.05 and 0.2 mL/min, depending on the experiment. Each continuous flow heterocyclisation synthesis was carried out for about 1.5 to 2 h. Table 4.2 shows the results for one the first silver catalysed heterocyclisation reactions run on continuous flow.

Table 4.2 Continuous flow heterocyclic synthesis catalysed by AgCF$_3$SO$_3$ at p = 150 bar, T = 50 °C and substrate (3-methylnon-4-yne-2,3-diol) flow rate = 0.1 mL/min.

Reaction	Procedure	Pressure (bar)	Temperature (ºC)	Ionic Liquid	Product (%)
3	Flow	150	50	[Octmpyr]Tf$_2$N	> 70

Fractions were collected every 0.25 h and GC analysis confirmed only the presence of the furan product in very good yields (> 70 %).

Also, NMR analysis showed the absence of the diol used as substrate in the reaction or the [Octmpyr]Tf$_2$N ionic liquid, as clear contaminants of the extracted product.

4.3.2.1 Optimisation of the Silver Catalysed Heterocyclisation Continuous Flow System

Taking in account the preliminary results obtained in continuous flow, some system optimisation studies were carried out.

a) Influence of the Pressure and Temperature

The system pressure was varied between 100 and 200 bar, together with a temperature variation within the range of 40 to 75 ºC. The substrate (3-methylnon-4-yne-2,3-diol) flow rate was varied and two different flow rates were used: 0.05 and 0.1 mL/min.

Continuous flow reactions were carried out for periods of time between 1.5 and 2 h, during which the amounts of furan product extracted were very constant from its start-up time. The start-up time is the time to when the first signs of product appear in the collecting vessel. It depends on both pressure and temperature and in this case, it could vary from 0.25 to 0.75 h (Figures 4.4 and 4.5).
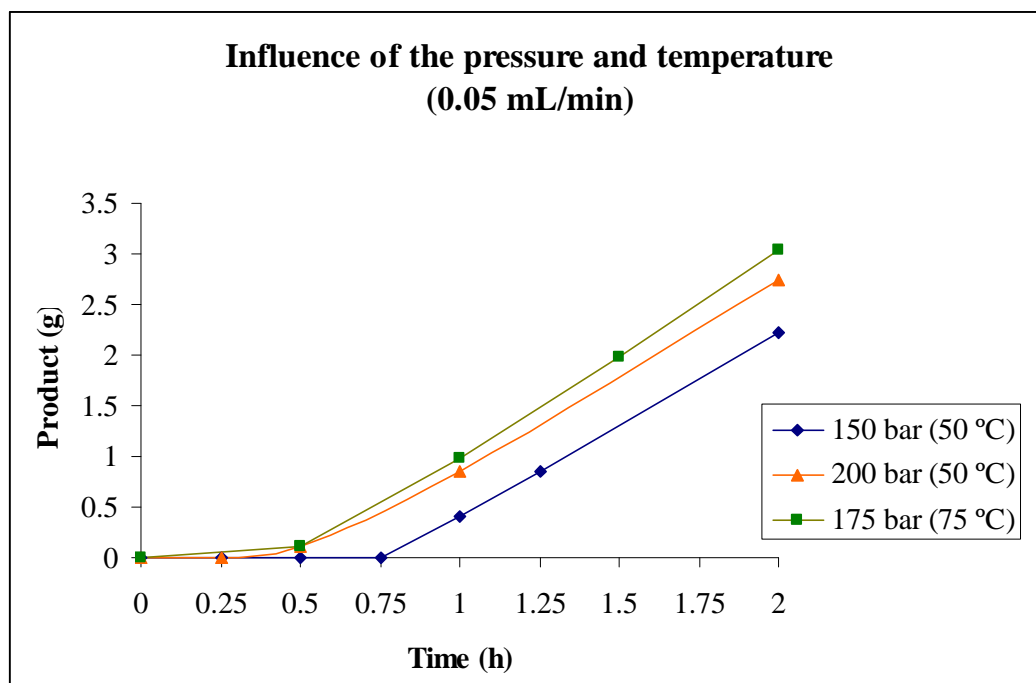
Figure 4.4 Influence of the variation of the pressure and the temperature on the continuous flow heterocyclisation of furans, catalysed by $AgCF_3SO_3$. Substrate (3-methylnon-4-yne-2,3-diol) flow rate = 0.05 mL/min and CO_2 flow rate = 1.0 nL/min.
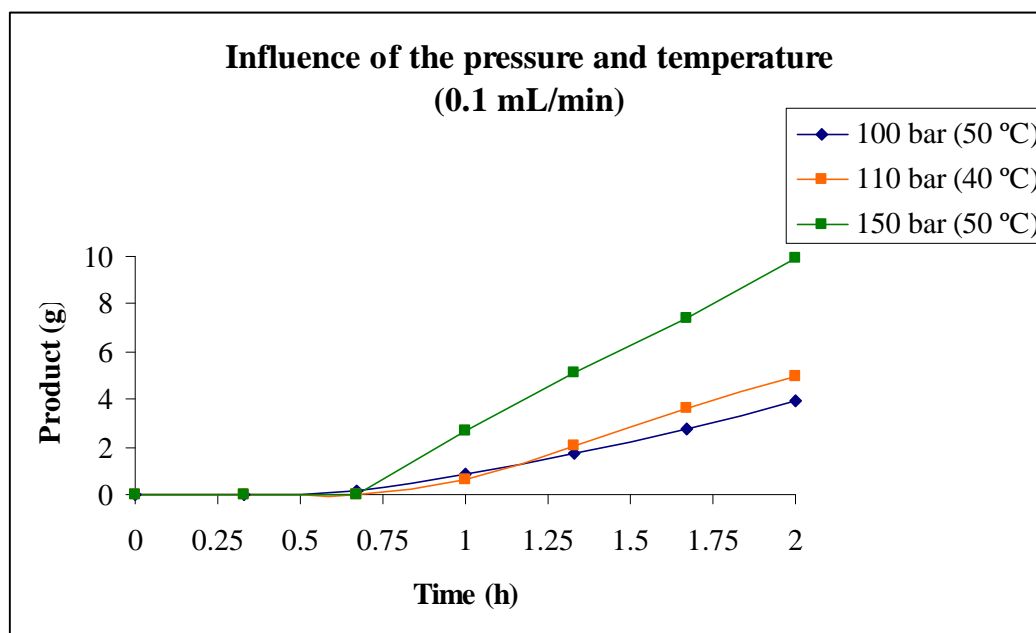
Figure 4.5 Influence of the variation of the pressure and the temperature on the continuous flow heterocyclisation of furans, catalysed by $AgCF_3SO_3$. Substrate (3-methylnon-4-yne-2,3-diol) flow rate = 0.1 mL/min and CO_2 flow rate = 1.0 nL/min.

From Figures 4.4 and 4.5 it is possible to observe that, even when varying the substrate flow rate, an increase of both pressure and temperature leads to a decrease in the start-up time of the reaction, *i.e.*, there is an improvement of the start-up time. Two good examples of this observation are the reactions carried out at (200 bar; 50 ºC) and (175 bar; 75 ºC) represented in Figure 4.4.

In terms of overall reaction efficiency, Figure 4.5 shows that an increase of the system pressure from 100 bar to 150 bar (temperature was kept at 50 ºC) increased substantially the amount of product obtained. This is probably due to an increase in residence time. As for the temperature, Figure 4.4 shows that the

reaction carried out at 175 bar and 75 ℃ obtained almost as good results as from the reaction carried out at 200 bar and 50 ℃. The increase on the temperature counter-balanced the drop of the system pressure.

b) *Influence of the Substrate Flow Rate*

Continuous flow reactions were carried out for periods of $t = 2$ h. The substrate (3-methylnon-4-yne-2,3-diol) flow rate was varied between 0.05 and 0.2 mL/min.
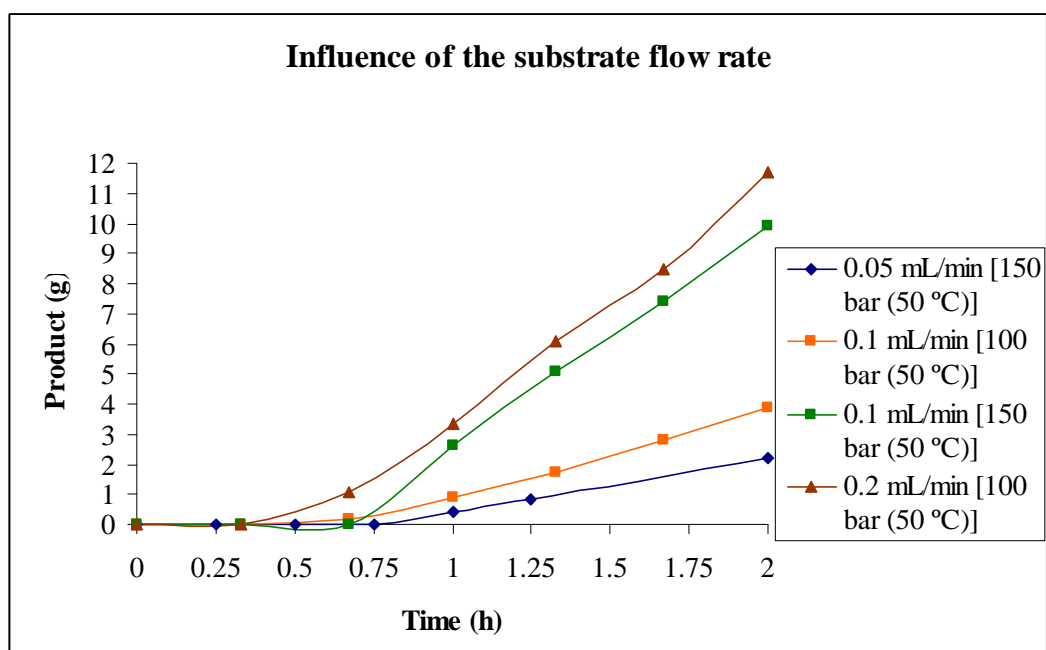
Figure 4.6 Influence of the variation of the substrate flow rate on the continuous flow heterocyclisation of furans, catalysed by $AgCF_3SO_3$. CO_2 flow rate $= 1.0$ nL/min. The same batch of catalyst was used for all the runs.

From Figure 4.6, it is possible to observe that the start-up time was reduced by about 20 min, just from doubling the substrate flow rate at (100 bar; 50 ºC) and again at (150 bar; 50 ºC). A plausible explanation is that a partitioning of the product exists between the ionic liquid and the flowing phase. Introducing larger amounts of substrate will mean that the equilibrium position will be reached faster and so the product appears in the exit flow sooner.

Examination of Figure 4.6 shows that doubling the rate of introduction of the substrate more than doubles the apparent rate of product formation (a short discussion about product collection efficiency has been done at the beginning of this Section). All samples collected under both sets of conditions only contain product. The apparent increase over double the rate is attributable to a higher percentage of product recovery.

c) *Influence of the Volume of Ionic Liquid*

As described in the Experimental Section (Section 4.2.2), the amount of silver catalyst used was always 10 w/w % related to the amount of ionic liquid used. Typically, silver triflate (1.36 g, 5.29 mmol) was dissolved in $[Octmpyr]Tf_2N$ (12 cm^3). Here, the amount of $[Octmpyr]Tf_2N$ was reduced to half (6 cm^3) and therefore, the amount of silver triflate was also reduced. The idea was to verify its influence on the reaction rate. The results are shown in Figure 4.7.
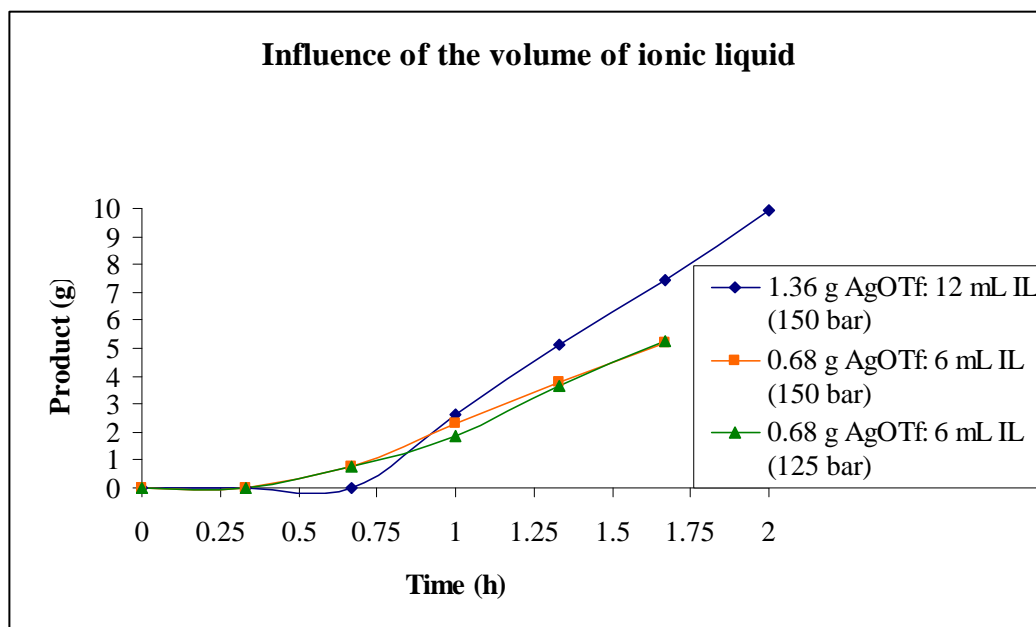
Figure 4.7 Influence of the variation of the volume of [Octmpyr]Tf_2N on the continuous flow heterocyclisation of furans, catalysed by $AgCF_3SO_3$. p = 150 and 125 bar, T = 50 ºC and CO_2 flow rate = 1.0 nL/min.

As expected, by lowering the amount of solvent ([Octmpyr]Tf_2N) and consequently, the amount of silver catalyst, the reaction rate decreases.

It was also possible to observe a reduction in the start-up time of about 20 min. This was observed at both 150 and 125 bar. From previous studies using this system, it is known that an increase in the concentration of substrate tend to improve the reaction efficiency.[24] By reducing the amount of [Octmpyr]Tf_2N used as solvent to half, and maintaining the substrate flow rate, the equilibrium amount of product dissolved in the ionic liquid will be less so that product will appear in the collecting vessel earlier.

The ICPMS analysis for the samples collected during this work showed silver leaching levels below 1 ppm for all the samples analysed.[8]

4.3.4 Silver Catalysed Heterocyclisation in Batch Mode using an Alternative Substrate: 1-(Hex-1-ynyl)cyclohexane-1,2-diol

Taking in account the good results obtained on the synthesis of 5-butyl-2,3-dimethylfuran using the $[Octmpyr]Tf_2N/scCO_2$ biphasic system, we decided to test a different a different substrate. The cyclisation of 1-(hex-1-ynyl)cyclohexane-1,2-diol catalysed by silver triflate (Scheme 4.10) was run in batch mode.

Scheme 4.10 Synthesis of 2-butyl-4,5,6,7-tetrahydrobenzofuran catalysed by silver triflate.

1-(hex-1-ynyl)cyclohexane-1,2-diol (2.5 g, 1.27×10^{-2} mol) was dissolved in $[Octmpyr]Tf_2N$ (6 cm^3) already containing the 10 w/w % silver triflate catalyst. The batch reaction was carried out under constant stirring at p = 150 bar (CO_2) and T = 50 ºC for t = 2 h. After that time, CO_2 flow was established for t = 30 min at a constant flow rate of 1.0 nL/min, for product extraction from the reaction medium. Table 4.3 shows the results obtained.

Table 4.3 Heterocyclic synthesis catalysed by $AgCF_3SO_3$ carried out in batch mode at p = 150 bar and T = 50 ºC for t = 2 h.

Reaction	Procedure	Pressure (bar)	Temperature (ºC)	Ionic Liquid	Product (%)
1	Batch	150	50	[Octmpyr]Tf$_2$N	80

GC analysis identified the resultant oil as the expected furan product, 2-butyl-4,5,6,7-tetrahydrobenzofuran (Scheme 4.10), which was obtained with a very good yield (80 %) when running the system at a pressure of 150 bar. NMR analysis shown no traces of the [Octmpyr]Tf$_2$N ionic liquid or of the diol used as starting material.

4.3.5 Overall Comparison between the Heterogeneous and the Homogeneous Flow Systems

The aim of this partnership was to develop and optimise a continuous flow homogeneous system capable of synthesising heteroaromatics, (in the present case, only specifically furans), catalysed by silver.

As previously described before in this Chapter, Knight and co-workers had already developed and optimised a continuous flow heterogeneous system with the same purpose.

And so, now that both systems have been studied and tested it is possible to do a more direct comparison of the results obtained.

Table 4.4 summarises the results obtained using the two processes.

Table 4.4 Silver-catalysed cyclisation of furans using continuous flow processes: heterogeneous *vs.* homogeneous.

	Heterogeneous	**Homogeneous**
Pressure	1 bar (N_2)	150 bar (CO_2)
Temperature	Room temperature	50 ºC
Solvent	Dichloromethane	[Octmpyr]Tf_2N
Substrate Flow Rate	1.0 mL/min	0.1 mL/min
Product Yield	> 95 %	> 70 %
Silver leaching	< 1 ppm	< 1 ppm
Catalyst Re-use	Yes	Yes
Reproducibility	Yes	Yes

From looking at Table 4.4, it is possible to say that both processes were successfully achieved and they are both an option in terms of continuous flow cyclisation. The desired furan product was obtained in excellent yields, high purity and without any traces whatsoever of by-product formation.

Overall, both systems have a very similar behaviour although the homogenous system comes with the main advantage of zero solvent waste.

4.4 Conclusions

The work presented in this Chapter was the result of a partnership between Cardiff University and the University of St Andrews. The idea was to test the successful heterocyclisation synthesis developed by Knight and co-workers in the ionic liquid/supercritical fluid biphasic system.

Hayes *et al.* developed and optimised a heterogeneous flow system where the silver-catalysed cyclisation of furans was carried out successfully and extremely good yields obtained (> 95 %) with small amounts of silver leaching.

The ionic liquid/scCO$_2$ homogeneous system was studied as a possible (and greener) alternative, if considering the possibility of having zero solvent waste during the process.

Due to the limited period of time we had to carry out this study, it was not possible to fully optimise the system. However, very good yields were obtained (> 70 %), the silver leaching was minimal (< 1 ppm) and the silver catalyst was able to be reused several times, with no noticed decrease on the reaction yields.

Taking into consideration the results obtained in this study, it is possible to conclude that a homogeneous flow system was successfully developed for the cyclisation of furans.

In terms of future work, it would be very interesting to go deeper in terms of the system optimisation: influence of the substrate flow rate, pressure, temperature, substrate concentration in the solvent, etc. It would also be very interesting to study the synthesis of other heteroaromatics, like for example, pyrroles in the homogeneous system.

Finally, direct comparison between the heterogeneous and the homogeneous processes shows that it is possible to obtain similar performances on both of them, which may be a very interesting fact for the chemical industry, especially the one related with the pharmaceutical sector.

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Chapter 5

Experimental

5. Experimental

5.1 General Experimental

All experiments were performed in oven-dried glassware, using a standard Schlenk line under a dry argon atmosphere. Argon was dried by passing it through a glass column filled with Cr(II)/silica.

Air sensitive liquid solutions were transferred between Schlenk flasks under an inert atmosphere either by cannula or by syringe. Suba seals were used as septa.

All gases were purchased from BOC gases. The synthesis gas was supplied as a 1:1 $CO:H_2$ ratio.

Deuterated solvents were purchased from Sigma-Aldrich, degassed by bubbling argon and stored under argon.

[Rh(acac)(CO)$_2$] was purchased from Acros Organics and used as received.

5.2 Purification of 1-octene

1-octene was purchased from Acros Organics. Although bought with a high purity level, it was always treated before being used in order to remove all the hydroperoxides which might still be present and which may cause the oxidation of the products when present during the reactions.

1-octene was degassed by bubbling argon through it for 30 min. Ammonium ferrous sulphate (Acros Organics) was dissolved in an equal volume of previously degassed distilled water to form a pale green saturated solution. The 1-octene was transferred into the ammonium ferrous sulphate saturated solution by cannula and the mixture was vigorously shaken and then allowed to separate. The organic phase was then transferred by cannula to another Schlenk tube. Finally, the organic phase was passed through a degassed alumina column and the purified 1-octene collected under argon. The 1-octene was kept under argon until being used.

5.3 Analytical Techniques

Gas chromatography analysis was used to analyse the fractions collected from the performed continuous flow reactions.

GCMS analysis was carried out using a Hewlett-Packard 5890 series gas chromatograph, equipped with a flame ionisation detector for quantitative analysis and a Hewlett-Packard HP6890 series fitted with a Supelco MDN-35 35% phenyl/65% methylpolysiloxane capillary column for qualitative analysis.

The temperature programme used was the following: Started at 50 ° C (4 minutes), Δ 20 ° C / minute to 130 ° C (2 minutes), Δ 20 ° C / minute to 260 ° C (13.5 minutes). The carrier gas used was helium at a flow rate of 1.4 mL/minute, with a split ratio of 100:1. Gas Chromatography Flame Ionisation Detection (GC – FID) was used to analyse all the product samples collected from the reactions carried out in continuous flow mode. The response factors of all the compounds were previously calibrated.

^{1}H and ^{31}P spectra were recorded on a Bruker AM 300 NMR spectrometer. ^{1}H spectra were referenced internally to deuterated solvents, which were referenced to TMS δ = 0 ppm. CD_2Cl_2: ^{1}H, δ = 5.35 ppm, $CDCl_3$: ^{1}H δ = 7.27 ppm. ^{31}P NMR spectra were referenced externally to phosphoric acid 85% H_3PO_4.

5.4 Synthesis

5.4.1 Synthesis of Ionic Liquids[1, 2]

Generally, an excess (up to 10 %) of the alkylating agent (e.g. bromobutane) was mixed with an amine (e.g. 1-methylimidazole), using either ethyl acetate or acetonitrile as a solvent, in a round bottom flask, under a nitrogen atmosphere.

The mixture was heated either using an oil bath or an electric mantle up to T = 70 ºC for t = 24 h (bromides) or t = 72 h (chlorides).
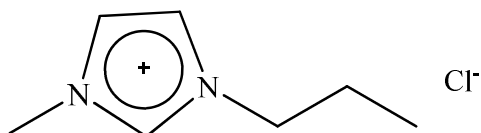
Any excess of the starting material was removed by washing with ethyl acetate and the final product was dried under vacuum.

5.4.1.1 1-Propyl-3-methylimidazolium Bromide [PrMIM]Br
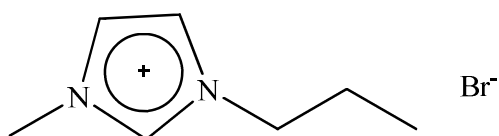
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 296.2 K): δ = 0.95 (3H, t, CH$_2$C*H$_3$*), 1.92 (2H, tq, C*H$_2$*CH$_3$), 4.02 (3H, s, NCH$_3$), 4.27 (2H, tt, NCH$_2$), 7.52, 7.63 (2H, 2 x d, NC(H)C(H)N), 10.3 (1H, s, NC(H)N) ppm.

5.4.1.2 1-Propyl-3-methylimidazolium Chloride [PrMIM]Cl[2]

^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 296.2 K): δ = 0.94 (3H, t, CH$_2$C*H$_3$*), 1.94 (2H, tq, C*H$_2$*CH$_3$), 4.05 (3H, s, NCH$_3$), 4.26 (2H, tt, NCH$_2$), 7.52, 7.59 (2H, 2 x d, NC(H)C(H)N), 10.7 (1H, s, NC(H)N) ppm.

5.4.1.3 1-Butyl-2,3-dimethylimidazolium Bromide [BDMIM]Br
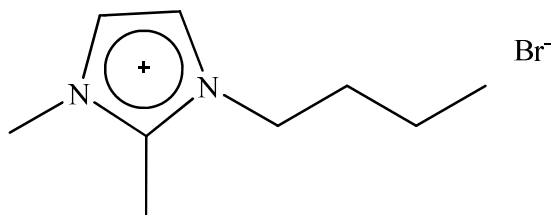
^{1}H NMR (300 MHz, CDCl$_3$, 296.3 K): δ = 0.98 (3H, t, CH$_2$C*H$_3$*), 1.38 (2H, tq, C*H$_2$*CH$_3$), 1.8 (2H, tt, NCH$_2$C*H$_2$*), 2.81 (3H, s, NC(CH$_3$)N), 4.02 (3H, s, NCH$_3$), 4.19 (2H, t, NCH$_2$), 7.43, 7.67 (2H, 2 x d, NC(H)C(H)N) ppm.

5.4.1.4 1-Butyl-2,3-dimethylimidazolium Chloride [BDMIM]Cl[2, 3]
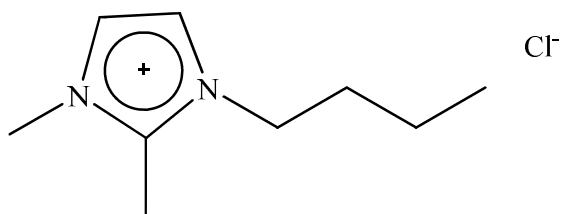
^{1}H NMR (300 MHz, CDCl$_3$, 296.3 K): δ = 0.89 (3H, t, CH$_2$C*H$_3$*), 1.31 (2H, tq, C*H$_2$*CH$_3$), 1.73 (2H, tt, NCH$_2$C*H$_2$*), 2.74 (3H, s, NC(CH$_3$)N), 3.98 (3H, s, NCH$_3$), 4.14 (2H, t, NCH$_2$), 7.47, 7.77 (2H, 2 x d, NC(H)C(H)N) ppm.

5.4.1.5 1-Octyl-3-methylimidazolium Bromide [OctMIM]Br[4-6]
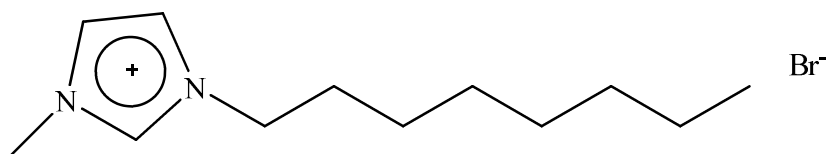
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 293.8 K): δ = 0.82 (3H, t, CH$_2$C*H$_3$*), 1.23 (10H, m, 5 x CH$_2$), 1.84 (2H, tt, NCH$_2$*CH$_2$*), 4.05 (3H, s, NCH$_3$), 4.25 (2H, t, NCH$_2$), 7.50, 7.64 (2H, 2 x t, NC(H)C(H)N), 10.3 (1H, s, NC(H)N) ppm.

5.4.1.6 1-Pentyl-3-methylimidazolium Chloride [PentMIM]Cl
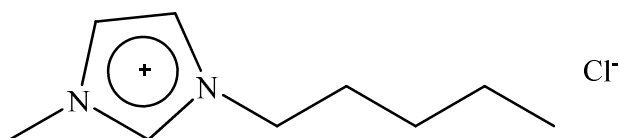
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 293.8 K): δ = 0.78 (3H, t, CH$_2$C*H$_3$*), 1.24 (4H, m, 2 x CH$_2$), 1.82 (2H, tt, NCH$_2$C*H$_2$*), 4.01 (3H, s, NCH$_3$), 4.24 (2H, t, NCH$_2$), 7.49, 7.63 (2H, 2 x t, NC(H)C(H)N), 10.5 (1H, s, NC(H)N) ppm.

5.4.1.7 1-Butyl-3-methylimidazolium Chloride [BMIM]Cl[7]
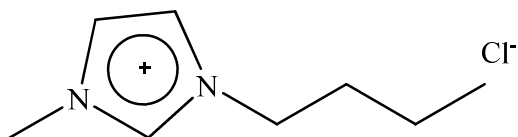
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.3 K): δ = 0.96 (3H, t, CH$_2$C*H$_3$*), 1.38 (2H, tq, *CH$_2$*CH$_3$), 1.88 (2H, tt, NCH$_2$C*H$_2$*), 4.08 (3H, s, NCH$_3$), 4.32 (2H, t, NCH$_2$), 7.43, 7.51 (2H, 2 x t, NC(H)C(H)N), 10.9 (1H, s, NC(H)N) ppm.

5.4.1.8 1-Octyl-3-methylpyridinium Bromide [Octmpyr]Br[4-6]
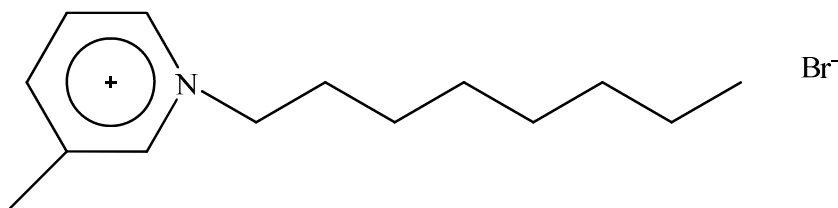
^{1}H NMR (300 MHz, CDCl$_3$, 294.4 K): δ = 0.76 (3H, t, CH$_2$C*H$_3$*), 1.20 (10H, m, 5 x CH$_2$), 1.99 (2H, tt, NCH$_2$*CH$_2$*), 2.59 (3H, s, *H$_3$*CCH), 4.88 (2H, t, NCH$_2$), 8.00 (1H, t, HCC*H*CH), 8.24 (1H, d, HCC*H*CH), 9.29 (2H, t, *H*CNC*H*) ppm.

5.4.1.9   1-Octyl-3-methylimidazolium   Bis(trifluoromethanesulfonyl)-amide [OctMIM]Tf$_2$N[2]
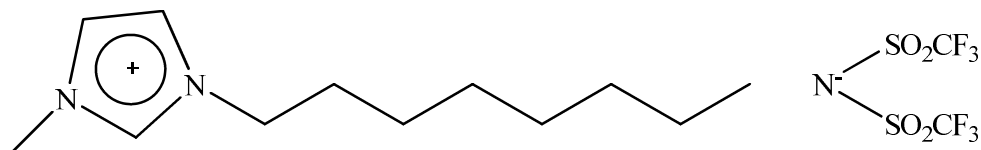
Li(Tf$_2$N) (253 g, 0.881 mol) was added to [OctMIM]Br (220 g, 0.799 mol) and dissolved in distilled H$_2$O (350 cm^3). The mixture was left stirring overnight at R.T.. After mixing, two phases were formed, both colourless. The bottom phase contained the ionic liquid product, and the top phase contained aqueous LiBr, which was decanted. The [OctMIM]Tf$_2$N product was washed several times with distilled H$_2$O (about 200 cm^3 each time) and tested with a 0.1 M AgNO$_3$ solution to check the precipitation of AgBr.

The ionic liquid product was finally dried in vacuum.

^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.4 K): δ = 0.91 (3H, t, CH$_2$CH_3), 1.32 (10H, m, 5 x CH$_2$), 1.88 (2H, tt, NCH$_2$CH_2), 3.94 (3H, s, NCH$_3$), 4.17 (2H, t, NCH$_2$), 7.33 (2H, 2 x s, NC(H)C(H)N), 8.66 (1H, s, NC(H)N) ppm.

5.4.1.10   1-Octyl-3-methylpyridinium   Bis(trifluoromethanesulfonyl)-amide

[Octmpyr]Tf₂N[4-6]
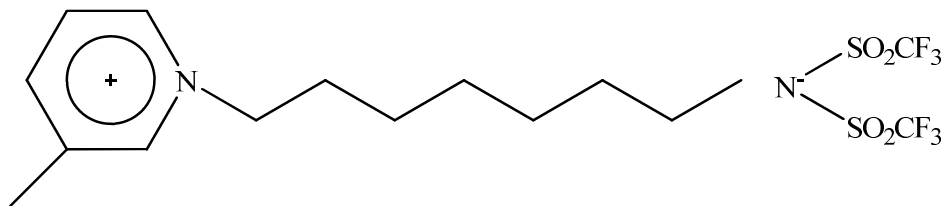
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.6 K): δ = 0.89 (3H, t, CH$_2$C*H$_3$*), 1.33 (10H, m, 5 x CH2), 2.00 (2H, tt, NCH$_2$*CH$_2$*), 2.62 (3H, s, *H$_3$*CCH), 4.55 (2H, t, NCH$_2$), 7.94 (1H, t, HCC*H*CH), 8.31 (1H, d, HCC*H*CH), 8.58 (2H, t, *H*CNC*H*) ppm.

5.4.2 Synthesis of Ionic Ligands

5.4.2.1 1-Propyl-3-methylimidazolium Diphenyl(3-sulfonatophenyl)-phosphine [PrMIM]TPPMS[2]

Na[TPPMS] (5.62 g, 1.40×10^{-2} mol) was dissolved in THF (10 cm³) and stirred rapidly. [PrMIM]Br (3.06 g, 1.49×10^{-2} mol) was dissolved in THF (200 cm³) and added drop wise to the solution and it was immediately possible to observe the formation of a white precipitate (NaBr). The solution was left stirring for t = 24 h at R. T. and after filtered through celite and the solvent removed under vacuum. The resulting residue was dissolved in acetone and layered with diethyl ether to obtain colourless crystals, which were dried in vacuum.
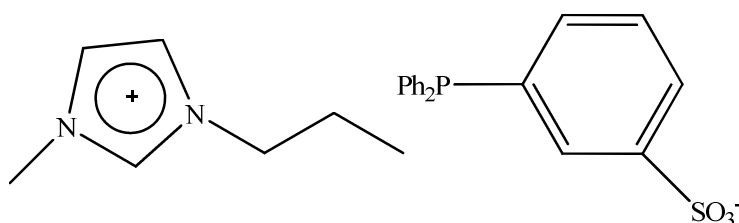
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.7 K): δ = 0.89 (3H, t, CH$_2$CH_3), 1.82 (2H, tq, CH_2CH$_3$), 3.87 (3H, s, NCH$_3$), 4.10 (2H, t, NCH$_2$), 7.13 – 7.41. (22H, m, Ph_2PC$_6$$H_4SO_3$), 7.74, 7.89 (2H, 2 x d, NC(H)C(H)N), 9.80 (1H, s, NC(H)N) ppm.

^{31}P NMR (121.4 MHz, CD$_2$Cl$_2$, 294.7 K) δ = - 4.156 ppm.

5.4.2.2 Preparation of the Ionic Ligands using Na[TPPTS][8]

For the trisulfonated ligands, the ion exchange was normally carried out by mixing the home made ionic liquid and the Na[TPPTS] (Aldrich or ABCR) at T = 50 ° C for t = 72 h, under an argon atmosphere, using degassed acetonitrile as a solvent. After this time, the solution was filtered through a bed of celite and the filter washed with degassed acetonitrile and the filtrate dried under vacuum.

5.4.2.2.1   1-Butyl-2,3-dimethylimidazolium   tri(m-sulfonyl)triphenylphosphine [BDMIM]TPPTS[8]
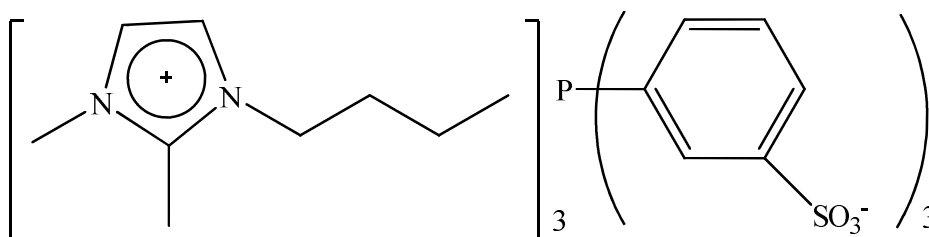
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.6 K): δ = 0.82 (9H, t, 3 x CH$_2$CH_3), 1.19 (6H, tq, 3 x CH_2CH$_3$), 1.58 (6H, tt, 3 x NCH$_2$CH_2), 2.43 (9H, s, 3 x NC(CH$_3$)N), 3.58 (9H, s, 3 x NCH$_3$), 3.90 (6H, t, 3 x NCH$_2$), 7.20, 7.60 (18H, m, 3 x P(C$_6$H$_4$SO$_3$)$_3$NC(H)C(H)N) ppm.

^{31}P NMR (121.4 MHz, CD$_2$Cl$_2$, 294.6 K) δ = - 2.537 ppm.

5.4.2.2.2   1-Pentyl-3-methylimidazolium   tri(m-   sulfonyl)triphenylphosphine

[PentMIM]TPPTS
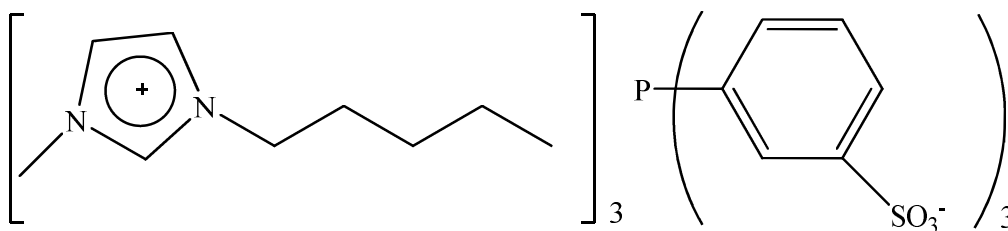
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.1 K): δ = 0.77 (9H, t, 3 x CH$_2$CH_3), 1.13 (12H, m, 3 x CH_2CH_2CH$_3$), 1.63 (6H, tt, NCH$_2$CH_2), 3.63 (9H, s, NCH$_3$), 3.95 (6H, t, 3 x NCH$_2$), 7.21, 7.61 (18H, m, 3 x P(C$_6$H$_4$SO$_3$)$_3$NC(H)C(H)N), 9.27 (3H, s, 3 x NC(H)N) ppm.

^{31}P NMR (121.4 MHz, CD$_2$Cl$_2$, 293.9 K) δ = - 2.906 ppm.

5.4.2.2.3   1-Octyl-3-methylimidazolium   tri(m-   sulfonyl)triphenylphosphine

[OctMIM]TPPTS
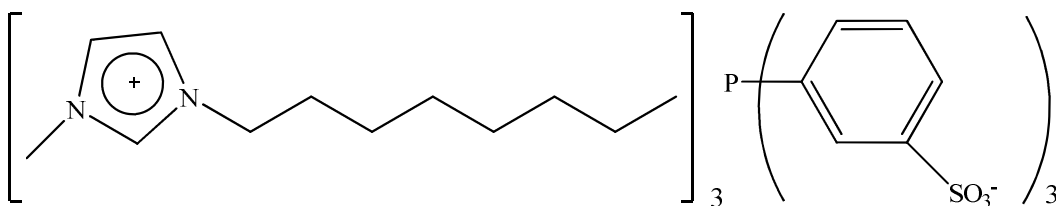
^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 294.1 K): δ = 0.86 (9H, t, 3 x CH$_2$CH_3), 1.26 (30H, m, 3 x CH_2CH_2CH_2CH_2CH_2CH$_3$), 1.77 (6H, tt, NCH$_2$CH_2), 3.80 (9H, s, NCH$_3$), 4.06 (6H, t, 3 x NCH$_2$), 7.35, 7.74 (18H, m, 3 x P(C$_6$H$_4$SO$_3$)$_3$NC(H)C(H)N), 9.57 (3H, s, 3 x NC(H)N) ppm.

^{31}P NMR (121.4 MHz, CD$_2$Cl$_2$, 294 K) δ = - 2.808 ppm.

5.4.3 Preparation of Na[TPPMS][9]

Fuming H_2SO_4 (20% excess SO_3) (100 cm^3) was measured into a 250 cm^3 round bottom flask chilled in ice water. Finely grounded PPh_3 (40 g) was added to the acid very slowly and the mixture stirred strongly between additions until complete dissolution.

After complete dissolution, the mixture was stirred and heated to T = 100 º C for t = 75 min using an oil bath. Next, it was allowed to cool down to room temperature and afterwards, carefully poured onto crushed ice (800 g) with stirring.

The solution was further cooled in iced water and carefully neutralized by the slow addition of NaOH (50% aqueous solution) until reaching a pH = 7. The resulting solution was then allowed to stand at room temperature for t = 30 min and then filtered through a Buchner funnel. The precipitate was redissolved in hot distilled water (800 g) while the flask was flushed with a continuous argon stream. The solution was allowed to cool down to room temperature and again filtered. The precipitate was collected into a pre-weighed crystallising basin and put into a desiccator under vacuum to dry over P_4O_{10}.

Product yield = 86 %

^{31}P NMR (121.4 MHz, D_2O, 293.9 K) δ = - 5.102 ppm.

5.5 The Continuous Flow Rig

5.5.1 The Apparatus and the Continuous Flow Process

All the continuous flow experiments (with exception for the ones presented in Chapter 3) were performed in the system shown below, in Figure 5.1.

AV	Air inlet valve
BV	Ball valve
CSTR	Continuously stirred tank reactor
CV	Check Valve
D	Dosimeter
FM	Flow meter
I	Intensifier
LCV	Liquid collection vessel
LP	Liquid pump
P	Pressure transducer
PCV	Pressure control valve
T	Thermocouple
SV	Shut-off valve
V	Vent

Figure 5.1 Scheme of the continuous flow reactor.

This rig was built by Webb *et al.*[2] and its continuously stirred tank reactor (CSTR) (Hastelloy, 30 cm^3) is fitted with two gas/liquid feed dip-tubes, a pressure transducer, a thermocouple and an outlet port.

Standard continuous flow procedure started by delivering carbon dioxide into the system at a constant pressure by using the air driven liquid pump. The CO/H_2 was delivered using an air driven intensifier, which was coupled to a Rheodyne injection unit (dosimeter) and the liquid substrates were delivered using a HPLC pump set at a constant pre-defined rate. Both gas and liquid substrates while being delivered into the CSTR passed through check valves and finally dissolved in the catalyst ionic solution already inside at a certain pressure and temperature required for the reaction to occur. The liquid products left the CSTR with the gas stream which was decompressed from the reaction pressure to about 2 – 7 bar at the first expansion valve. This valve was connected to a first liquid collector vessel, where most of the liquid fractions were collected. The gas stream would then pass into a second expansion valve and collector vessel for further decompression in order to reach atmospheric pressure. At last, the gas stream was passed through a flow meter, used to control the gas during the whole continuous flow process, and then vented.

5.6 References

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Chapter 6

Conclusions and Further Work

6. Conclusions and Further Work

6.1 Conclusions

The aim of this project was to improve the previously obtained results when the ionic liquid/scCO$_2$ biphasic system was developed and used to carry out the hydroformylation of long chain alkenes (1-octene) in continuous flow mode. This previous work, which involved the use of [PrMIM][TPPMS] ligands proved to be quite successful at 200 bar pressure and 100 ºC.[1] However, phase behaviour studies revealed that it is also possible to extract the hydroformylation products from the reaction medium using scCO$_2$ at 100 bar pressure and 100 ºC and so, new experimental conditions were developed using the [PrMIM][TPPMS] ligand.[2] This set of experiments is not described in the present thesis since the main aim of these phase behaviour studies was simply to verify the possibility of reducing the operating system pressure before moving on with our work.

It is well know that the ligand design plays an important role in determining the retention of the rhodium catalyst in the reaction medium, and therefore, we decided to replace TPPMS with TPPTS since the presence of three sulfonated groups should increase the catalyst retention. Two new ionic ligands were then synthesised (by cation exchange between our own home-made ionic liquids and water-soluble phosphines) and used in this study, [PentMIM][TPPTS] and [OctMIM][TPPTS].

The use of these new ligands improved the first results obtained using this system, in terms of catalyst stability and activity under new experimental conditions. We started from using an IL/scCO$_2$ at 200 bar and decreased this initial pressure by half, to 100 bar. The results presented have shown that in most cases, the turnover frequencies were higher than the ones obtained by Webb *et al.* while running the system using exactly the same experimental flow conditions. However, the biggest improvement was being able of keep obtaining high turnover frequencies, when running the [OctMIM]Tf$_2$N/scCO$_2$ biphasic system at pressures below 200 bar (150 bar and even 100 bar). This can be an attractive factor for the commercial industrialisation of the process.

The [PentMIM][TPPTS] ionic ligand was also tested in a SILP (Supported Ionic Liquid Phase) system, which was used to carry out the hydroformylation of 1-octene, in continuous flow mode. However, this was not an ordinary SILP system, since we used the new "without gases" approach, meaning that the *syn* gas used as a reactant in the hydroformylation reaction was synthesised *in situ* by decomposing formaldehyde at T = 450 ºC. The two SILP based catalysts, prepared with different ionic liquid loadings (14 and 44 w/w %), were extensively tested under several different experimental conditions.

Results have show that both SILP based catalysts presented a very efficient and stable behaviour and very high conversions were achieved. We think this might be due to the fact that the reaction took place in the liquid-phase.

This system has the advantage of joining the best of both homogeneous and heterogeneous systems, plus the fact of avoiding the use of cylinders.

The IL/scCO$_2$ homogeneous biphasic system was extended to the study of other reactions. The heterocyclisation of furans catalysed by silver was successfully carried out in continuous flow mode using a homogeneous system. This was achieved after the development and optimisation of a heterogeneous flow system at Cardiff University for the same purpose.[3] A direct comparison of both systems has shown that both are capable of producing very good results, in very good yields, with low silver-catalyst lost, although the homogeneous system comes with the advantage of zero solvent waste. From a commercial point of view, these results can open a "new door" for the synthesis of heteroaromatics, which so far, have been industrially produced in batch mode.

6.2 Further Work

In terms of further work, it would be very interesting to change the so far used ionic liquid solvent, [OctMIM]Tf$_2$N, for another ionic liquid which would be capable of dissolving the [TPPTS]Na directly, avoiding the need to perform a cation exchange reaction first.

A good example of an ionic liquid to use would be a 1-alkyl-3-methylimidazolium *p*-toluenesulfonate ([RMIM][*p*-CH$_3$C$_6$H$_4$SO$_3$]).[4] We actually tried to synthesise this ionic liquid during this work, in order to test in our continuous flow system. However, instead of following its preparation described in the literature[4], we decided to chose a new method, which consisted on the ion exchange between the

sodium p-toluene sulfonate and the [OctMIM]Br. Although this would be a much faster method, we never achieved either a great yield or a pure ionic liquid.

It would also be interesting to further extend the continuous flow ionic liquid/scCO$_2$ system to the study of other reactions.

One of these reactions would be the methoxycarbonylation of 1-octene. Although we tried to carry out this reaction using our system[5], we found it very hard to extract the methyl nonanoate product. First we thought this could be because the ionic liquid used as solvent in the reaction could be a better solvent for this compound than the CO$_2$, meaning that we would have to saturate the ionic liquid to "force" the product out. Since that did not work, we turned to the product's volatility and ended up by installing a cold trap in the rig, where the product was then collected, but never in very good amounts, neglecting the mass balance.

Another reaction that has been studied during this time but that it would be interesting to return to, is the dihydroxylation of 1-hexene catalysed by K$_2$OsO$_4$.2H$_2$O (potassium osmate dihydrate).[6, 7] This reaction is already being successfully carried out in a semi-continuous mode, with the 1,2-hexanediol product being extracted with CO$_2$ flow. However, when we tried to carry it out continuously in the IL/scCO$_2$ system, we were exposed to several (unexpected) situations.

First, we realised that it was very hard to collect any product, when carrying out the reaction in continuous flow. This was totally unexpected, since Serbanovic *et al.* had been carrying the reaction in semi-continuous mode and so, this had never

affected their work. Only after adding a cold trap (dry ice + acetone) in the system and reducing the CO_2 flow to the minimum possible we were capable of collecting samples. However, it was with great surprise that we realised, after GC analysis, that there was no conversion at all. With these results in hand, we questioned whether this was caused by the reaction's kinetics of if the experimental conditions for the semi-continuous mode were not adequate at all for the same reaction when in flow mode.

In terms of the rig itself, it would be interesting to invest some time in developing a new way for introducing air sensitive catalyst complexes into the CSTR. So far, these have been injected by syringe under N_2 atmosphere, after disconnecting the outlet part of the CSTR, which may lead to a weak point in the system. The ideal would be to insert a T piece in that same outlet, working like a tap and avoiding the wear of the outlet part of the CSTR.

Overall, the work here described shows the development of the IL/scCO$_2$ concept. It is the first reported continuous flow hydroformylation of 1-octene catalysed by rhodium using ionic liquid ligands, performed at system pressures as low as 150 and 100 bar. One of these ionic ligands was also used as a SILP-based catalyst and reported on the first continuous flow hydroformylation of 1-octene on a "without gases" system.

Finally, it is the first reported continuous flow silver-catalysed heterocyclisation of furan using a homogeneous system.

6.3 References

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