New Strategies for Multiphase Catalysis using Supercritical Carbon Dioxide

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List of abbreviations

[4MBP][BTA] = 4-methyl-1-butylpyridinium bis(trifluoromethylsulfonyl)imide
[Ac] = acetate
acac = acetylacetonate
ADMET = Acyclic Diene Metathesis
ATR = Attenuated Total Reflectance
BARF = tetrakis-3,5-bis(trifluoromethyl)-phenylborate
BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
BINOL = 2,2'dihydroxy-1,1'-binaphthyl
[BMIM] = 1-Butyl-3-methylimidazolium salt
[BMIM][PF6] = 1-Butyl-3-methylimidazolium hexafluorophosphate
CESS = Catalysis and Extraction using Supercritical Solvent
cod = 1,5-cyclooctadiene
d_c = Critical Density
d_r = Reduced Density
[EMIM] = 1-Ethyl-3-methylimidazolium salt
FBS = Fluorous Biphasic System
HAPs = Hazardous Air Pollutants
hfacac = hexafluoroacetylacetonate
[HMIM] = 1-hexyl-3-methylimidazolium salt
[iBMIM] = 1-isobuthyl-3-methylimidazolium salt
ICP = Inductively Coupled Plasma
IL = Ionic Liquid
MEA imine = (2-ethyl-6-methyl-phenyl)-(2-methoxy-1-methyl-ethylidene)-amine
[MMIM] = 1,3-di-methylimidazolium salt
MOP-OMe = 2-Diphenylphosphino-2'-methoxy-1-1'-binaphthyl
nbd = norbornadiene
[OMIM] = 1-Octyl-3-methylimidazolium salt
P_c = Critical Pressure
PEG = Poly(ethylene glycol)
[PMIM] = 1-Penthyl-3-methylimidazolium salt
P_r = Reduced Pressure
RCM = Ring Closing Metathesis
RTIL = Room Temperature Ionic Liquid
SCF = Supercritical Fluid
SCW = Supercritical Water
SHOP = Shell Higher-Olefin Process
STP = standard temperature and pressure (1 atm at room temperature)
T_c = Critical Temperature
THF = Tetrahydrofurane
TOF = Turn Over Frequency
TON = Turn Over Number
TPP = triphenylphosphine
TPPTS = Trisulfonated triphenylphosphine
T_r = Reduced Temperature
TRPTC = Thermo-Regulated Phase Transfer Catalysis
VOCs = Volatile Organic Compounds

1 Introduction

1.1 Concepts of Green Chemistry

Green is a strong color. Green is the color of the chlorophyll and green is the color of the money.

S. K. Ritter in C&EN July 16, 2001.

The general definition of *green chemistry* is the **design** and development of a chemical product and/or process that reduces or better eliminates the use and generation of **hazardous** substances.[1] Every substance and the way it is made *via* chemical reactions can be analyzed at least in principle using life-cycle considerations. In other words, anything chemists synthesize in their laboratories might be potentially introduced in the environment causing its inevitable perturbation. Life cycle assessment (LCA) is a powerful tool for industrial ecology to facilitate understanding and characterization of the range and scope of environmental impacts at all stages within a product or process.[2] Activities in the field of *green chemistry* are focused on research for new chemical methods in order to find economically acceptable and less polluting industrial process. The concept of "design" is an essential element of this approach. In practice, there exists a set of criteria, methodologies and regulations, which should be followed in order to realize a clean chemical process. The term "hazardous" includes all family of issues such as explosion, flammability, toxicology, carcinogenicity, mutagenicity, climate change and pollution, which should be taken into account even before starting a laboratory production of any chemical substance.

The design of an environmentally benign chemical process may be guided by the 12 principles of *green chemistry* listed below.[1,3]

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i. **Prevention**: It is better to prevent waste than to treat or clean up waste after it has been created.

ii. **Atom economy**: Synthetic methods should be design to maximize the incorporation of all materials used in the process into the final product.

iii. **Less Hazardous Chemical Syntheses**: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and environment.

iv. **Design Safer Chemicals**: Chemical products should be design to effect their desired function while minimizing their toxicity.

v. **Safer Solvents and Auxiliaries**: The use of auxiliary substances, solvents, separation agents and others, should be made unnecessary wherever possible and innocuous when used.

vi. **Design for Energy Efficiency**: Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible synthetic methods should be conducted at ambient temperature and pressure.

vii. **Use Renewable Feedstocks**: A raw material or feedstock should be renewable rather then depleting whenever technically and economically practicable.

viii. **Reduce Derivatives**: Unnecessary derivatization, i. e. use of blocking groups protection/deprotection and temporary modification of physical/chemical processes, should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

ix. **Catalysis**: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

x. **Design for Degradation**: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

xi. **Real-Time Analysis for Pollution Prevention**: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

xii. **Inherently Safer Chemistry for Accident Prevention**: Substances used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

To obey every single principle may appear difficult and it is not always clear how this can fit the economy of a chemical company. One practical approach for a first approximate guideline to evaluate different processes is to consider the so called *environmental factor* (see Table 1-1, E = kg of by-product / kg of product) that has been analyzed for various segments of the chemical market.[4] Here by-products are defined as everything that is formed in a process except the product.

Table 1-1: Environmentally factor [kg of by-product / kg of product].

	Amount of waste (tons / year)	*E*-factor
Petrochemicals	10^6 - 10^8	~ 0.1
Basic chemicals	10^4 - 10^6	1 - 5
Fine chemicals	10^2 - 10^4	5 - 50
Pharmaceutical	10^1 - 10^3	25 - 100

The *E* factor increases going down-stream from petrochemical to fine chemicals and specialties. This is partially due to the fact that the production of fine chemicals generally involves multi-step synthesis and stoichiometric reagents rather than catalytic methods. The selectivity of a reaction, the yield of product divided by the amount of substrate converted, provides little indication of the amount of waste generated in the process. Thus, the overall stoichiometry has to be considered. Research in the field of *green chemistry* has been also focused in finding alternative synthetic strategies for the design of chemical transformations which maximize the incorporation of all material used in the process (atom-efficiency or atom economy).[5] This is another metric that gives indication on the efficiency of a chemical process, but as major limitation it does not include, for example, any consideration on the solvents used or on toxicity of reagents and products.

The use of environmentally benign solvents or the application of solventless system represents one of the most active areas of *green chemistry*. Typical organic solvents are classified as *v*olatile *o*rganic *c*ompounds (VOCs) or, *h*azardous *a*ir *p*ollutant*s* (HAPs), and are often flammable, toxic or carcinogenic. The use of supercritical fluids to replace conventional organic solvents has gained much interest within the *green chemistry* society. Among them, supercritical CO_2 (see chapter 2.2.1) has received the most attention because its critical point (T_c = 31.1 °C, P_c = 73.75 bar) is mild in comparison with this of other solvents.[6] Furthermore, carbon dioxide is non toxic, inexpensive, nonflammable, can be separated from the product by depressurization and recompressed for recycling. It must be specified that the application of carbon dioxide as a solvent does not increase the anthropogenic greenhouse gas emission as it does not generate any additional CO_2. Some very important applications of carbon dioxide as solvent are found already in the dry cleaning industry as a replacement solvent for perchloroethylene,[7] in caffeine extraction as an alternative to methylenechloride[8] and in semiconductor manufacturing where replacement of water, used in conventional processing, avoids the damage to the surface of the silicon wafers.[9] The emerging use of $scCO_2$ as reaction media in industrial heterogeneous catalysis provides an excellent example of a fruitful collaboration between industry and academia. In the U.K. the partnership of Thomas Swan & Co. Ltd with researchers from the university of Nottingham has developed a multipurpose plant for organic synthesis using supercritical fluids with a capacity up to 1000 tons per year.[10,11] For homogeneous catalysis, carbon dioxide has the general disadvantage to be a poor solvent for many metal catalysts. Thus, "CO_2-philic" modification of the complexes is necessary to obtain homogeneous catalytic solutions if carbon dioxide is used as only solvent.[12] Nevertheless, the application of this solvent is attractive also for organometallic chemistry.

The use of water as a benign and inexpensive solvent for chemical transformations and processes can be also very beneficial for the environment. Nowadays a number of catalytic organic reactions can be carried out in water upon proper modification of the catalyst and the reaction conditions.[13] Although, incompatibility with many metal complexes, solubility of substrates and potential pollution of groundwater are posing important limitations of water as solvent for chemical transformations, aqueous systems still hold many promises for *green* catalysis.

Ionic liquids (ILs; see chapter 2.2.2) are a relatively new class of alternative solvents. They are attractive because of their negligible vapor pressure and their interesting interactions with organometallic catalysts.[14] In principle, a huge variety of ILs can be synthesized by varying the combination of the cation and the anion, meaning that they can be optimized for each application.[15] While questions of intrinsic hazards and cost of this new class of solvents must still be answered,[16] clearly their non-volatility and the possibility to design an optimized solvent for a potential application might give benefits to the environment.

Catalysis is one of the fundamental pillars of *green chemistry*. Catalytic reactions are generally preferred to stoichiometric because they reduce energy requirements, can decrease the complexity of separation procedures due to increased selectivity, and they should minimize the quantities of reagents needed. There is little doubt that the 2001 Nobel Prize-winning work of Sharpless, Noyori, and Knowles met many *green chemistry* goals.[17] Their contribution in the field of enantioselective catalysis has been crucial in producing single enantiomer compounds, particularly for the pharmaceutical industry.

1.2 "Regulated" system for multiphase catalysis

Catalysis is a powerful tool that facilitates an enormous number of chemical transformations. It can be classified according to heterogeneous, homogeneous and biological processes and it is, as previously mentioned, an essential technology for the field of *green chemistry*. As shown in Figure 1-1, the basic ingredients of catalysis are substrates and a catalyst which for homogeneous system is a soluble metal complex.[18]

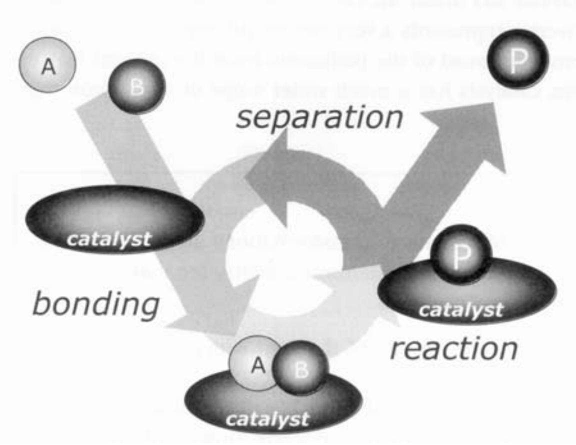


Figure 1-1: General scheme of a catalytic reaction. Taken from reference [18c].

Currently there is an ever-increasing quest for new catalyst systems that allow faster and very selective reactions, together with new recycling methodologies. Homogeneous catalysis where catalyst, reagents and products are in the same phase, generally offers several advantages such as faster reaction rates, higher selectivity and structurally diverse modification of the catalyst by the use of the appropriate ancillary ligands. Furthermore, a homogeneous system can be characterized using a wide range of in situ spectroscopy techniques, allowing deep understanding of reaction mechanism and kinetics. Unfortunately, the difficulty of separating the catalyst from the reaction mixture increases the economic and environmental barrier to a broader application of homogeneous systems.[19] In order to overcome these limitations, biphasic or more generally multiphase catalysis can offer clear advantages.

In an ideal phase-separable or biphasic system (see Figure 1-2), the catalyst and associated ligands would be dissolved in one phase and the reactants and products would be completely soluble in a second phase. At the end of the reaction, the products are separated from the catalyst phase, which can be recycled.[20] As a general drawback, this system may suffer of mass transfer limitations. Therefore, it is necessary to ensure excellent mixing or even complete miscibility of the phases under the reaction conditions to allow efficient interaction between the reagents in order to achieve high reaction rates ("regulated" biphasic catalysis).

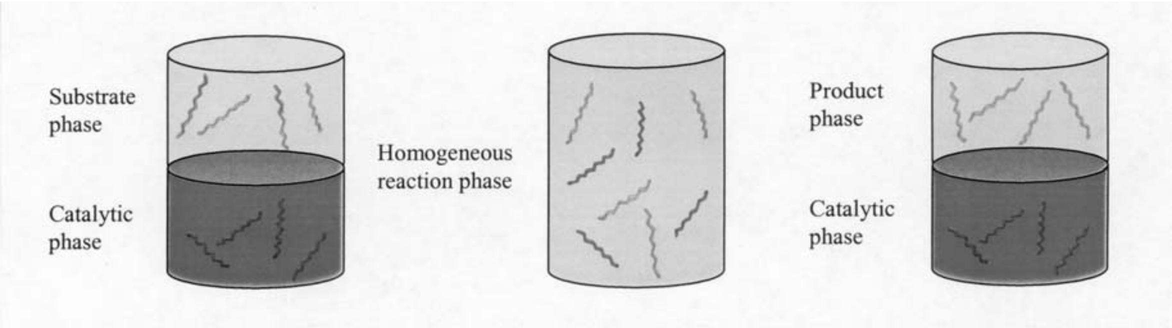


Figure 1-2: Reaction/separation scheme for "regulated" biphasic catalysis.

The Shell higher-olefin process (SHOP) was the first commercially applied methodology taking advantage of a biphasic liquid/liquid system where the products formed an upper (organic) phase.[21] The extremely efficient and selective nickel catalyst for the SHOP process was discovered in the early 60s. However, the cost of the metal complex and the need to recycle the catalyst caused Shell Development in California to sideline this highly selective catalyst until an efficient method for recycling was discovered. The oligomerization of ethene with a cationic nickel complex is now carried out in a polar solvent, typically 1,4-butanendiol. The α-olefin products are easily separated from the reaction mixture because of their low solubility in this solvent.[18a,21] Today α-olefins are produced mainly by this method for ethylene oligomerization because of the high availability of the starting material, and the wide range of applications of straight-chain olefins has caused the linear olefins market to continue growing.

The possibility of using water for two-phase catalysis was envisaged for industrial application in the early 70s taking the hydroformylation of propene as an example.[22] The metal complex containing hydrophilic ligands is soluble in water, and the reaction products are separated from the catalytic solution by simple phase decantation. The Ruhrchemie/Rhône-Poulenc process, for the rhodium catalyzed hydroformylation of light olefins, has been successfully applied as a water/organic biphasic system using trisulfonated triphenylphosphine (TPPTS) as ligand. It was shown that only a small fraction of the precious metal is leached in the organic phase (< 0.1 ppm of Rh). The Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propene and butene is an efficient method for catalyst recycling and provides high selectivity and reaction rates. A considerable restriction is that higher olefins, which are not water soluble ($\geq C_6$), are not suited for this technology.[23]

The hydroformylation of olefins with five or more carbon atoms accounts for about 25% of the worldwide capacity of oxo products. For this reason, an efficient method for the hydroformylation of higher olefin that allows to catalyst recycling by phase separation would be highly desirable. Several approaches to overcome the problem of low space-time yields in biphasic aqueous catalysis are possible:

1. The amphiphilic approach: the use of phosphine ligands containing weakly basic or acidic functionalities will either improve the solubility of higher olefins, *via* formation of micelles, or increase the reaction rate by preferential concentration of the catalyst at the interface of the water/organic phase. These phosphine ligands can also be used to perform a reaction in a homogeneous organic phase and are then extracted at the end using an acidic or basic aqueous solution.[24]
2. Modification of the Ruhrchemie/Rhône-Poulenc process: the use of co-solvents (*e.g.* polar alcoholic solvents), detergent cations or modified cyclodextrins to enhance solubility and mobility of reagents across the phase boundary.[25]
3. Increasing the surface area of the phase boundary *via* mechanical methods.
4. The *t*hermo-*r*egulated *p*hase *t*ransfer *c*atalysis (TRPTC): a general process in which a catalyst is transferred from a phase A to another phase B, immiscible with the first one, in respond on temperature changes. Particularly a metal catalyst modified with poly(ethylene glycol) derived ligands will be soluble in water but not in organic solvents. Upon heating the poly(ethylene glycol) chain undergoes to a phase transfer and the catalyst becomes more soluble in the organic solvents: this phase transfer is reversible.[26]

Another approach to immobilization of catalytic precursor in aqueous biphasic system is the use of water-soluble polymer or oligomer.[27]

Considering non-aqueous biphasic approaches the following examples need to be mentioned at this stage of the discussion.

Fluorous systems have been demonstrated to posses attractive solubility properties when applied to catalysis in biphasic systems.[28] At room temperature perfluorinated alkanes, dialkyl ethers or triyalkylamines have very low miscibility with common organic solvents such as toluene or THF, and form biphasic mixtures. A metal catalyst modified with ligands containing a certain number of fluorinated groups, so called *ponytails*, will partition preferentially into the fluorous phase, while substrate resides in the organic solvent. In many cases such *f*luorous *b*iphasic *s*ystems (FBS) can merge into a single-phase upon heating allow to higher reaction rates. Separation of the products is then achieved simply by cooling down the system. They have the disadvantages of requiring substantial synthetic modification of the metal complex and use of expensive fluorinated solvents that are persistent in the environment.

Fluorinated metal complexes may also find catalytic applications with supercritical carbon dioxide as solvent. The presence of perfluoroalkyl-based *CO_2-philic* groups in the ligands attached to the metal center renders the complex soluble in carbon dioxide, thus generating a fully homogeneous system at the values of pressure and temperature achieved during the reaction.[6a-b,29] A significantly lower degree of fluorination is sufficient as compared to FBS.[30] By changing temperature and/or pressure, the solvent power of CO_2 (see chapter 2.2.1) can be adjusted so that the catalyst precipitates, while the products of the reaction remain soluble in CO_2 and can be successfully extracted. This process is known as CESS (*C*atalysis and *E*xtraction using *S*upercritical *S*olutions).

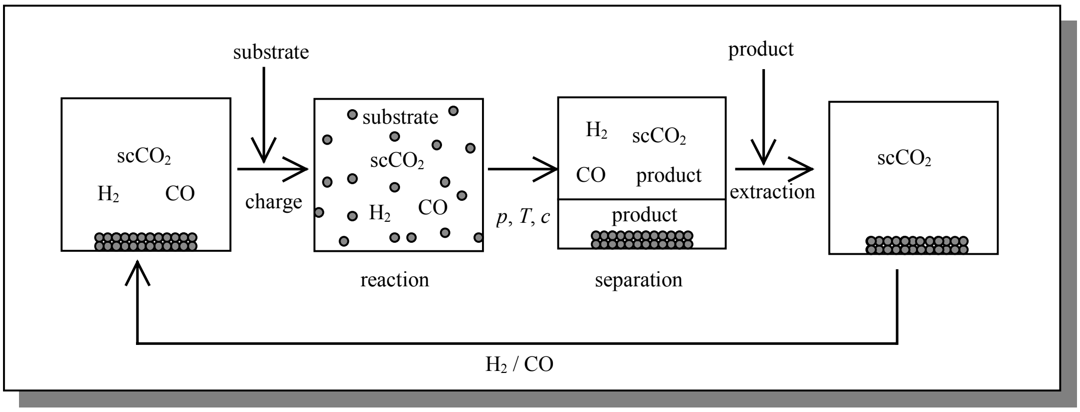


Figure 1-3: Schematic representation of the CESS process exemplified for the hydroformylation reaction.

Another approach to biphasic system involves the use of ionic liquids (see chapter 2.2.2) alone or in combination with a second immiscible organic solvent or water. Metal catalysts and reagents are readily dissolved in the ionic liquid phase, and at the end of the reaction the product can be distilled out from the reaction mixture or removed by extraction using a solvent that is immiscible with the IL.[31] In relation to this, it is apparent that the combination of ionic liquids with compressed or supercritical carbon dioxide may offer a very efficient alternative strategy for biphasic catalysis. Brennecke and co-workers first reported that even relatively low volatile organic compounds can be extracted from ionic liquids using supercritical carbon dioxide.[32] Since this time, much effort has been applied in searching new applications of this biphasic system. Carbon dioxide dissolves readily in ionic liquids to facilitate the extraction, but ionic liquids are immiscible with carbon dioxide so pure product can be recovered. The phase behavior of [BMIM][PF_6] with CO_2 has been extensively studied by Brennecke. Carbon dioxide is highly soluble in this ionic liquid, up to a mole fraction of 0.6 at 80 bar.[32] The composition of the CO_2 phase has been seen as essentially pure carbon dioxide, with no detectable ionic liquid, indicating a solubility of less than 10^{-5} mole fraction. Furthermore, it has been suggested that the presence of compressed carbon dioxide with ionic liquids may enhance solubility of other gases in the ionic phase, consequently improving the mass transfer and reaction rates. In some cases, as will be discussed later on this thesis, this outcome can be rather dramatic.

Chapter 2 of this thesis deals with catalysis in ionic liquid/carbon dioxide systems in relation to some physical chemical characteristics such as gas solubility, conductivity and polarity of the system. Furthermore, the activity, selectivity and recycling of catalysts in IL/CO_2 environments will be discussed. At the time when this work started no examples concerning biphasic catalysis in IL/CO_2 systems had been reported in the literature, although many publications already existed in the field of organic and organometallic reactions in ionic liquid media. Since 2001 and simultaneously with the first communication of some of the results of this thesis, a series of examples for transition metal catalysis in IL/CO_2 have been published and a short review of this development is give in chapter 2.1.

The combination of scCO_2 with water using the advantages of the system as a reaction medium, and the possibility to design and synthesize water soluble metal catalysts, could lead to truly environmentally friendly processes.[33] This will eliminate the use of organic solvents and give access to easy product/catalyst separation and catalyst recycling protocols. A variant of this involving inverted biphasic catalysis system where supercritical CO_2 is the stationary catalyst phase and water the continuous phase has recently been described for Rh-catalyzed hydroformylation of polar substrates.[34] Product separation and catalyst recycling is possible without depressurizing the autoclave simply by removal the water phase which contains the reaction products. Both in the water-scCO_2 system and in the inverted methodology all the components of the catalysis must be stable against acidic conditions since carbonic acid solutions formed under these conditions have a pH of around 3.[35]

Recently Heldebrandt and Jessop introduced an attractive new system for multiphase catalysis using poly(ethylene glycol) combined with carbon dioxide.[36] Poly(ethylene glycol) (PEG) is a benign and readily available material used in the food and beverages industry and for medical purpose. This approach can be considered as complementary to the IL/CO_2 and water/CO_2 systems. Liquid PEG can dissolve many organometallic compounds and accordingly be used as a stationary phase without any need to modify the chemical structure of the catalyst. At ambient condition only low molecular weight PEGs are liquid but their high solubility in supercritical carbon dioxide renders this combination useless for biphasic catalysis. PEGs with higher molecular weight are waxy solids, but exposure to high pressure CO_2 lowers their melting point enough to make them suitable as solvents for homogeneous catalysis. As in the IL/CO_2 system, carbon dioxide allows for an efficient recovery of the reaction products, leaving the catalyst in the PEG phase.

In chapter 3 of the thesis a completely new strategy for multiphasic catalysis will be reported. This will involve the combination of carbon dioxide with metal complexes containing poly(ethylene glycol) modified phosphine ligands, and using no other solvents. This approach leads to a system which is fully homogeneous under the reaction conditions. Precipitation and separation of the catalyst from the reaction products is possible by pressurizing with carbon dioxide, thus taking advantage of the peculiar phase behavior of the PEG-modified catalyst and the supercritical fluid. No other examples of the combination of CO_2 with PEG-modified ligands have been reported in the literature to date, although hydroformylation in the presence of supercritical carbon dioxide using seemingly insoluble metal complexes has been already reported.[37]

As a general conclusion of this introductory chapter, it should be pointed out that in the field of *green chemistry* there are ever increasing efforts toward finding alternative and more efficient strategies for the immobilization of organometallic catalysts. Obviously all the possible alternative approaches for catalyst recycling can not be described in full detail here. Thermal methods, catalyst heterogenization and membrane technology are other valid alternatives that are attracting interest. However, biphasic (liquid/liquid or liquid/"supercritical") systems seems to be one of the most promising approaches. The crossover between homogeneous and heterogeneous system appears ideal for combining their respective advantages for metal catalyzed reactions. In this context, the use of non-traditional solvents, either alone or in combined systems, represents a major step toward this achievement.

1.3 Aim and scope of this thesis

The target of the research reported in this thesis was the development of an effective strategy for the efficient recycling of a multipurpose catalyst. Ideally, the immobilized metal complex should act as a *catalyst cartridge* applicable in a variety of catalytic reactions without using any volatile organic solvents but only carbon dioxide. In this case carbon dioxide has the function of mobile phase, increases the reactivity, dissolves reagents in the catalytic phase and allows products isolation in a solvent and metal free manner. As mobile phase, supercritical or simply compressed carbon dioxide would allow an efficient separation of products from the metal complex so that the *cartridge* can be used again either for the same reaction with a different substrate, or as a greater challenge for a completely different reaction.

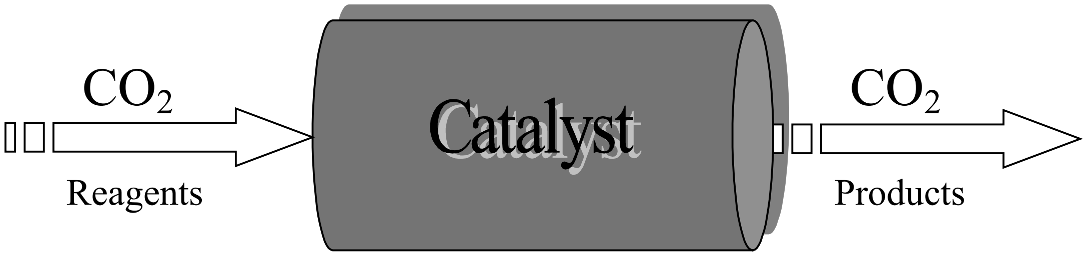


Figure 1-4: Ideal *catalyst cartridge* for multipurpose catalysis in a generic multiphase catalytic reaction.

In order to fulfill these difficult tasks two new approaches toward multiphase catalysis will be explored: the potential of carbon dioxide combined with ionic liquids in one case, and with poly(ethylene glycol) modified phosphine ligands in the other, will be extensively treated in the following chapters.

Considering the first approach in more details, two established types of organometallic catalysts have been applied for the hydrovinylation of aryl olefins and the hydrogenation of substituted C-N double bonds, using a combination of compressed, liquid or supercritical carbon dioxide with ionic liquids. Since ionic liquids and carbon dioxide contrast in almost every physical property, it is expected that the reaction performance of a generic catalyst should differ between the ionic liquid alone and in the combined system. Furthermore, the performance would be expected to differ in different ILs. Thus, it is expected that there is no universal ionic liquid but a specific one will be required for each reaction.

In these systems, the catalyst will be dissolved in the ionic phase leading to a homogeneous system. The second phase should contain catalyst-free carbon dioxide and reaction products. Recycling is carried out using a stream of compressed carbon dioxide which will be expanded into a cold trap where products will be collected free of solvent and metal. Furthermore, some fundamental properties of the IL/CO_2 system will be explored in order to understand specific features of this biphasic system. The final aim is to develop an effective methodology not limited to a batch-wise recycling approach, but with continuous extraction of reaction products.

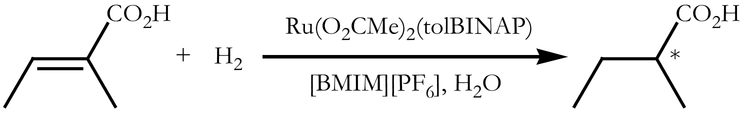
The second strategy toward multiphasic catalysis discussed in the thesis deals with the application of a poly(ethylene glycol) modified rhodium catalyst in a variety of reactions. Phosphine ligands containing poly(ethylene glycol) chains of various length are synthesized in order to obtain a rhodium catalyst of appropriate solubility properties. No other volatile organic solvent is used during the catalytic reactions. Since poly(ethylene glycol) of high molecular weight is known to be not soluble in supercritical carbon dioxide, the recycling of the catalyst and extraction of the reaction products should be possible by optimization of the pressure e temperature of the reaction vessel. The phase behavior between PEG-modified complexes and carbon dioxide is expected to correlate with the length and the number of poly(ethylene glycol) chains in the phosphine ligand. Design of a ligand which is soluble in the substrate but insoluble in carbon dioxide is a key feature of this project. This new *green* protocol is intended to leave the metal catalyst in the reactor completely free of reaction products and reagents. Thus, the same catalyst can potentially be used to carry out another cycle with a different substrate or even a different reaction. Here the main scope is to build up a multipurpose *catalyst cartridge*, avoiding any VOCs by the use of only carbon dioxide.

2 Catalysis in ionic liquid/carbon dioxide

2.1 Current Status of the field

Supercritical carbon dioxide (see chapter 2.2.1) and Ionic liquid (see chapter 2.2.2) are finding ever increasing interest as new biphasic system for organometallic catalysis. Both solvents have been largely used alone as solvent for various reactions although they both present some limitations. Used in combination, their different miscibility leads to a biphasic system whose success for catalytic applications is based on the solubility of carbon dioxide in the ionic liquid and, at the same time, on the insolubility of the IL in CO_2. Brennecke and co-workers where among the first to fully investigate the particular phase behavior of IL/CO_2,[32] some details will be discussed in chapter 2.2.3. They reported about the extraction of naphthalene from [BMIM][PF_6] with supercritical carbon dioxide. The aromatic compound was successfully extracted and the ionic liquid recovered in a pure form. Furthermore, without a large expansion in volume, the ionic liquid phase may contain more than 0.6 mol fraction of carbon dioxide depending on the pressure.

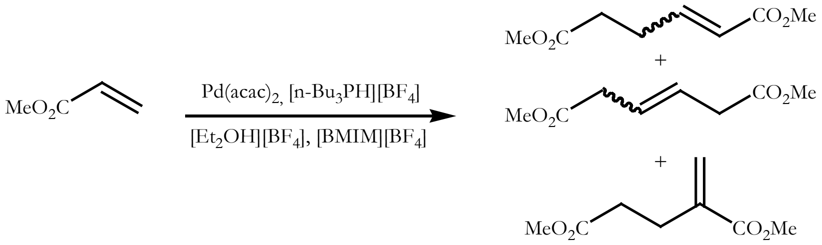
Since this seminal work, some publications have been appeared on organometallic as well as enzyme-catalyzed reactions in this biphasic system. Both batch and continuous flow processes were developed. Chiral ruthenium catalysts based on BINAP-type ligands were used for enantioselective hydrogenation of α,β-unsaturated acids in [BMIM][PF_6].[38] For some substrates, the outcome of the reaction is strongly influenced by the addition of protic co-solvents such as water or isopropanol. Carbon dioxide was used to extract the products and recycle the metal catalyst which showed stable activity and selectivity for at least 5 cycles.



Scheme 2-1: Enantioselective hydrogenation of tiglic acid in wet ionic liquid.

The Wilkinson's catalyst $RhCl(PPh_3)_3$ was used in the biphasic system [BMIM][PF_6]/scCO_2 for the hydrogenation of 1-decene and cyclohexene.[39] The reaction mixture consisted of a colorless carbon dioxide phase above a yellow ionic liquid. Product recovery and catalyst recycling were demonstrated with the hydrogenation of 1-decene. The rhodium catalyst was recycled up to four times without loss of activity. Besides, the hydrogenation of CO_2 in the presence of dialkylamines to give *N,N*-dialkylformamides was carried out in IL/CO_2 using some ruthenium complexes.[39] Here the ionic liquid dissolves the ruthenium catalyst and leads to a distinct phase distribution of the polar carbamate intermediates and the less polar products formed during the conversion of CO_2. As result the selectivity of the reaction is increased in comparison with the use of $scCO_2$ as the sole reaction medium.

The ionic liquid [BMIM][BF_4] was used in combination with carbon dioxide for the palladium-catalyzed dimerization of methyl acrylate.[40] Turnover numbers up to 560 and turnover frequencies up to 195 h^{-1} were obtained under optimized reaction conditions. Furthermore, substrate and product distribution between the two phases and the extraction capability of carbon dioxide was investigated. The high solubility of the dimers in $scCO_2$ for pressure > 150 bar open the possibility to investigate the reaction under continuous flow conditions.

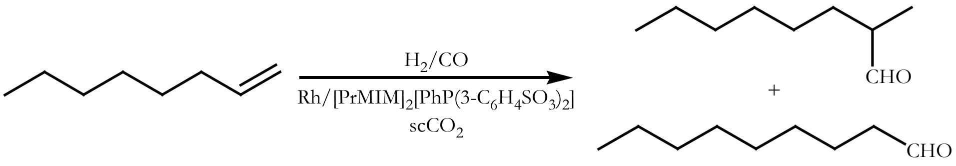


Scheme 2-2: Acrylate dimerization in IL/$scCO_2$ system.

As a more challenging task, ionic liquid and compressed or supercritical carbon dioxide may allow for continuous flow metal catalyzed reactions. To date only two examples are reported in the literature on this topic: the hydroformylation of long-chain alkenes[41] and the enantioselective hydrovinylation of styrene with the Wilke's complex.[42]

In the case of the hydroformylation the authors reported about some first attempt to perform the reaction using [BMIM][PF_6] and triphenylphosphite as the rhodium based ligand. Phosphite ligands proved to be incompatible with this ionic liquid because of small amounts of HF arising from the reaction of the anion with water, leading to catalyst deactivation.[41] Recycling in this case was not successfully. The use of sulfonated triphenylphosphines, for which both the ligands and the rhodium complexes are not soluble in supercritical carbon dioxide, showed low activity because of the low solubility in the ionic liquid.[41] Finally, the use of imidazolium salts of monosulfonated triphenylphosphine, e.g. [BMIM][Ph_2P(*m*-$C_6H_4SO_3$)], which combine chemical stability with high solubility in ionic liquid such as

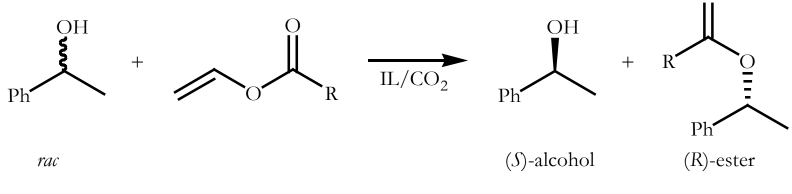
[BMIM][PF_6], opened the way for a very efficient catalyst system for the hydroformylation reaction in IL/CO_2 system.



Scheme 2-3: Continuous flow hydroformylation of 1-octene in IL/$scCO_2$ system.

The nickel catalyzed hydrovinylation of styrene will be discussed in details in chapter 2.3.

Ionic liquid/carbon dioxide system has been also recently proposed as reaction medium for biocatalytic transesterification reactions and kinetic resolution of 1-phenylethanol. In one case an aqueous solution of *Candida antarctica* lipase B (CAL B) was dissolved in [EMIM][BTA] or [BMIM][BTA] with glass wool. Both the synthesis of butyl butyrate from vinyl butyrate and butan-1-ol, and the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl propionate were selected as reaction models. In all cases, the synthetic activity of each enzyme-IL system was continuously tested by operation/storage cycles.[43] A suspension of CAL B in [BMIM][BTA] was used as the biocatalyst in the second example. The acylation of 1-octanol by vinyl acetate was investigated with a continuous flow system in which a $scCO_2$ stream, into which the reactants were injected, was flowed through the IL-suspended enzyme. The output was almost identical to the input, and the system operated for 24 h with a yield of 0.1 kg L^{-1} of reactor volume per hour.[44a] A continuous reaction system was also utilized for the kinetic resolution of racemic 1-phenylethanol by reaction with vinyl esters in the IL/enzyme suspension. Stepwise expansion of $scCO_2$ efficiently separated the unreacted (*S*)-alcohol from the converted (*R*)-ester.[44b]



Scheme 2-4: Continuous flow enzymatic kinetic resolution in IL/$scCO_2$.

The increasing interest toward application of IL/CO_2 systems may be related to the two main complementary characteristics of these two systems. Solubility and stability of organometallic or enzymatic catalysts in ILs and their very poor solubility in carbon dioxide on one side and generally high solubility of many reactants and products in carbon dioxide.

2.2 Properties of supercritical fluids and ionic liquids

2.2.1 Supercritical carbon dioxide

A supercritical fluid (SCF) is a compound at conditions above its critical pressure and its critical temperature (p_c, T_c), but below the pressure required to condense it into a solid.[6a] At the critical point the gas and the liquid phase merge together and become indistinguishable (see Figure 2-1).

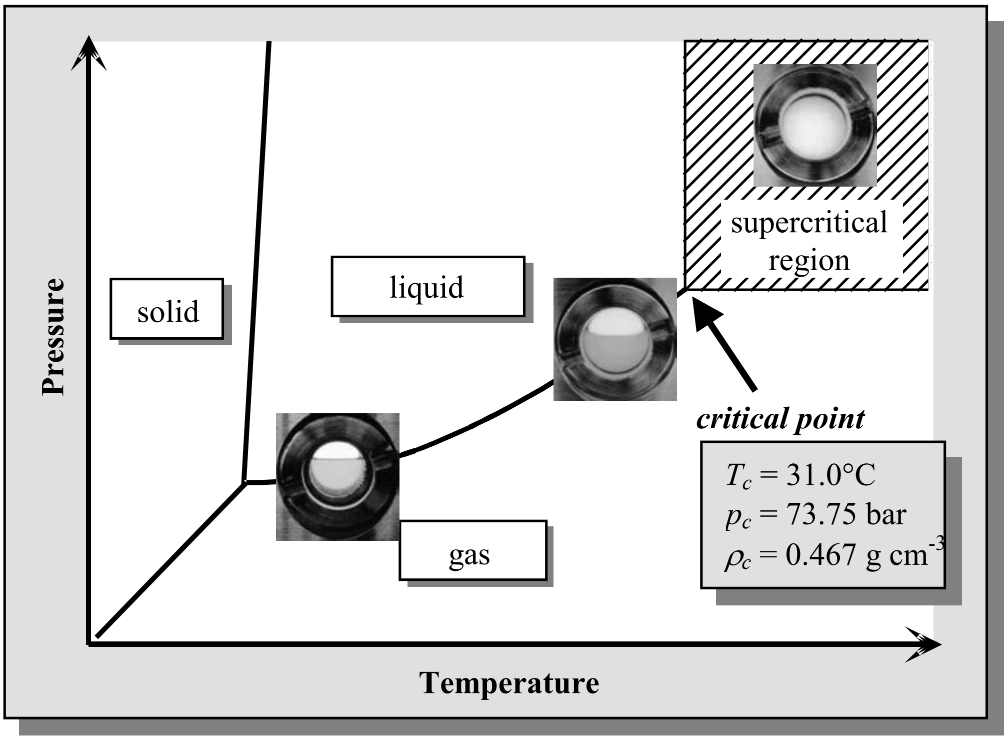


Figure 2-1: Section of the phase diagram of carbon dioxide. The pictures illustrate the vanishing of the meniscus which separate the liquid carbon dioxide phase from the gas at the critical point. A small amount of highly CO_2-soluble metal complex was added for a better contrast.

Supercritical fluids are often described using parameters called reduced temperature (T_r), reduced pressure (p_r) and reduced density (d_r). Those are defined as the actual value of temperature, pressure and density divided by T_c, p_c and d_c respectively. The law of the corresponding states implies that compounds behave similarly under the same values of reduced variables. Even if there are fairly large deviations in proximity of the critical state, it allows for the comparison of different compounds at various conditions.

$$T_r = \frac{T}{T_c} \Leftrightarrow p_r = \frac{p}{p_c} \Leftrightarrow dr = \frac{d}{d_c} \quad \textbf{(1)}$$

When discussing the properties of SCFs it is often useful to refer to a plot of the variation of the density (*d*) as a function of pressure and temperature. Figure 2-2 shows the density and the Hildebrand parameter for CO_2 as function of pressure at different isotherms.[45] Density changes continuously but rather sharply with variation of pressure in the compressibility region. For a certain temperature, increasing the pressure leads to higher value of density. For example at 37 °C the density of CO_2 is only 0.33 g mL^{-1} at 80 bar, but it rises to 0.80 g mL^{-1} at 150 bar.[46] On the other side, for a defined value of pressure, higher temperature gives lower density. The critical density (d_c) is the density value at the critical point and for CO_2 it is d_c = 0.467 g mL^{-1}. The plot in Figure 2-2 refers to the bulk density of CO_2, but locally the system may have fluctuations which lead to microscopic areas of increased or decreased density. This phenomena is known as local density augmentation and it is more pronounced very near to the critical point because of the high compressibility in this region. This characteristic may be used to determine, via scattering of visible light, the critical point of a fluid.

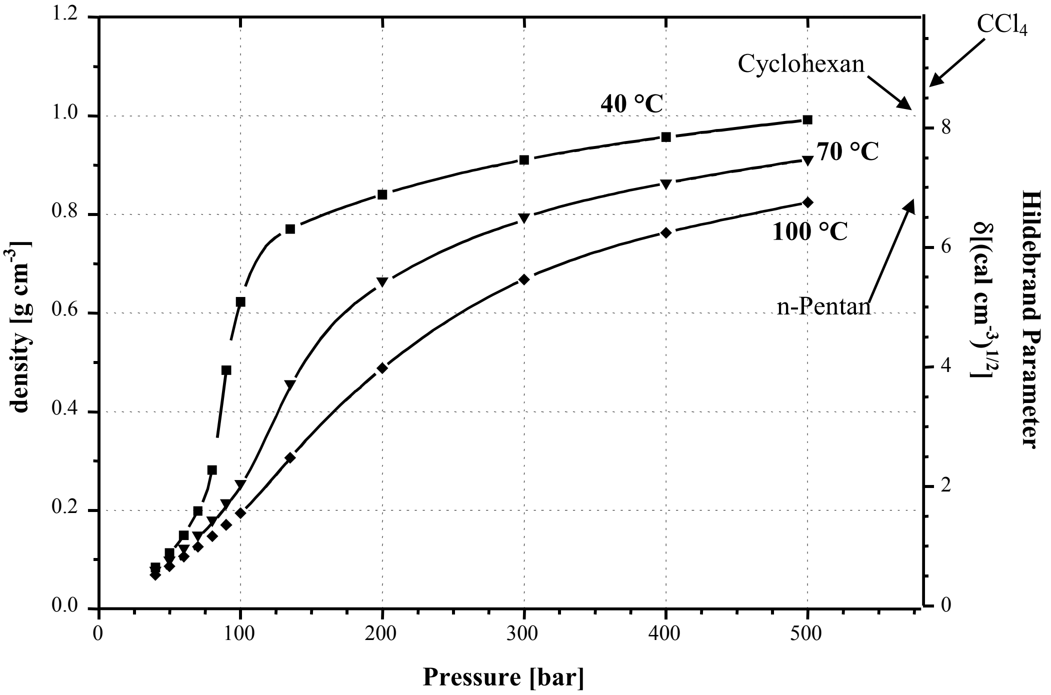


Figure 2-2: Plot of the density and the solvent power of $scCO_2$ as function of pressure at different temperatures.

Several solvent properties are directly related to the bulk density and will consequently have a pressure and temperature dependence similar to the curves shown in Figure 2-2. One of the most important is the so called "solvent power" of a fluid which provides the basis for the use of supercritical fluids for highly selective separation processes such as natural product extraction. Solvent power can be defined in various ways, a commonly used method being the Hildebrand parameter. This has been found to be directly proportional to the density of the SCF.[45b] On the plot in Figure 2-2, the solvent power of some typical organic solvents are marked on the Hildebrand scale in comparison with the tunability of carbon dioxide.

Another important parameter showing qualitative similar behavior is the dielectric constant ε. The absolute values of the variation in ε is directly related to the nature of the SCF (see Figure 2-3). Considering CO_2 at $T_r = 1$, ε varies from 1.3 at $d_r = 1$ to just above 1.6 at $d_r = 2$, which means that carbon dioxide remains a very non-polar solvent even for relatively large changes in pressure and temperature. For other more polar fluids, such as fluoroform or water, the same changes of density lead to rather drastic variations of ε.[6a]

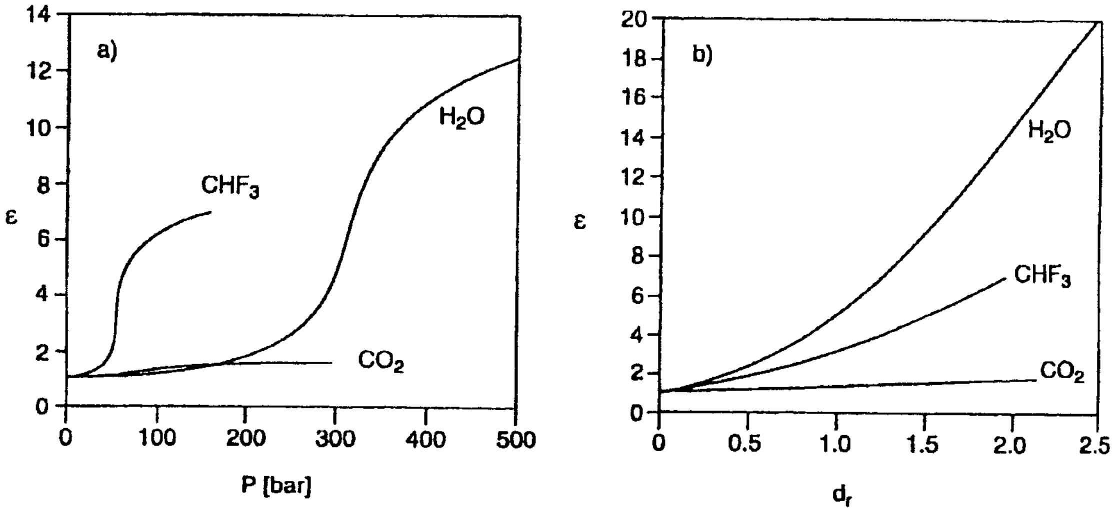


Figure 2-3: Variation of the dielectric constant of H_2O (at 400 °C, $T_r = 1.04$), CO_2 (at 40 °C, $T_r = 1.03$, and CHF_3 (30 °C, $T_r = 1.01$) as a function of pressure and reduced density. Taken from reference [6a].

Figure 2-4 further summarizes the variations of typical physico-chemical properties of carbon dioxide with pressure along a near critical isotherm. It is clear that those properties of the fluid can be altered drastically, from gas-like to liquid-like behavior by isothermally varying the pressure around P_c. The strongest variation of these properties is essentially concentrated around the critical point; further away from this point, all the properties become much less sensitive to pressure and temperature variations.[6a,47]

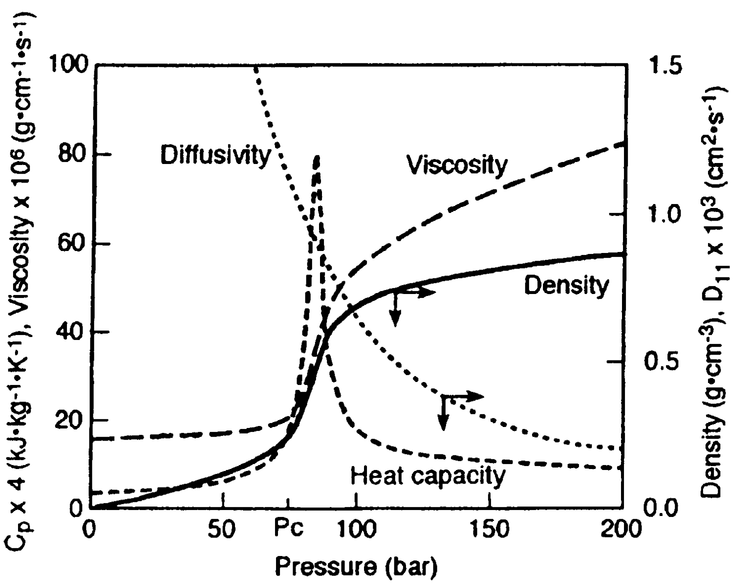


Figure 2-4: Variation of the physico-chemical properties as function of pressure in the vicinity of the critical point for CO_2 (Temperature for μ, ρ and C_p, 310 K; for D_{11}, 323 K). Taken from reference [47b].

The diffusion coefficient and viscosity represent transport properties that affect rates of mass transfer. In general these properties are at least one order of magnitude higher (diffusion coefficient), and lower (viscosity) in SCFs compared with liquid solvents. The diffusion of compounds in SCFs will occur at faster rates than in liquid solvents. However, this does not mean that all limitations of mass transfer will be absent in all SCF applications. Indeed, in the case of extraction of a solute from a liquid to a SCF phase, the resistance to diffusion in the liquid phase will probably control the overall rate of the mass transfer. As shown in Figure 2-4 for carbon dioxide, heat capacity reaches its highest value around the critical point having roughly the same values above or below the critical point.

All figures and diagrams shown so far are only valid for pure carbon dioxide. The phase behavior of mixtures is more complex. It is not sufficient to adjust the temperature and the pressure just above the critical values of the pure CO_2 to assure a single-phase system in the presence of other components. For example, a reaction mixture, a system made of at least three components (substrate, product and solvent), is already extremely complex. In most cases where even more components with variable composition are present, a full description of the phase behavior is a challenging task.[48] In order to fully exploit the physical properties of the supercritical state and to monitor the behavior of multiphase systems, it is mandatory to carry out chemical reactions in SCFs using a window equipped reactor that allows a visual control of the reaction mixture.

Figure 2-5: High pressure reactors used for exploratory studies on chemical synthesis using $scCO_2$.

The most important applications of SCFs are related to the solubility (y) of a compound in this media, defined in terms of mole fraction of the solute in the supercritical phase. From the ideal gas law, the solubility of a compound in a gas is given by its vapor pressure (p^{sat}) divided by the pressure (p). In the supercritical phase, however, the solubility is several orders of magnitude higher than the one predicted with the ideal gas law. This phenomenon is described with the enhancement factor E:

$$\text{Enhancement factor } E = \frac{yp}{p^{sat}} \quad \mathbf{(2)}$$

The E factor strongly depends on variations of density, and as a result, the solubility is strongly related to variations of pressure and temperature. As shown in Table 2-1, the solubility of a generic compound is related to its molecular interaction with the supercritical fluid.[6a,47] Fluoroform, which is a rather polar solvent and has the highest density at the given conditions, exhibits the lowest solubility of naphthalene, a nonpolar solute. On the other hand, ethane, a nonpolar solvent, but with much lower density, has the highest solubility of naphthalene. Supercritical carbon dioxide, a nonpolar solvent although with a quadrupole moment, has a very high density, as well as a significantly high solubility of naphthalene. Thus, the overall effect of polarity on the solubility of a compound follows in a first approximation the general rule of liquid extraction *"like dissolve like"*.

Table 2-1: Solubility of naphthalene in various SCFs at 200 bar and 45 °C.

Solvent	Solubility (mole fraction)	Density (g/mL)
Ethane	4.75×10^{-2}	0.39
Carbon dioxide	2.42×10^{-2}	0.81
Fluoroform	1.17×10^{-2}	0.94

Taken from reference [6a].

This simple analogy is however not sufficient to describe the solvent properties of SCFs. Figure 2-6 shows the solubility of naphthalene in supercritical carbon dioxide for three different isotherms. The symbols indicate experimental data, the lines are obtained *via* calculation methods, and the dotted line represents the ideal gas law.[49] Following one isotherm, the solubility changes drastically near the critical point whereas variations of solubility are much less pronounced at high pressure. This behavior simply reflects the rapidly increasing density around the critical point. The dependence of the solubility on temperature is generally more complex and involves considerations on the vapor pressure of the solute as well as on the density of the SCF.

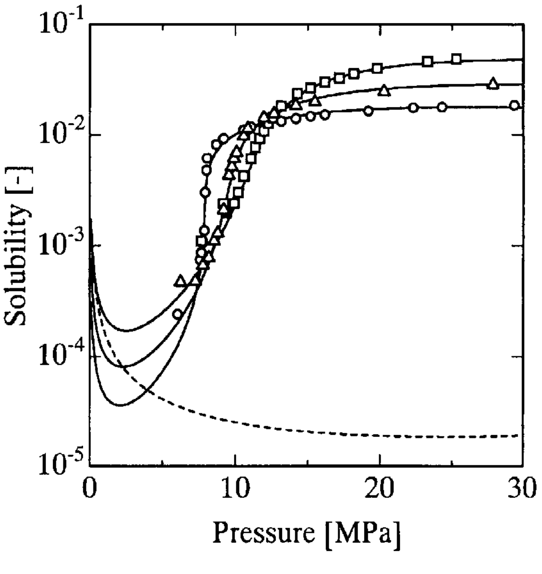


Figure 2-6: Solubility of naphthalene in carbon dioxide at (○) 35 °C, (▲) 45 °C and (□) 55 °C. (---) value obtained considering the ideal gas law at 55 °C. Taken from reference [49].

As shown in Figure 2-6 the isotherms intersect within a restricted region of pressure: the crossover of two lines divides the graph into the *retrograde region* on the left, and the *solute vapor pressure dominant* on the right. Between these two regions, there is a change in the temperature dependency of the solubility. In the left area, the solubility decreases as temperature increases because the density of the SCF falls sharply, even if the vapor pressure of the solute obviously increases. In the right region, the density of the system is less sensitive to pressure and the vapor pressure of the solute becomes dominant as solubility increases with the temperature.[6a,49]

In Figure 2-7, some of the most common SCFs are displayed as a function of their critical data.[6a] Carbon dioxide has very mild critical data that can be controlled readily in a laboratory and on an industrial scale. Carbon dioxide is surely the most widely used supercritical fluid also because of its non flammability, non toxicity and it is available in bulk with high purity. Furthermore, it is a good solvent for low to medium molecular weight organic substances. Ethane and ethene are marginally better solvents for non polar compounds but their flammability represents a major draw back for a broader application of these SCFs.

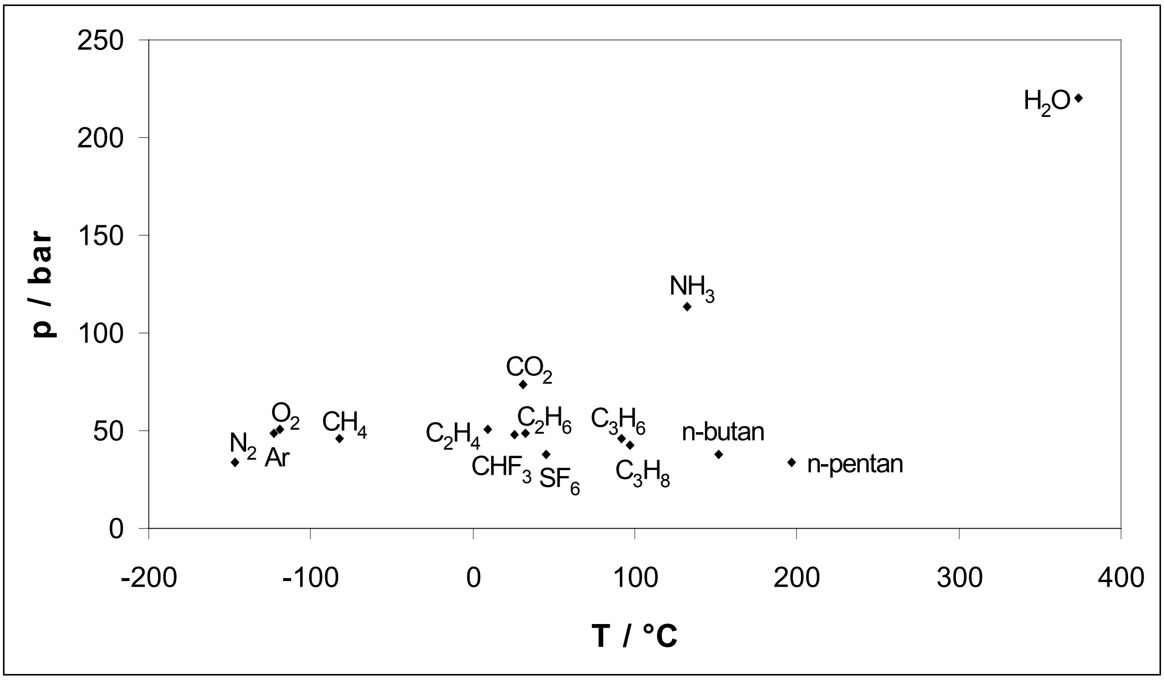


Figure 2-7: Critical data of some common supercritical fluids.

Supercritical water (SCW), despite its rather extreme critical data (T_c = 374 °C, p_c = 220.6 bar, d_c = 0.32 g/mL), has received much attention particularly for the treatment of organic waste.[50] It exhibits typical SCFs properties such as variation of the dielectric constant (ε), viscosity and density.[51] In addition, the unique behavior of SCW has its origin in the change of the intermolecular structure at elevated temperature, especially concerning the hydrogen bond network.[52] Structural studies of water in its liquid and supercritical state has been performed *via* calculation and neutron diffraction[53] in order to elucidate those changes on the molecular level. So far, the two different approaches still have a large level of discrepancy. In proximity of the critical point, the dielectric constant is reduced to the point that water behaves as a low polar organic solvent that dissolves non-polar organic waste. In the presence of an oxidant, ideally O_2, the organics will react to form mainly CO_2 and H_2O.

$$C_xH_y \;+\; (x+y)/4O_2 \longrightarrow xCO_2 \;+\; y/2H_2O$$

Scheme 2-5: Oxidation under supercritical water conditions (SCWO).

Supercritical fluids, when used as reaction media, can offer a certain number of potential advantages. Metal-complex-catalyzed reactions may benefit by being carried out in supercritical fluids as proven from the scientific work reported in the past 15 years.[29,54] As SCFs are able to dissolve various compounds, they can bring reagents in the same phase allowing for efficient reaction. Furthermore, gases such as hydrogen, carbon monoxide, *etc.* are miscible with SCFs, enhancing reaction rates where the concentration of those gases is a determining factor. SCFs may also induce separation of compounds from a reaction mixture allowing one to *switch-off* a particular reaction or, on the contrary, by pushing equilibria to completion. The diffusion coefficient is an important parameter that can influence reaction rates. This is normally much higher in supercritical fluids than common organic solvents. Consequently, reactions controlled by diffusion may be faster in supercritical solvents. Some SCFs, such as H_2O, NH_3 and MeOH, have certain reactivity and coordination capability, which may alter the course of a reaction. Even the inert CO_2 can have potential interaction with catalytic active intermediates. Carbon dioxide inserts into metal-hydride, -alkyl, -alkoxide or -amide bonds, thus it may be possible to use CO_2 as both solvent and feedstock at the same time.[55] Reactions in CO_2 may also be influenced by the interaction of reagents and/or products with the fluid, forming protecting groups.[56] However, these interactions may also negatively influence the performance of a catalyst. For example, CO_2 can be reduced to CO that can be a poison for some catalysts or reaction with dissolved water and alcohol can lead to the formation of inactive metal carbonates.[57] In biphasic water and carbon dioxide systems, the aqueous phase has a pH of around 3 which can cause deactivation of the catalyst.[35]

The solubility of a metal complex in carbon dioxide is surely a key point for the design and the application of a reaction in this medium. As previously mentioned, carbon dioxide remains a relatively non-polar solvent while metal complexes are very often charged compounds. Many catalysts are indeed not sufficiently soluble in liquid or supercritical carbon dioxide. A way to overcome this limitation is the use of CO_2-philic ligands framework to modify metal catalysts. Noyori and coworkers discovered that trialkyl phosphines complexes are more CO_2 soluble in comparison with triaryl phosphine complexes.[55] Leitner and co-workers developed the concept of binding CO_2-philic groups to a metal complex by using perfluorinated alkyl tails of type $(CH_2)_x(CF_2)_yF$.[12] These perfluorinated chains can be attached to the ligand with a straightforward synthesis and they do not interfere with the metal center if the electronwithdrawing perfluoromethylene groups are sufficiently far away from it. Furthermore, the metal complex modified with these chains provides a solubility which is enough for NMR spectroscopic investigations.[58] Tumas reported that even cationic complexes may be soluble enough in carbon dioxide for catalytic purposes if they contain a lipophilic conterion such as triflate (trifluoromethylsulfonate) or BARF (tetrakis-(3,5-bis(trifluoromethyl)-phenylborate).[59] The factors which may enhance the solubility of metal complexes in carbon dioxide can be summarized as follow: the ligand should contain few to no aromatic rings, should contain perfluoroalkyl, siloxyl or branched alkyl groups; complexes should be fairly volatile, non-polar, uncharged, hydrophobic and should contain many CO_2-philic groups; charged complexes should have a CO_2-philic counterion. With the proper design of the catalyst, the use of CO_2 can allow efficient recycling of the metal complex taking advantage of the CESS process (*C*atalysis and *E*xtraction using *S*upercritical *S*olutions).[6a]

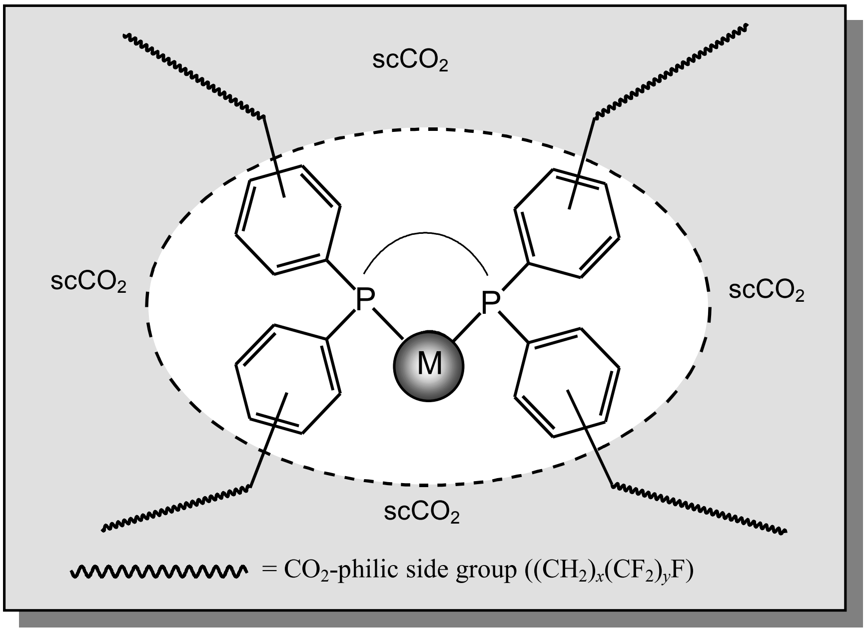
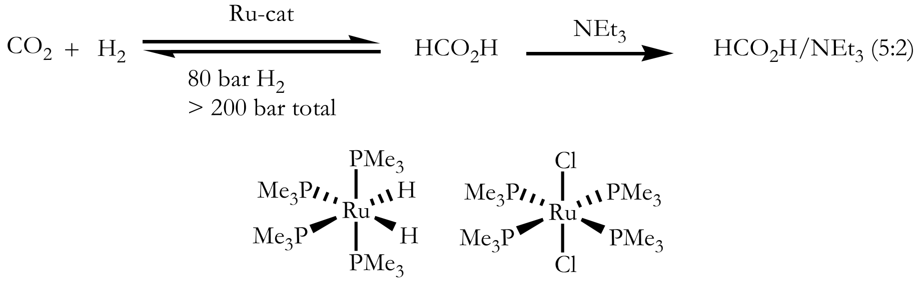


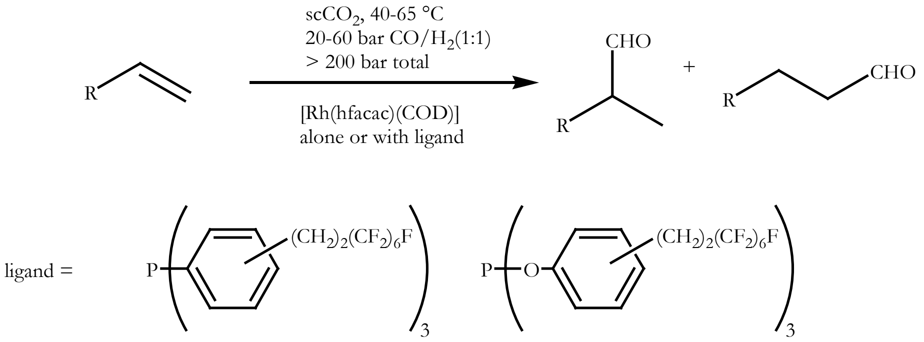
Figure 2-8: Phosphine metal complex containing perfluorinated CO_2-philic chains.

Supercritical carbon dioxide has a complete miscibility with other gases, and this can be particularly exploited in hydrogenation reactions. Noteworthy, the hydrogenation of carbon dioxide itself to formic acid catalyzed by ruthenium complexes has been reported by Jessop (see Scheme 2-6).[55]



Scheme 2-6: Ruthenium catalyzed hydrogenation of CO_2 under supercritical conditions and some ruthenium complexes used as catalysts or catalyst precursors.

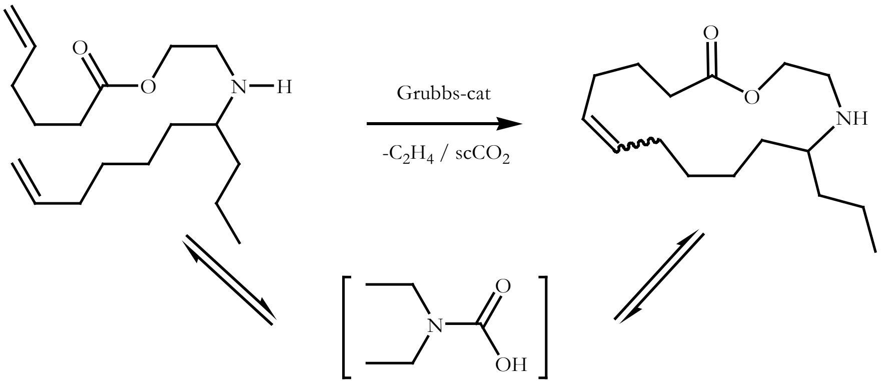
Hydroformylation is the addition of CO and H_2 to a double bond to form an aldehyde, and has been successfully applied in supercritical carbon dioxide using [Rh(hfacac)(cod)] either with perfluorinated phosphine ligands or as unmodified complex (see Scheme 2-7).[60]



Scheme 2-7: Rhodium catalyzed hydroformylation of olefins in supercritical carbon dioxide, R = C_6H_{13}. Perfluorinated ligands are often described with the notation x-H_yF_z indicating alkyl substituents of general formula $(CH_2)_y(CF_2)_zF$ with x giving the substitution position relative to the phosphorous atom.

The reaction rate has been found to be higher at supercritical conditions compared with common organic solvents. Furthermore, the hydroformylation of 1-octene has been carried out using the CESS methodology to recycle the catalyst with rather low rhodium leaching in the extracted products.[60]

The tuning capability of carbon dioxide may also have a very strong influence in the selectivity of a reaction. For example, the olefin metathesis of an unsaturated ester carried out in high density (high pressure) CO_2 leads preferentially to the ring closing metathesis product (RCM), whereas at low density (low pressure) the oligomers derived from acyclic diene metathesis (ADMET) are the major products.[56] The olefin metathesis in supercritical carbon dioxide also provides the first example of the use of CO_2 as solvent and reversible protecting group. Grubbs catalyst usually tolerates a wide variety of functional groups, but is deactivated by secondary or primary amines in conventional solvents. Dienes containing NH group will not give the RCM product in conventional solvents. Scheme 2-8 illustrates a successful example of RCM in supercritical carbon dioxide where the formation of the macrocycle is possible because of the reversible formation of the corresponding carbamic acid.



Scheme 2-8: Carbon dioxide as reversible protecting group and solvent in the RCM reaction.

As a general conclusion, the unique characteristics of supercritical fluids may offer many advantages when they are used as media for chemical reactions. Some SCFs certainly represent an environmentally friendly alternative to common organic solvents. In particular, this applies to water and carbon dioxide. CO_2 seems particularly attractive as it has already found industrial application in various technological areas.[7-9]

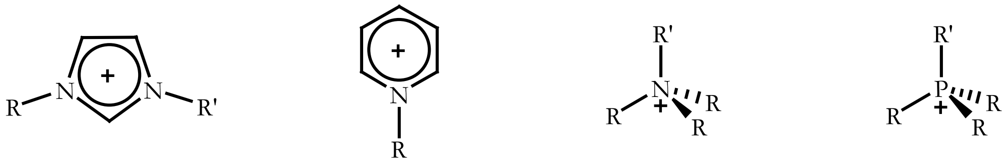
2.2.2 Ionic liquids

Low temperature molten salts, often nowadays referred to as ionic liquids (ILs) are liquids containing only ions, and represent a class of compounds that may be efficiently used as solvents. By choosing the right combination of cations and anions it is possible to prepare ionic liquids that are liquid at and below room temperature; these have been sometimes referred to as room-temperature ionic liquids (RTILs).[61] Many authors refer to ILs for salts with melting points below 100 °C. This choice, made on the premise of improving the range of uses of those salts, is rather arbitrary, and indeed a large number of synthetic applications can occur at temperatures far beyond that limit. Ionic liquids are not new, and some of them have been known for many years: $[EtNH_3][NO_3]$ (liquid at 12 °C) was first reported in 1914.[62]

In the late 1940s ionic liquids containing chloroaluminate anions were developed by Hurley and Weir for use in electrochemistry.[63] In the 1970s Wilkes, Hussey and Osteryoung developed 1,3-dialkylimidazolium salts again mainly for electrochemical applications.[64] Nevertheless, it has only been in the past few years that these materials have been proposed as attractive solvents for synthetic chemistry.[14a,65] In one of the first application, dated only in 1986, a chloroaluminate ionic liquid proved to be an efficient medium for Friedel-Crafts reaction.[65b] Since then, an ever increasing interest in these solvents has evolved for a variety of chemical transformations, essentially for the following reasons:

- They are capable of dissolving a large number of organic and inorganic compounds, allowing reagents to be brought in the same phase.
- They can be made of weakly coordinating anions.
- The may have coordinating anions which can interact with metal catalysts or reaction intermediates allowing, for example, enhancement of selectivity.
- They can be immiscible with many organic solvents, even with water, providing a new possibility for multiphase systems.
- They have negligible vapor pressure, so they are non-volatile and thus will not be emitted to the environment by evaporation. Volatile products can be removed readily by distillation.

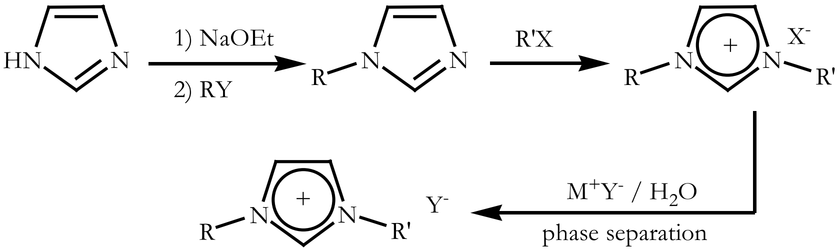
Figure 2-9 shows the most common cations used in their synthesis, although many others have been reported.



Imidazolium Pyridinium Ammonium Phosphonium

Figure 2-9: Important cations in ionic liquids.

Typical anions are $[PF_6]^-$, $[BF_4]^-$, $[NO_3]^-$, $[(CF_3SO_2)_2N]^-$, $[AlCl_4]^-$, $[CF_3SO_3]^-$, $[Cl]^-$, $[Br]^-$, but this list is far from exhaustive. The variety of possible combinations of cations and anions is one reason why ionic liquids have been referred to as "designer solvents".[66] The chloroaluminate based ionic liquids are moisture- and air-sensitive, react with alcohols and acetone causing obvious disadvantages. Since the synthesis of "neutral" ionic liquids based on anion such as $[BF_4]^-$ has been reported, research was strongly focused on this class of compounds. However, for many technical applications stability toward the hydrolysis of the anion of the ionic liquid has to be considered. If the anion of the ionic liquid is not stable against hydrolysis, HF or HCl may be liberate into the environment. Recently, the synthesis, characterization and catalytic application of several new halogen-free and hydrolysis stable ionic liquids have been presented.[67] A wide range of cations and anions is now known to be suitable for the creation of RTILs, allowing the synthesis of a plethora of different materials.



Scheme 2-9: Straightforward synthesis of imidazolium type ionic liquids.

The synthetic approach to some of the most common ionic liquids, typified by that for the imidazolium salts, is usually straightforward and a variety of 1-alkylimidazoles are indeed commercially available. They can be easily synthesized by deprotonation of imidazole using sodium ethanoate, followed by alkylation in ethanol or acetonitrile as a solvent.[68] The following alkylation step can be carried out without added solvent if the alkylating agent is liquid, or in methylene chloride or trichloroethane at reflux for several hours depending on the reactivity of the alkyl halide. In this way, for example, the 1-butyl-3-methylimidazolium chloride ([BMIM][Cl], melting point of 65 °C) can be synthesized in high yield and purity (see Scheme 2-9, first two steps). Once the halide salt is obtained, the next step is to perform the anion exchange using, in the easiest case, the water/methylene chloride biphasic system as shown in the second part of the scheme. Following this method, with $Na[PF_6]$ as source of anion, 1-butyl-3-methylimidazolium hexafluorophosphate ($[BMIM][PF_6]$) can be successfully synthesized as a colorless liquid which has a melting point below 0 °C. In some cases the anion exchange reaction can be performed in pure water and the immiscible ionic liquid can be easily separated. More detailed description of all the possible synthetic routes and purification methodologies of ionic liquids are described in reference.[14a]

Figure 2-10: Colorless sample of the ionic liquid [BMIM][PF_6].

Most of the recently reported ionic liquids are claimed to be air and moisture stable, as opposed to halogenoaluminate types which are rather difficult to handle. However, most ammonium and imidazolium salts are hygroscopic, a factor that must be taken into account while using these salts as solvents. As mentioned they have no measurable vapor pressure, allowing effective product isolation by distillation. However, this simple approach requires some consideration of their thermal stability. The thermal stability of ionic liquids depends on the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds. As a general rule, ammonium and phosphonium salts are generally less thermally stable than imidazolium based ionic liquids. For example, [EMIM][BF_4] has been reported to be stable up to 300 °C,[69] and some ionic liquids have shown stability up to 400 °C, indicating a wide margin for possible application in organic and organometallic reactions.

The melting point of ILs is clearly one of their most important characteristics, and at the same time, with some limitations, one of the most rationalized so far. With regard to the cation, low symmetry, good distribution of the charge, and weak intermolecular interactions can lower the melting point (see Figure 2-11).[70]

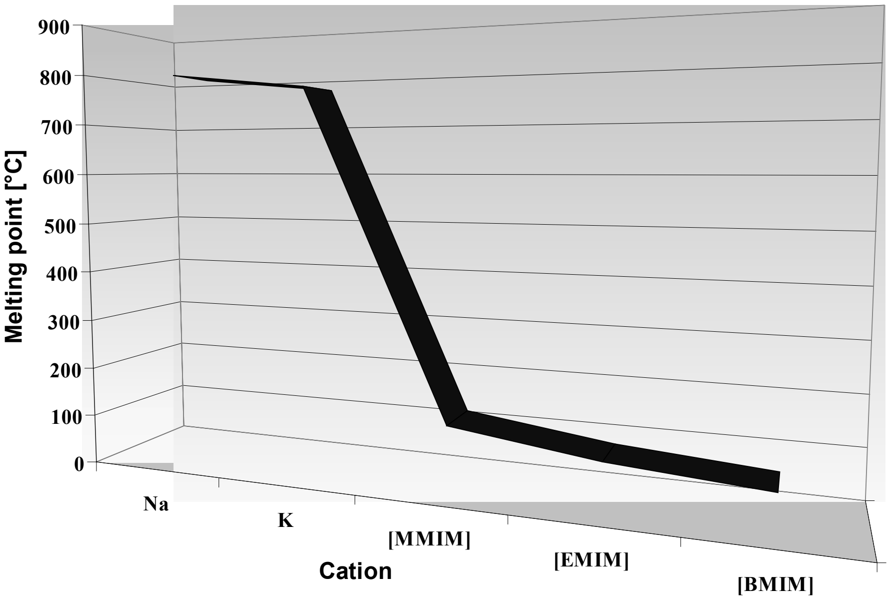


Figure 2-11: Influence of different cations on the melting point of chloride salts.

Concerning the anion influence, in most cases increased size and delocalization of the negative charge lowers the melting point.[70] Table 2-2 shows the temperature dependence for some ethyl-methylimidazolium salts with a variety of anions. The easily available chloride salt already has a melting point below 100 °C so it can be considered as an ionic liquid with respect to the general definition. The tetrafluoroborate has a melting point below room temperature while the trifluoroacetate salt melts below 0°C.

Table 2-2: Temperature dependence of the melting point of $[EMIM]^+$ ionic liquids as function of anions.

Imidazolium salt	Melting point [°C]
[EMIM][Cl]	87
$[EMIM][NO_3]$	38
$[EMIM][AlCl_4]$	7
$[EMIM][BF_4]$	6
$[EMIM][CF_3SO_3]$	-9
$[EMIM][CF_3CO_2]$	-14

Adapted from references [70a].

The tuning of solubility properties of ionic liquids represents an important feature of these solvents. Non polar octene, a model substrate for the hydroformylation reaction, can have improved solubility by some modification in the structure of the cation. Generally, increasing the nonpolar character of the cation leads to an increase of the octene solubility. For example, the solubility of octene in 1-alkyl-3-methyl imidazolium ionic liquids significantly increases on increasing the length of the alkyl chain.[71] On the other hand, the influence of the anion on solubility properties is demonstrated for the example by a selection of $[BMIM]^+$ salts: the chloride, bromide and acetate are water soluble whereas the hexafluorophosphate, bis(trifluoromethylsulfonyl)imide give biphasic systems with water.[68]

Other important characteristics of ionic liquids are density and viscosity. The comparison between several chloroaluminate and bromoaluminate imidazolium based ionic liquids reveals that there is an almost linear relationship between density and the length of the *N*-alkyl chain in the imidazolium cation.[72] Variation of the anion leads to certain density ranges within which a fine adjustment is possible by choice of the cation.[68] Viscosity in ionic liquids appears to be governed essentially by van der Waals and H-bonding interactions. The structure of the cation can have a major influence on viscosity. Alkyl chain lengthening or fluorination as well as alkyl chain ramification increases viscosity.[68]

The acidity and the coordination capability of an ionic liquid is essentially related to its anion. Many strongly basic/coordinating or strongly acidic/non-coordinating ILs may be synthesized by careful selection of the anion (see Table 2-3).[73] Again, a large number of combinations are possible meaning that fine tuning of the ionic liquid is possible.

Table 2-3: Coordinative characteristic of various anions.

Basic/strongly coordinating			**Neutral/Weakly coordinating**		**Acidic/non-coordinating**	
$[Cl]^-$	$[Ac]^-$	$[SO_4]^{2-}$	$[AlCl_4]^-$	$[SbF_6]^-$	$[Al_2Cl_7]^-$	$[Al_3Cl_{10}]^-$
	$[NO_3]^-$		$[CuCl_2]^-$	$[BF_4]^-$	$[Cu_2Cl_3]^-$	$[Cu_3Cl_4]^-$

Adapted from references [70a].

Conductivity is also an important characteristic of ionic liquids related to the ion mobility and to the number of charge carriers. Conductivity can be defined as:

$$\sigma = \sum n_i \mu_i q_i \quad (3)$$

where n_i is the number of charge carriers of species i, q_i the charge and μ_i the mobility.[74] Therefore, conductivity of ionic liquids depends mainly on viscosity which influences ion mobility. In addition, the effect on the ion size must be stressed as well, as anions of smaller size lead to higher conductivity.[68] Table 2-4 shows viscosity, conductivity and density values for some common ionic liquids. Viscosity and conductivity of ionic liquid in presence of carbon dioxide will be discussed later in this chapter.

Table 2-4: Viscosity, conductivity and density for some ionic liquids.

Ionic liquid	**Viscosity** (cP (0.01 g cm^{-1} s^{-1}))	**Conductivity** (mS cm^{-1})	**Density** (g cm^{-3})
[MMIM][BTA]	44	8.4	1.559
[BMIM][BTA]	52	3.9	1.429
[*i*BMIM][BTA]	83	2.6	1.428
[CF_3CH_2MIM][BTA]	248	0.98	1.656
[BMIM][CF_3SO_3]	90	3.7	1.290
[BMIM][CF_3CO_2]	73	3.2	1.209
[BMIM][$CF_3(CF_2)_3SO_3$]	373	0.45	1.473

Adapted from reference [68].

Solvent polarity is a physical property which may influence the outcome of a chemical reaction and it should be considered when using ionic liquids as solvents. The classical concept of polarity as related to molecular dipoles is not directly transferable to a solvent consisting of discrete ions. However, it is possible to refer to an empirical scale of solvent polarity using solvatochromic dyes. These are compounds which display a shift in emission or absorption band maxima according to the polarity of the solvent in which they are dissolved.[75] Nile Red is a common dye used for this purpose and it has also been used to determine ionic liquid polarity. Nile Red is positively solvatochromic, which means that when dissolved in solvent with an increased polarity the wavelength of its visible absorption maximum (λ_{max}) moves to longer wavelengths (lower energies). Among positively solvatochromic dyes, Nile Red displays one of the largest bathochromic shift known. For example, changing from pentane to water, λ_{max} increases by 110 nm.[76] Using this methodology polarity of a variety of ionic liquids have been measured.[77] For $[BMIM]^+$ based ionic liquids, polarity decreases with increasing anion size suggesting that the negative charge becomes less available for interaction with the solute. A variation of alkyl substituent chain length in the cation can also influence polarity: from 4 to 6 carbon atoms polarity increases, decreasing again for longer chains. Some of these data are shown in Table 2-5.

Table 2-5: λ_{max} and molar transition energies (E_{nr}) for ionic liquid [XMIM][Y] and common conventional solvents.

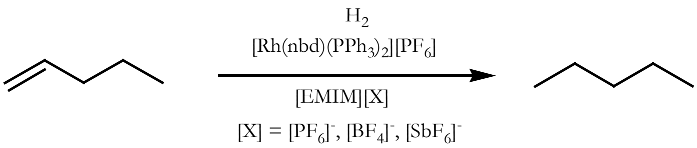
Ionic liquid	λ_{max} (nm)	E_{nr} (kJ mol^{-1})
[BMIM][NO_2]	556.0	215.1
[BMIM][BF_4]	550.8	217.2
[BMIM][PF_6]	547.5	218.5
[BMIM][BTA]	548.7	218.0
[HMIM][PF_6]	551.7	216.8
[HMIM][BF_4]	551.9	216.8
Methanol	549.5	217.7
Ethanol	548.4	218.2
1-butanol	547.5	218.5

$E_{nr} = (h\ c\ N_A / \lambda_{max})\cdot 10^6$, where h is Planck's constant, c is the speed of light, N_A is Avogadro's number and λ_{max} is the wavelength of maximum absorption (nm). Adapted from reference [77].

The results of this study represent only a snapshot and do not give a complete answer regarding the polarity of ionic liquids, but indicates their relative polarity and trends within the series. The authors conclude that all ionic liquids tested are in the same range of polarity of solvents such as methanol, ethanol and 1-butanol, according to the relative polarity scale made by Deye.[76] Besides, solvent polarity has been also investigated from other authors using different dyes but still a complete description of polarity of ILs has not been achieved.[78,79,80,81,82]

Another important characteristic of ILs is their miscibility with other liquids. They are generally miscible with liquids that have medium and high dielectric constants: short chain alcohols and ketones, dichloromethane, THF. On the other hand, they are largely immiscible with less polar solvents such as toluene, diethyl ether, alkanes, dioxane.[68]

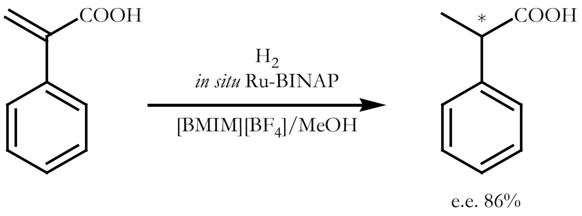
As mentioned, ionic liquids can dissolve many organic and organometallic compounds, therefore are possible solvents for homogeneous catalytic reactions. Depending on the coordinative properties of the anion, they can be regarded as an "innocent" solvent or as a co-catalyst. Chauvin and co-workers reported about the first example of immobilization of a rhodium complex in a biphasic system without the use of specially designed ligands. The hydrogenation of 1-pentene was successfully achieved by the complex $[Rh(nbd)(PPh_3)_2][PF_6]$ immobilized in [BMIM][X] ([X] = PF_6^-, BF_4^-, SbF_6^-), see Scheme 2-10.[83]



Scheme 2-10: Biphasic hydrogenation of 1-pentene in [BMIM][X] ionic liquids.

Although the reactants have only a limited solubility in the ionic liquid, high reaction rates were obtained. All catalytic solutions could be recycled and rhodium leaching was below the detection limit of 0.02%. The authors observed that traces of chloride in the ionic liquid caused the suppression of the hydrogenation reaction and poisoning of the catalyst. This factor will be discussed further in chapter 2.4.2.

Enantioselective hydrogenation in ionic liquid is also possible. One example is the hydrogenation of 2-arylacrylic acid to 2-phenylpropionic acid with Ru-BINAP in $[BMIM][BF_4]$ see Scheme 2-11.[84]



Scheme 2-11: Ruthenium catalyzed enantioselective hydrogenation of 2-arylacrylic acid in $[BMIM][BF_4]$.

The reaction is performed in $[BMIM][BF_4]$ with methanol or 2-propanol as co-solvent, and the catalyst can be reused with the same activity and selectivity after separation of the hydrogenated products. Hydrogen solubility in $[BMIM][PF_6]$ was sufficient to guarantee fairly good reaction rates and selectivities in the example reported. Nevertheless, solubility of hydrogen in ionic liquids seems to be of crucial importance to determine whether the ILs are appropriate for hydrogenation reactions or not. Substrates for enantioselective hydrogenation are conveniently grouped in two categories: substrates for which high concentration of H_2 leads to high enantiomeric excess and substrates for which high enantioselectivity is obtained at low concentration of H_2.[85] With high pressure NMR techniques[86] it has been possible to determine the solubility of hydrogen in a variety of ionic liquids (see Figure 2-12). The measurement of hydrogen solubility and the Henry's constant at atmospheric pressure was not possible because the dissolved hydrogen was below the detection limit of the method. In all cases tested, a pressure of 100 bar was necessary to clearly resolve the hydrogen peak and to integrate it relatively to the solvent peak. Solubility of hydrogen has been calculated as varying between $0.62 \cdot 10^{-3}$ and $0.98 \cdot 10^{-3}$ mol L^{-1} at 1 atm. This hydrogen availability is lower than in common organic solvents (methanol $3.75 \cdot 10^{-3}$ mol L^{-1}, toluene $3.5 \cdot 10^{-3}$ mol L^{-1} and cyclohexane $3.63 \cdot 10^{-3}$ mol L^{-1} at 1 atm).[87] From these studies, one could predict that enantioselective hydrogenation of substrates which favor low hydrogen concentration can be successfully performed in ionic liquids. When high hydrogen availability is needed ionic liquids may not be the right solvent choice.[88] Obviously, low concentration/availability of hydrogen in general can potentially influence reaction rates in a negative manner, although this was not observed in the reported example.[87] The combination of an ionic liquid with compressed or supercritical carbon dioxide may have a dramatic effect on hydrogen solubility as will be discussed in the following chapter.

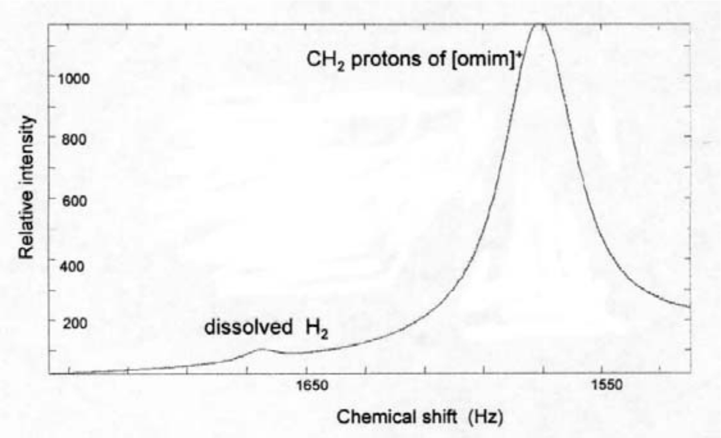
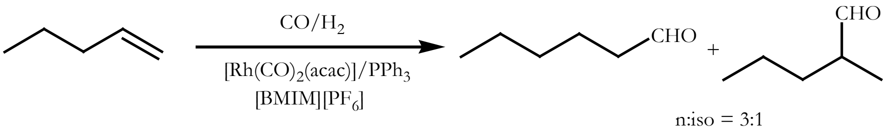


Figure 2-12: Determination of hydrogen solubility with high pressure NMR technique. The dissolved dihydrogen was integrated relative to the methylene protons of [OMIM][BF_4] (1-octyl-3-methylimidazolium tetrafluoroborate). Taken from reference [87].

Hydroformylation reactions, either platinum-, cobalt- or rhodium-catalyzed, have also been tested in ionic liquid media.[89] The hydroformylation of 1-pentene has been investigated in room temperature molten salt using $[Rh(CO)_2(acac)]/PPh_3$.[83,90] For example, in [BMIM][PF_6] a TOF (turn over frequency) up to 333 h^{-1} has been achieved despite of the low substrate solubility in the IL. Furthermore, the biphasic system allowed a simple catalyst recovery and product separation. However, leaching of the catalyst in the organic phase was observed.

Replacing the triphenylphosphine with monosulfonated triphenylphosphane (tppms) suppressed this drawback, but the activity of the system was much lower.



Scheme 2-12: Rhodium catalyzed hydroformylation of 1-pentene in [BMIM][PF_6].

The importance of ionic liquids as solvents for organic reactions and metal catalyzed reactions is growing continuously as demonstrated by the large number of scientific publications appearing over the last few years.[91] This interest is not only due to their environmental friendliness, which has still to be confirmed in many aspects,[92] but also due to their potential benefit arising from their use in metal catalyzed reactions.

2.2.3 Properties of ionic liquid/carbon dioxide systems

2.2.3.1 Literature survey

Ionic liquids have a substantial advantage over common organic solvents: they have a vanishingly small vapor pressure.[14a] For this reason they can be potentially used as a replacement of organic solvents in traditional processes in order to eliminate the large volume of fugitive emissions typical of VOCs. Research in the field of ionic liquids has mainly been focused on their applicability as solvents for chemical reactions[31,70] while investigation and development of separation methods is relatively unexplored. Distillation (or evaporation) is one of the most common methods although it can not be utilized for thermally labile or low volatility compounds. Solvent extraction or phase separation are also possible, with the limitation that in the first case VOCs are used. Some ILs are not miscible with water and this surely represents a *green* alternative for extraction of water-soluble compounds. Recently, Rogers and co-workers developed a reversible pH-dependent liquid-liquid partitioning of a solute between water and ionic liquid phase.[93] Cross-contamination as well as partitioning of solute between the two phases limits the extent of solute extractions.

Another option, first introduced by Brennecke and co-workers, involves supercritical fluids extraction using CO_2 as second phase.[32,94] Quantitative extraction of naphthalene from 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) with supercritical carbon dioxide was successfully demonstrated in this example. Subsequent work has shown that a wide variety of other solutes can be extracted from [BMIM][PF_6] with CO_2 with quantitative recovery of products.[94] These works have shown that supercritical carbon dioxide extraction is a viable method for isolation of solutes from ionic liquids. The phase behavior of IL-CO_2 systems is of crucial importance to take full advantage of this methodology. Ionic liquid-carbon dioxide systems are indeed a fairly unusual biphasic system: although a large quantity of carbon dioxide is dissolved in the lower ionic phase, no measurable amount of ionic liquid is present in the CO_2 phase. The system remains biphasic even at very high pressure of carbon dioxide.[32] This unique phase behavior has no precedent if compared with any common liquid/CO_2 systems[95] and it makes such extraction processes extremely attractive. Indeed, no ionic liquid would be present in the extracted product, and carbon dioxide can be released by depressurization leaving a pure solute at the end of the extraction process.

Solubility of carbon dioxide in the binary system [BMIM][PF_6]/CO_2 has been measured at various temperatures.[32b] The mole fraction of carbon dioxide in the ionic liquid tested increases dramatically with increasing pressure, reaching 0.72 mole fraction at 40 °C and 93 bar. As expected, increasing the temperature has the opposite effect of reducing CO_2 solubility, although this temperature dependence is much less pronounced than the pressure effect. The large degree of carbon dioxide solubility in the ionic phase is reflected in a reduction of the viscosity of the liquid which is macroscopically observed by the reduced drag on the stirring magnet. Figure 2-13 shows the solubility of carbon dioxide in [BMIM][PF_6].

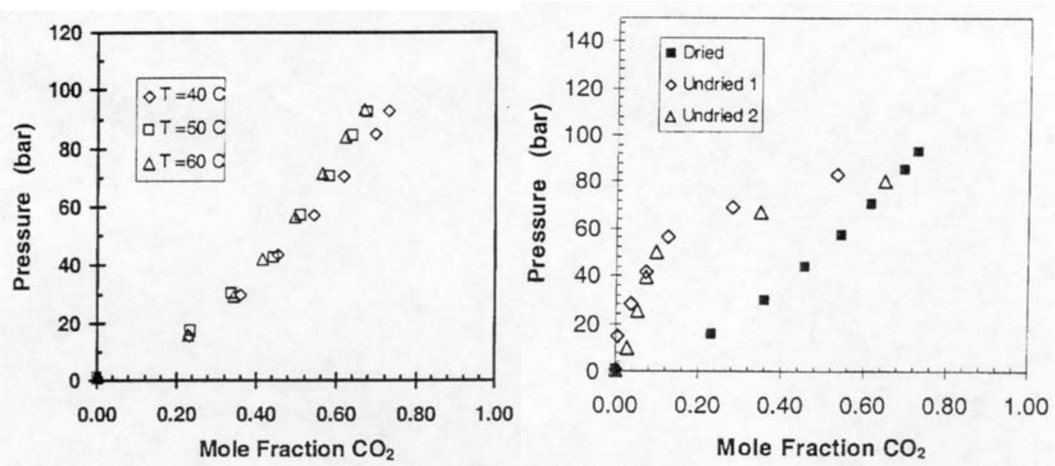


Figure 2-13: Mole fraction of carbon dioxide in [BMIM][PF_6] as function of temperature (left) and as function of water content (right). Taken from reference [32b].

Carbon dioxide solubility in ionic liquids can be influenced by the presence of water in the ionic solution. Looking at figure Figure 2-13, the plot on the right shows the solubility of CO_2 in two wet samples of ionic liquid in comparison with a dried one. The difference in CO_2 solubility at 57 bar is large: 0.54 mole fraction for the dried sample compared to 0.13 for the water-saturated sample.[32] This difference in phase behavior is not surprising considering the known CO_2-phobic characteristics of water, as seen from the mutually low solubility of water and carbon dioxide even at high pressure.[96] Furthermore, the formation of carbonic acid resulting from the reaction of CO_2 and water results in a reduction of the aqueous phase pH to about 3.[35] Thus, considering potential catalytic applications of IL/CO_2 systems, drying of the ionic solution prior to use may be of dramatic importance to obtain good results in catalysis. The high solubility of carbon dioxide in ionic liquids seems to be a general characteristic of this biphasic system. In general, ILs containing fluorinated anions display higher CO_2 solubility. In particular, ionic liquids with the $[PF_6]^-$ anion have the greatest CO_2 solubility among those measured while $[BF_4]^-$ based ionic liquids show approximately 10% lower solubility of CO_2. The solubility of ionic liquids in the CO_2-rich phase has also been investigated using UV-VIS. No appreciable absorption peak corresponding to the imidazolium cation was observed, indicating a solubility lower than $5 \cdot 10^{-7}$ mol L^{-1} in the CO_2-rich phase.[32b] This observation is of fundamental importance for the application of this new system in biphasic catalysis, as will be discussed further in the present thesis.

Another interesting physical property of the IL/CO_2 system is their volumetric behavior. Dilation of a liquid is a well-known phenomenon resulting from dissolution of gases into liquids. For example, a toluene-CO_2 system at 40 °C and 70 bar will give a 134% increase in volume of the liquid organic phase compared with the same solvent in absence of CO_2. The dissolution of CO_2 in organic solvents to expand them and reduce their solvent strength is indeed the basis of the gas anti-solvent (GAS) process to precipitate solutes from liquids.[97] Ionic liquids do not follow this trend, as they show only small dilation of volume when pressurized with carbon dioxide.[32b]

High pressure carbon dioxide also induces reduction of the melting temperature of ionic liquids. This phenomenon has been macroscopically inferred from solid-liquid crystal transition using *in situ* ATR-IR spectroscopy.[98] The example reported in literature deals with $[C_{16}MIM][PF_6]$ which has a melting point of 75°C, at which point a liquid crystalline phase is formed. Pressurizing the salt with carbon dioxide causes a reduction in melting point to 50 °C, along with changes in the IR spectrum consistent with the formation of a liquid crystalline phase. This interesting phase behavior clearly opens the way to a freedom of fine tuning ionic liquids not only with temperature changes but also with pressure.

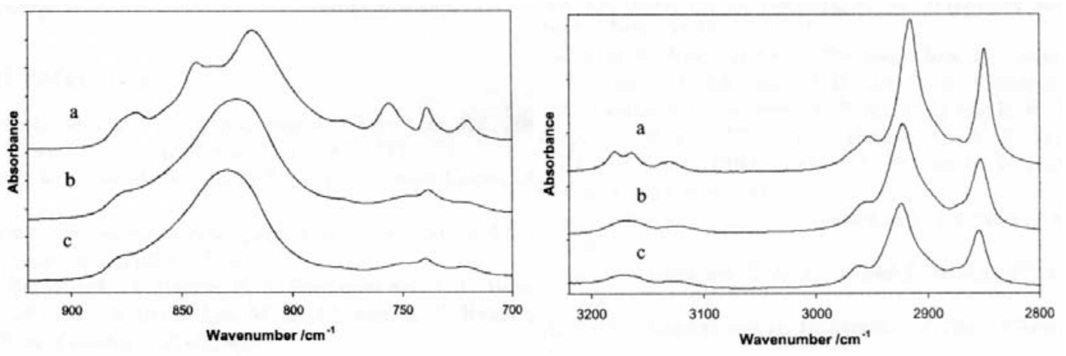


Figure 2-14: ATR-IR spectra of $[C_{16}MIM][PF_6]$ in the $\nu(PF_6)$ region (right) and aromatic $\nu(CH)$, aliphatic $\nu(CH_2)$ region (left). (a) solid sample at room temperature, (b) melt at 75 °C (liquid crystalline phase), (c) with 70 bar of CO_2 at 50 °C. Taken from reference [98].

2.2.3.2 Physical chemical properties of IL/CO_2 system studied in the present thesis.

At the start of the work presented here, no examples had been reported in literature concerning investigations of the conductivity of ionic liquids in presence of carbon dioxide, although the conductivity of several ionic liquids in the absence of CO_2 had already been reported. The conductivity of [EMIM][BTA] has been reported to be 8.8 mS cm^{-1} at 20 °C.[68] The conductivity of the [EMIM][BTA]/CO_2 system has been investigated as part of the work presented here. A high pressure conductivity cell was loaded with 7 mL of ionic liquid. Carbon dioxide has been charged in the cell and the measurements were taken at 25 °C after equilibration of the system, results are depicted in Table 2-6. After the first set of experiments, carbon dioxide was released from the high pressure cell which was maintained under high vacuum for several hours before repeating the measurement to confirm the results. In absence of carbon dioxide literature values were reproduced (see entry 1 and 6, Table 2-6). It can be seen that the presence of CO_2 increases the conductivity of the ionic liquid. Conductivity does not increase linearly with the pressure, at least in the pressure range observed, and it reaches its maximum at 60 bar. Thus, conductivity did not change doubling the amount of carbon dioxide in the cell (entry 2 and 3, table Table 2-6), at 100 and 120 bar conductivity is around 12-13 mS cm^{-1}. Releasing the CO_2 pressure from the cell and measuring the conductivity, it can be noted that there is an increasing of conductivity between the CO_2 saturated sample and the IL at 60 bar: 10 mS cm^{-1} in the first case and 13 mS cm^{-1} in the presence of 3.4 g of carbon dioxide (see entry 2, 4 and 7; Table 2-6). Exposure of the IL to prolonged high vacuum conductivity returns to its starting value (entry 1, 5 and 6; Table 2-6).

Apparently, there is no difference between the conductivity measured under argon and under vacuum (entry 1, 5 and 6, Table 2-6), which means that the dissolved argon does not influence conductivity of the IL. Noteworthy, increased values of conductivity were confirmed by charging the high pressure cell again with roughly the same amount of carbon dioxide (entry 7 and 8, Table 2-6). Thus conductivity of the system [EMIM][BTA] reaches its maximum value of 13 mS cm^{-1} by the effect of the CO_2 pressure.

Table 2-6: High pressure conductivity measurements in [EMIM][BTA]

Entry	Conditions	CO_2 [g]	σ [$mS \cdot cm^{-1}$]
1	Under argon	--	8.6
2	60 bar CO_2	3.4 g	13.1
3	100 bar CO_2	6.0 g	13.1
4	CO_2-saturated IL solution	Undefined	10.0
5	After prolonged high vacuum	--	8.6
6	Under argon	--	8.5
7	60 bar CO_2	3.5 g	12.1
8	120 bar CO_2	8.8 g	12.0

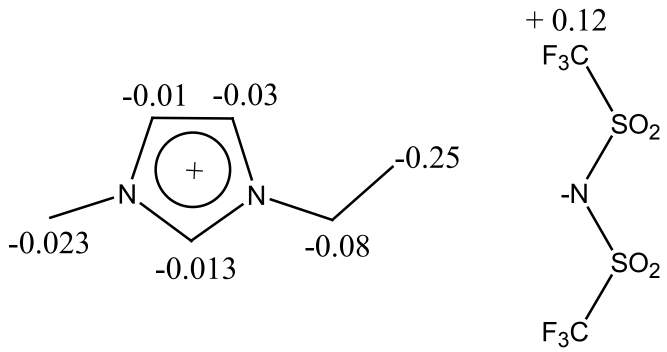
Conductivity σ is related to the number of charges and their mobility, and it can be expressed, as noted previously, by the following equation:

$$\sigma = \sum n_i \mu_i q_i \quad (3)$$

where n_i is the number of charges of the species i, q_i the charge, μ_i the mobility of the ion.[74] The dissolved CO_2 affects the conductivity of the IL in different ways. Firstly the viscosity of the ionic liquid is decreased under carbon dioxide pressure,[99] leading to an increased ion mobility, and thus also an increase in conductivity. Kazarian[100] and coworkers have demonstrated *via* ATR-IR spectroscopy that CO_2 forms weak Lewis acid-base interactions with the fluorinated anions of the IL. This interaction may reduce the degree of association of the ions and thus increase the number of charges, also leading to an increase in conductivity. Secondly, the volume expansion of the ionic liquid in presence of compressed carbon dioxide would cause a dilution of charge and consequently a decrease of conductivity, even if this last phenomenon is probably less pronounced as previously mentioned.

Recently Zhang *et. al*. reported their measurements on the conductivity of [BMIM][PF_6] at several pressures of carbon dioxide and their data are largely consistent with the results presented here. Firstly, conductivity increases with increasing of pressure being 2.97 mS cm^{-1} in absence of carbon dioxide, and 16.2 mS cm^{-1} at 130 bar (measurements taken at 40 °C).[101] In addition, they found a *quasi*-linear relationship between the pressure of carbon dioxide and the conductivity, at least between 40 and 100 bar. The conductivity of ionic liquids is larger at higher temperature over the entire pressure range. This is understandable because the mobility of the charged species should be larger and more ion pairs are dissociated at higher temperature. Increasing conductivity in the IL/CO_2 system also has to be considered in catalytic reactions in this media, as will be discussed in chapter 2.3.

In order to further investigate interactions between ionic liquids and carbon dioxide, a solution of [EMIM][BTA] at various pressures of CO_2 has been studied using high pressure NMR. Knowing that Lewis-acid interaction between the anions and carbon dioxide had been observed by *in situ* ATR-IR,[100] it should be tested whether there would be also evidence for IL/CO_2 interaction from NMR data. A high pressure NMR sapphire tube was charged with [EMIM][BTA] and ^1H, ^{13}C, ^{19}F NMR spectra were measured. The tube was then charged with different pressures of CO_2 (40, 90, 150 bar) and after vigorous shaking, the measurements had been repeated. However, no significant spectral differences were observed even at the highest pressure. The Figure 2-15 shows the deviations between the pure ionic liquid and the ionic liquid in the presence of 150 bar of compressed carbon dioxide expressed as Δ ppm. The values indicated are in the same range of the experimental error of the method and thus cannot be inferred to result from specific interactions between the ionic liquid and the carbon dioxide molecules.



Neat ionic liquid : J_{CF} = 320.6 Hz
IL at 150 bar CO_2 : J_{CF} = 320.8 Hz

Figure 2-15: Deviation of the chemical shift in the ^1H and ^{19}F NMR spectra: the numbers indicated are Δ (ppm) = δ (ppm) value of the pure sample - δ (ppm) value of the IL pressurized with 150 bar of CO_2.

However, high pressure NMR was successfully used to determine the solubility of hydrogen in ionic liquids. As stated previously, it is possible to observe the hydrogen peak in a NMR spectra of a pure ionic liquid sample (see chapter 2.2.2 and Figure 2-12). Furthermore, by integration of the hydrogen peak relative to the methylene protons in the ionic liquid, it is possible to quantify the amount of hydrogen dissolved in the IL. Hydrogen solubility/availability may be extremely important for hydrogenation reactions as will be discussed in chapter 2.4. The ionic liquid [EMIM][BTA] has been used here to assess the influence of carbon dioxide on the hydrogen solubility.

A sapphire NMR tube was charged with a pure sample of [EMIM][BTA] and then pressurized with 30 bar of H_2. After vigorous shaking of the sapphire tube, the NMR of the IL solution was recorded and no hydrogen signal in the appropriate spectra region was detected. This is in line with the low solubilities measured independently by Dyson *et al.*.[87] A repeated measurement was carried out to assure that $[H_2]$ had reached its maximum value. After adding carbon dioxide to the system, reaching a total pressure of 120 bar, the signal related to the molecular hydrogen was now clearly observed with a chemical shift of 4.3 ppm (see Figure 2-16). As expected the viscosity of the ionic liquid decreased drastically resulting in an improved resolution of the NMR peaks. Once the CO_2 pressure was released, a complete disappearance of the hydrogen signal was observed. The solubility of hydrogen in this system has been calculated as 0.14 mol L^{-1}. This value, measured at 30 bar of H_2 partial pressure, is comparable to the value in common organic solvent at the same conditions, and it is several times bigger then that of some common ionic liquids (see Table 2-7). This enhancement of hydrogen availability in the ionic solvent illustrates the benefits arising from the combination of these two media. The present results allow for the first time to quantify the enhancement of hydrogen solubility in ionic liquid by the effect of carbon dioxide.

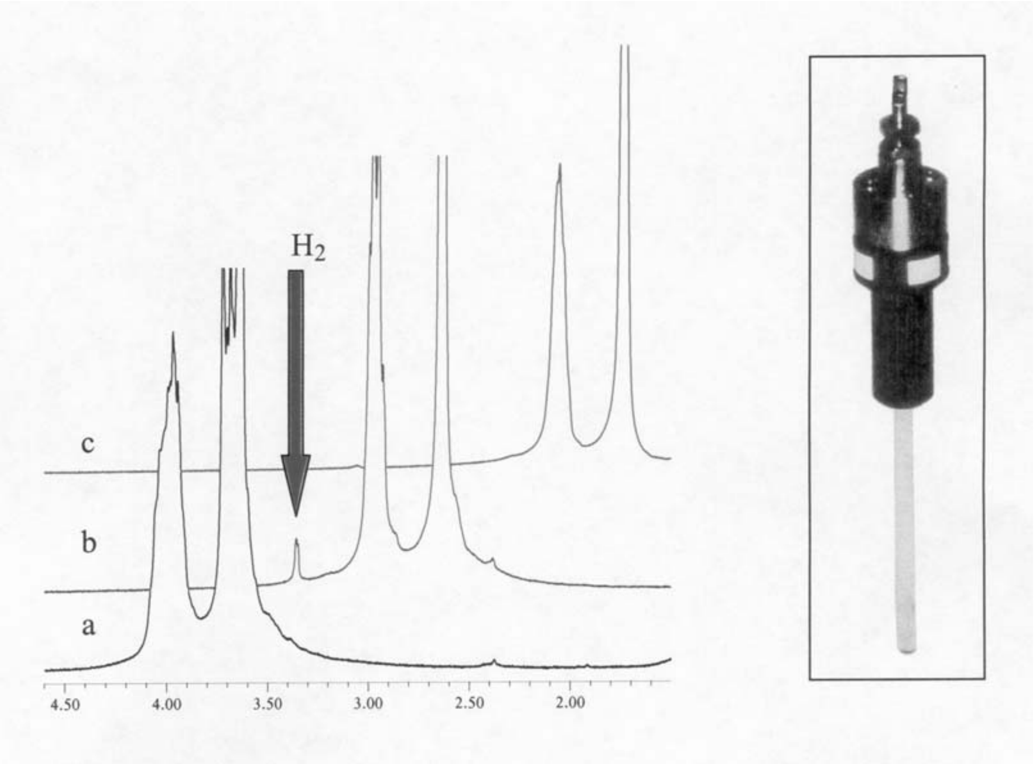


Figure 2-16: High pressure NMR studies on the hydrogen solubility in [EMIM][BTA]. Left: section of the NMR spectra of the ionic liquid. Black line (a) neat sample of ionic liquid with 30 Bar of hydrogen; Blue line (b) same sample with additional pressure of carbon dioxide (total pressure 120 bar); Red line (c) disappearance of the signal after releasing of carbon dioxide pressure. Right: High pressure NMR sapphire tube used for the experiment.

Table 2-7 summarizes for comparison the Henry's constant, hydrogen solubility and density of water, organic solvents and some common ionic liquids calculated by Dyson and co-workers.[87]

Table 2-7: Solubility of H_2 in water, organic solvents, and ionic liquid at 0.101 MPa.

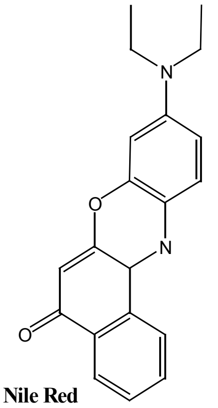
Solvent	Henry's constant, k_H/MPa	$[H_2]$/M	Density/g mL^{-1}
Water	$6.8 \cdot 10^3$	$0.81 \cdot 10^{-3}$	0.998
Methanol	$6.6 \cdot 10^2$	$3.75 \cdot 10^{-3}$	0.791
Toluene	$2.7 \cdot 10^2$	$3.50 \cdot 10^{-3}$	1.496
Cyclohexane	$2.6 \cdot 10^2$	$3.63 \cdot 10^{-3}$	0.777
[BMIM][BTA]	$4.5 \cdot 10^2$	$0.77 \cdot 10^{-3}$	1.433
[BMIM][PF_6]	$6.6 \cdot 10^2$	$0.73 \cdot 10^{-3}$	1.363
[BMIM][BF_4]	$5.8 \cdot 10^2$	$0.86 \cdot 10^{-3}$	1.120
[OMIM][BF_4]	$6.4 \cdot 10^2$	$0.62 \cdot 10^{-3}$	1.106

$K_H = P_{H2}/X_{H2}$, where the partial pressure of hydrogen is expressed in MPa. Taken from reference [87].

Another important characteristic of a solvent that may ultimately influence the outcome of a chemical transformation is the solvent polarity, which can be quantified using spectroscopic techniques as mentioned in chapter 2.2.2. There are indeed several empirical scales of solvent polarity which have been made using solvatochromic dyes. The use of this technique has been previously reported by several authors[77-82] to define the polarity of some ionic liquids. The polarity of [EMIM][BTA] with compressed carbon dioxide was measured using the solvatochromic dye Nile Red (see figure in Table 2-8). Nile Red is positively solvatochromic, when dissolved in increasingly polar media the wavelength of its visible absorption maximum (λ_{max}) moves to longer wavelength (lower energies). A high pressure UV cell was charged with a solution $2 \cdot 10^{-4}$ mol L^{-1} of Nile Red in 6 mL of [EMIM][BTA] and the maximum absorption (λ_{max}) was recorded in the pure ionic liquid and at various pressure of liquid carbon dioxide: results are depicted in Table 2-8.

Table 2-8: Wavelengths of maximum absorption (λ_{max}) and molar transition energies (E_{NR}) for Nile Red in [EMIM][BTA] at different pressure of carbon dioxide.

Conditions	CO_2 [g]	λ_{max}	E_{NR}(kJ mol^{-1})
Under argon	--	542.4	220.5
50 bar @ 25 °C	1	544.6	219.7
100 bar @ 25 °C	5.86	543.6	220.1
140 bar @ 25 °C	6.56	544.2	219.8
After prolonged vacuum	--	544.8	219.6



Nile Red

$E_{nr} = (h\ c\ N_A / \lambda_{max})\cdot 10^6$, where h is Planck's constant, c is the speed of light, N_A is Avogadro's number and λ_{max} is the wavelength of maximum absorption (nm).

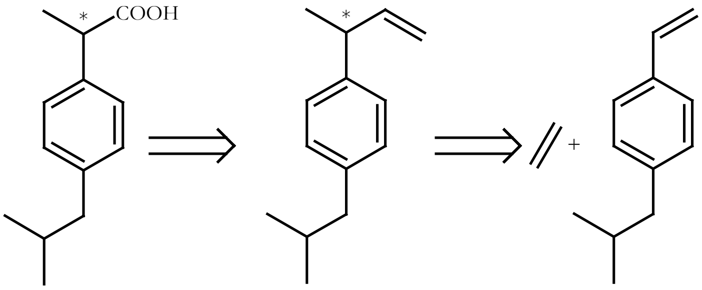
Table 2-8 indicates the wavelength of maximum absorption and the molar transition energies for Nile Red dissolved in [EMIM][BTA]. The value observed for the pure ionic liquid is in agreement with that reported in the literature[77] but no really significant deviations were observed even at high pressure carbon dioxide. From this study polarity of [EMIM][BTA] seems to be not effected by the CO_2 pressure. On the other side, the exact meaning of polarity is complex, many interactions can be present such as hydrogen bonding, π-interactions or van der Waals forces etc. Ionic liquids are even more complicated because either the cation and the anion may have specific interaction with a solute. Furthermore, interaction of carbon dioxide with the ions of the IL and with the solute itself may give a more complicated picture. Moreover, Nile Red was presumably not sufficient sensitive to underline deviations in the presence of carbon dioxide. A range of different probes are probably required to give a full picture of the strength of different types of solute-solvent interaction in the system IL/CO_2, this is still an open field to be explored. Brennecke and co-workers have very recently studied the solvent strength of IL/CO_2 systems using three different solvatochromic probes.[102] The result of that study indicate that even the addition of large amount of CO_2 have only marginal effect on the solvating power of ILs. They used 4-nitroaniline, *N,N*-diethyl-4-nitroaniline and Reichardt's dye 33 as probes, and they conclude that polarity/polarizability, hydrogen bond donating and accepting ability does not change in the IL/CO_2 systems studied. It seems that because of the very small expansion of the ionic liquids volume with carbon dioxide pressure, ILs maintain their solvent strength even at high CO_2 composition. From this few information on IL/CO_2 systems it may be concluded that CO_2 does not greatly affect the strength of the interionic interactions in the ionic liquid. Thus, reactions influenced by specific solute-solvent interactions are not likely to be affected by the addition of carbon dioxide.

High-pressure investigations on the physical chemical properties of the IL/CO_2 system are extremely important in understanding the unique characteristics of this new solvent system, and must be considered for catalytic applications as well as for supercritical extraction processes.

2.3 Nickel catalyzed hydrovinylation reaction

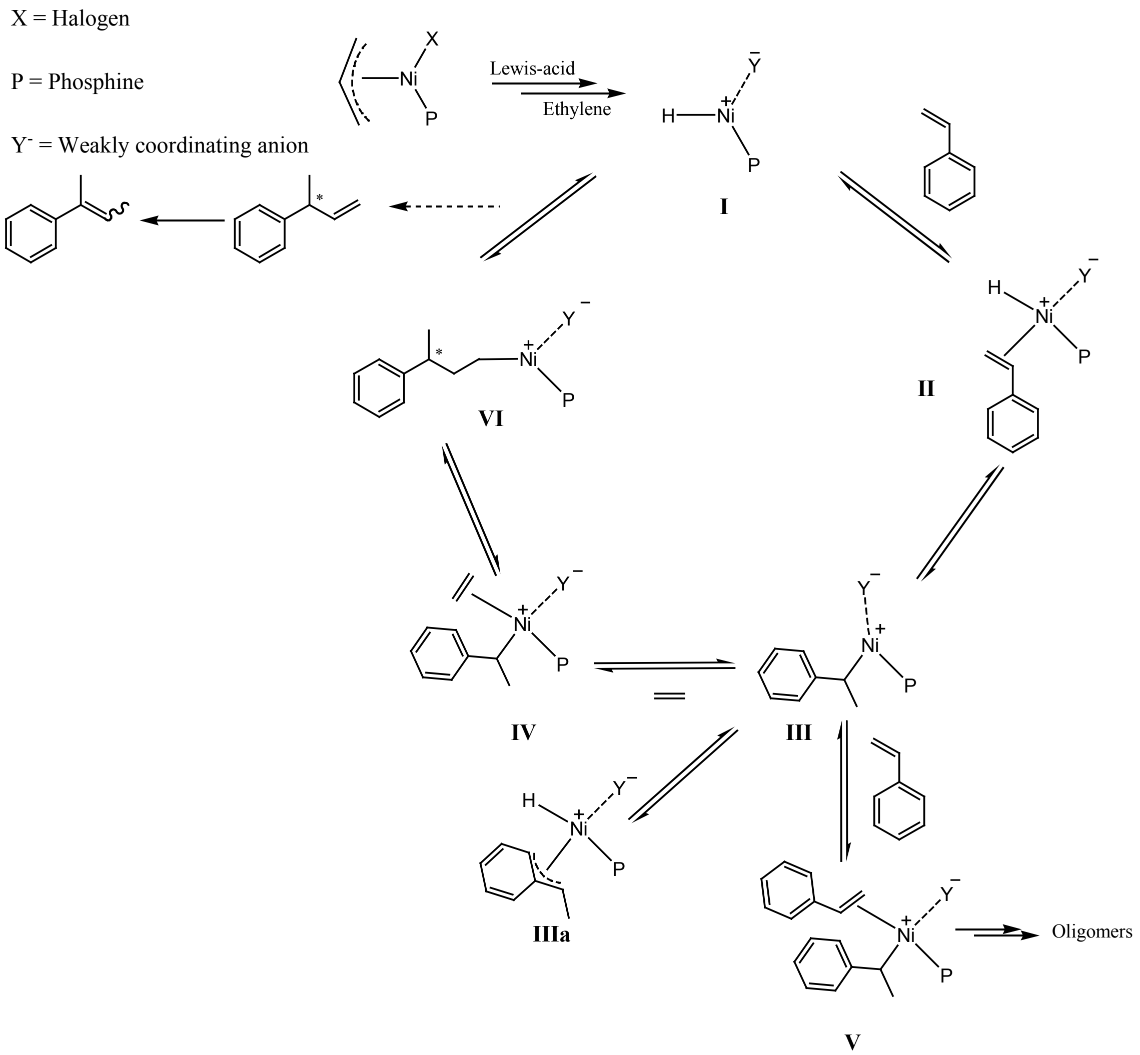
2.3.1 Background

Enantioselective C-C bond forming reactions are of great significance for modern organic synthesis. This kind of chemical transformation has potential industrial applications for the synthesis of high value pharmaceutical and agrochemical intermediates. Furthermore, the development of new, waste free and highly selective chemical transformations is one of the main goals in the field of *green chemistry*. The Ni-catalyzed codimerization of simple olefins represents a very intriguing transformation of this kind, which is still in a need of further investigation. In particular, the addition of ethylene to other olefins, the hydrovinylation reaction,[103,104,105,106] if applied to vinylarenes can be an efficient tool for the synthesis of interesting building blocks for further transformation. For example, it has been proposed for the preparation of 3-aryl-1-butenes, that may be oxidized to give 3-arylpropanoic acids, which are active ingredients of well known anti-inflammatory drugs.[107]



Scheme 2-13: Retrosynthetic approach to Ibuprofen involving the enantioselective hydrovinylation as a key step.

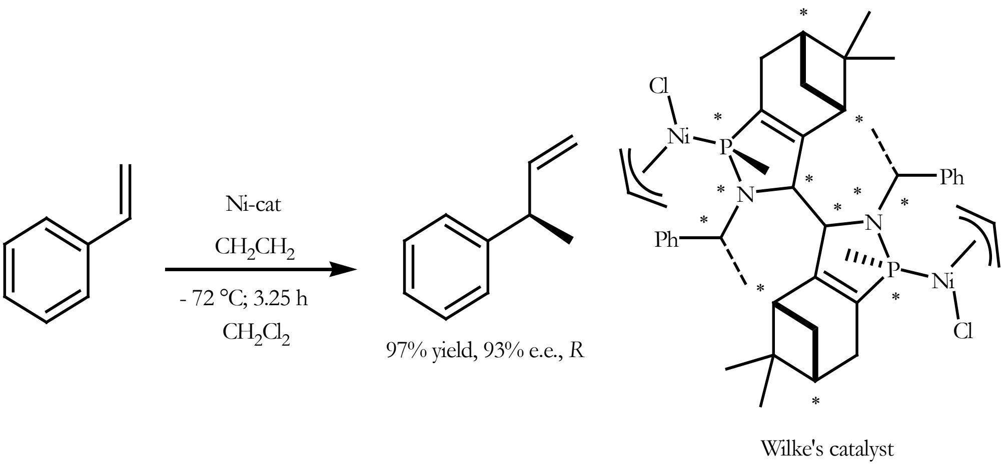
Among various metals able to catalyze the hydrovinylation reaction, nickel and palladium are the most active, with nickel showing generally higher selectivities. The mechanism commonly accepted involves a cationic nickel hydride associated with a weak coordinating counterion which is formed by a Lewis-acid assisted dissociation of the Ni-X bond from the phosphine complex **I** (see Scheme 2-14).[105]



Scheme 2-14: Mechanism of the hydrovinylation reaction.

The nickel cationic complex **I** undergoes coordination and insertion of the styrene molecule preferentially in the position 2 which is stabilized from the η^3-coordination in the molecule **IIIa**. Complex **III** should coordinate a molecule of ethylene to give the intermediate **IV** and not with another molecule of styrene to give the intermediate **V**, which will lead to oligomers, possible side products of the reaction. Ethylene insertion and β-hydride elimination will complete the catalytic cycle leading to the desired product. Further isomerization of the formed 3-aryl-1-butene can lead to 2-aryl-2-butenes *via* the same nickel hydride complex that catalyzes the hydrovinylation with one enantiomer being easier to isomerize than the other.

The enantioselective variant of this reaction is certainly very attractive because of its potential as a tool to build chiral molecules.[106] The highest enantioselectivity has been obtained so far with a very special azaphospholene ligand discovered by Wilke and co-workers (see Scheme 2-15).[108]



Scheme 2-15: The enantioselective hydrovinylation of styrene and the Wilke's catalyst.

The Wilke's ligand is often described with the notation (*RR*) referring to the (-)-(*R*)-myrtenal and (+)-(*R*)-1-phenylethylamine which are used for its synthesis. This notation is not a formal definition of the absolute configuration of this molecule which contains 12 stereogenic centers.[109] Attempts to simplify the ligand structure have not been successful, and even the diastereomer (*RS*) made from the (+)-(*S*)-1-phenylethylamine is much less reactive and selective (only 8% e.e.). The best results in terms of regioselectivity and enantioselectivity are obtained at very low temperatures using the highly flammable $Et_3Al_2Cl_3$ as the chloride abstracting agent. Furthermore, the use of methylene chloride as solvent makes the process less environmentally attractive. Replacing the Lewis acid in the Wilke's system with other salts containing low coordinating anion may give a new protocol with enhanced selectivity.[110,111] In attempt to quantify the pronounced anion effect, the molar conductivity of the catalytic solution has been considered for the outcome of the reaction. The molar conductivity of several Wilke's catalyst/AgX or Et_nAlCl_{3-n} methylene chloride solutions (where X = $[BF_4]^-$, $[SO_3CF_3]^-$, $[ClO_4]^-$, $[PF_6]^-$, $[SbF_6]^-$) have been correlated with the enantioselectivity obtained, with the same solutions, in the hydrovinylation reaction of cyclopentadiene.[112] Enantioselectivity is high for those systems in which the anion can be expected to interact with the metal center, and low for those systems where it is likely that the ions are separated. Thus higher enantioselectivity is obtained with aluminum salts such as $[Et_2AlCl_2]^-$, or $[SO_3CF_3]^-$, which also have lower molar conductivity, while lower e.e.'s are obtained with $[ClO_4]^-$ or $[PF_6]^-$ salts which have higher molar conductivity.

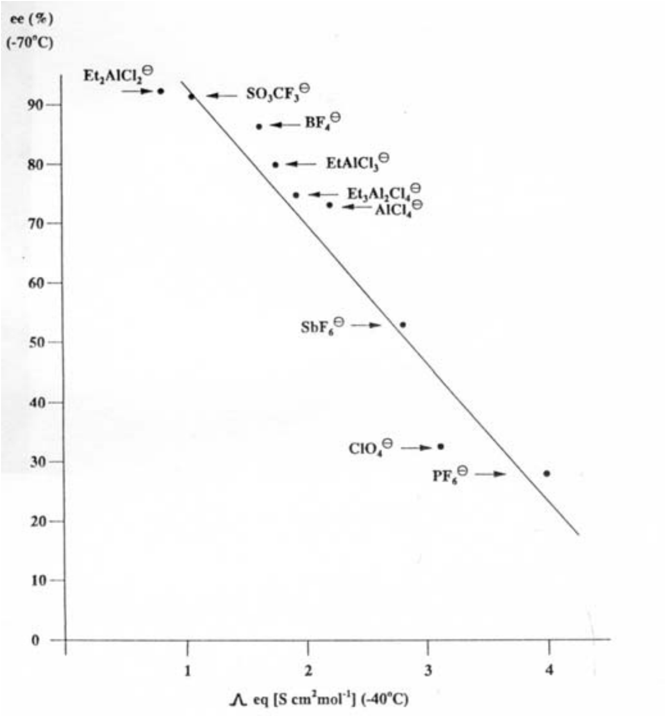


Figure 2-17: Enantioselectivity of the hydrovinylation of cyclopentadiene to (-)-(*R*)-3-vinyl cyclopent-1-ene as a function of the molar conductivity of Wilke's catalyst/AgX or Et_nAlCl_{3-n} in CH_2Cl_2. Taken from references [112].

A wide library of chiral ligands was applied in the hydrovinylation in order to gain more information on the origin of the enantioselectivity of this reaction. The use of chelating phosphines, BINAP types for example, led to no reaction because of the requirement of an open coordination site in the hydrovinylation reaction mechanism (see Scheme 2-14).[111] Alternatively, monophosphine ligands, containing a hemilabile group, may find successful applications if combined with a low coordinating anion. Selectivity up to 98% e.e. was obtained in the hydrovinylation of 2-methoxy-6-vinylnaphthalene with MOP-OMe with BARF (BARF = $B[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_4^-$) as counter anion.[111,113]

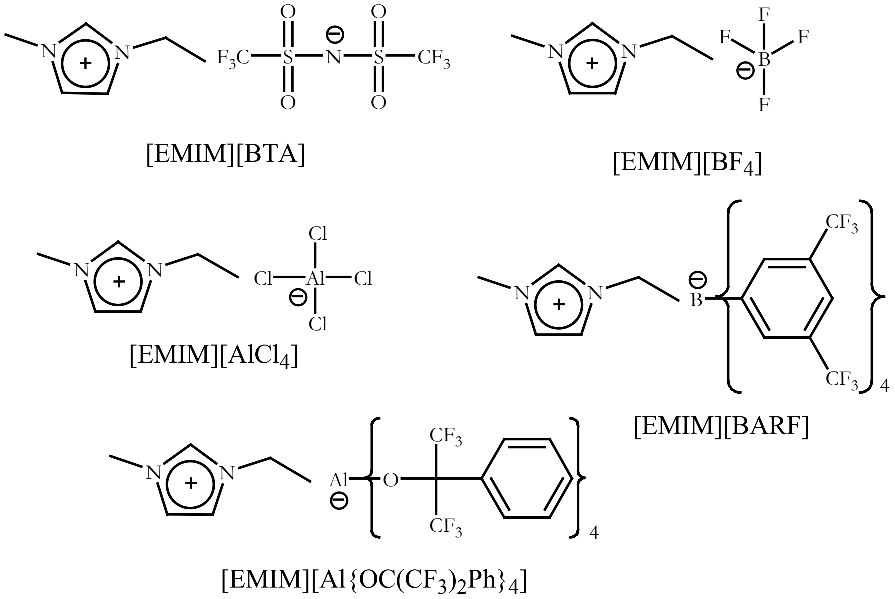
Recently, some other monodentate ligands have found increasing interest in the hydrovinylation of styrene derivatives; for example, RajanBabu and co-workers have applied a variety of readily available carbohydrate-derived diarylphosphinites obtaining high activity and selectivity. This sugar-phosphinites lead to enantiomeric excess up to 89% with a selectivity generally higher than 99%.[114] Leitner *et al.* reported that the well known Feringa's phosphoroamidite ligand can be successfully applied in this reaction. Enantioselectivity up to 91% and 89% yield has been reported for the hydrovinylation of styrene derivatives using either BARF or $[Al(OC(CF_3)_2Ph)_4]^-$ as counterion.[115]

Despite of the fairly large amount of information available on the enantioselective hydrovinylation reaction, very little has been addressed so far with regard to *greener* protocols applicable to this metal catalyzed transformation. Leitner and co-workers reported on the nickel catalyzed enantioselective hydrovinylation of styrene in supercritical carbon dioxide. The Wilke's catalyst can be successfully applied in the hydrovinylation of styrene in liquid and supercritical CO_2 after activation with alkali salts of weekly-coordinating anions such as BARF.[116] The system provided high regio- and enantioselectivity together with a quite remarkable turnover frequency of greater than 1300 h^{-1}. Another intriguing property was the possibility of isolating the product by CO_2 extraction technique obtaining an enriched mixture in (1-methyl-allyl)-benzene. Thus, the desired product can be removed selectively from the reaction mixture. Unfortunately, the system showed its major drawback when applied to the recycling of the catalyst. Already after 4 cycles the activity of the system decreased from 99% to 33% of conversion, while the enantioselectivity did not drop drastically.[116]

As already pointed out in the discussion, ionic liquids may represent a valid alternative for organometallic reactions. Ionic liquids are able to dissolve organic compounds as well as metal catalysts. Thus, ILs may be chosen as solvent also in the hydrovinylation reaction. Obviously some questions concerning hydrovinylation in ionic liquid media have to be answered. For example, nothing is known about the stability and solubility of the Wilke's catalyst in this ionic solvent. Is the catalyst activated in this new system or is a co-catalyst necessary? Are reagents soluble enough to guarantee acceptable reaction rates? Is the ionic liquid able to influence reaction rates or selectivity depending on the nature of the cation and anion in the system or it will behave as an "innocent" solvent? Finally, will combining ionic liquid with carbon dioxide possibly lead to an efficient and practicable method for catalyst recycling?

2.3.2 Activation, tuning, and immobilization of the Wilke's catalyst in IL/CO_2

The ionic liquids used were all synthesized according to standard literature procedures[68] and/or obtained from Solvent Innovation GmbH, Cologne.[14b] Imidazolium and pyridinium type ionic liquids were synthesized starting from the commercial available 1-methyl-*1H*-imidazole or 4-methyl-pyridine which after reaction with the appropriate alkyl halide yield the 1-ethyl-3-methyl-imidazolium and 1-butyl-4-methyl-pyridinium salt respectively. Anion exchange in dry acetone or alternatively in water/methylene chloride biphasic system, with a sodium or potassium salt led to high yield and purity ionic liquids. When necessary, the ionic liquid obtained was dissolved in methylene chloride and filtered through silica to eliminated traces of colored undefined impurities. After removing the solvent under high vacuum, a colorless to pale yellow ionic liquid suitable for catalytic purposes was generally obtained.



[EMIM][BTA]

[EMIM][BF_4]

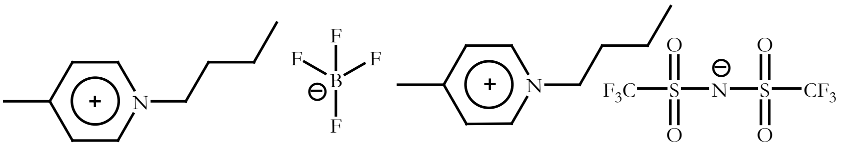
[EMIM][$AlCl_4$]

[EMIM][BARF]

[EMIM][$Al\{OC(CF_3)_2Ph\}_4$]

Figure 2-18: **E**thyl**m**ethyl**im**idazolium cation [EMIM] salts used here in the hydrovinylation of styrene.

The figures above and below shows the salts which have been tested here as solvent in the hydrovinylation of styrene in the presence of carbon dioxide. Noteworthy, [EMIM][BARF] and [EMIM][$Al\{OC(CF_3)_2Ph\}_4$] are solid at room temperature (melting point higher than 60°C), but under CO_2 pressure their melting point is lowered so that they are liquid at reaction conditions. [EMIM][BARF] is liquid under carbon dioxide pressure even for temperature lower than 0 °C in the reaction mixture.



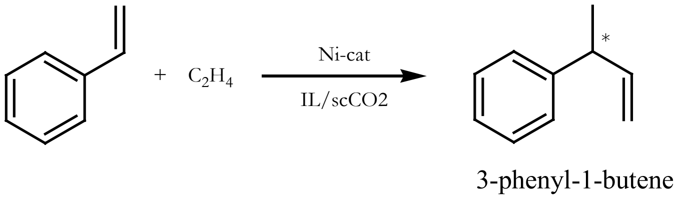
[4-MBP][BF_4]

[4-MBP][BTA]

Figure 2-19: **4-m**ethyl**b**utyli**p**yridinium cation [4-MBP] salts used as solvent in the hydrovinylation of styrene.

A key step of this study was to ascertain the activation of the nickel complex in the biphasic system IL/CO_2. The Wilke's catalyst has been activated in all ionic liquid-carbon dioxide systems under investigation and the efficiency of the activation was studied in dependent on the nature of the ionic liquid (Scheme 2-16; Table 2-9). With the right design of the ionic solvent, varying cation and anion, the performance of the catalyst can be strongly influenced. Comparison of the results in different ionic liquids having [EMIM] as the common cation reveals that the level of conversion drops in the order $[BARF]^- > [AlCl_4]^- > [Al\{OC(CF_3)_2Ph\}_4]^- > [BTA]^- > [BF_4]^-$ (entries 1-5, Table 2-9) for the same reaction time. This trend may be correlated with the estimated nucleophilicity/coordination strength of the anions which increases in the series. Thus, ionic liquids containing low coordinating anion should lead to a higher activity of the Wilke's catalyst. The intriguing result obtained offers a good example in which the ionic liquid acts not only as innocent solvent but also as co-catalyst at the same time.

The high activity of the nickel catalyst in [EMIM][BARF] and [EMIM][$AlCl_4$] results to a significant amount of consecutive isomerization and oligomerization even at room temperature (entry 4-5; Table 2-9), therefore higher enantioselectivity have been obtained in this reaction (see chapter 2.3.1). The specific environment of the ionic solvent system appears to activate the catalyst Wilke's catalyst beyond a simple anion exchange reaction. This is emphasized by the observation that even the addition of a 100-fold excess of Li[BTA] or Na[BF_4] in pure CO_2 lead at best to a moderate activation of Wilke's catalyst as compared to any of the ionic liquids with the corresponding counterions (entries 8-9; Table 2-9).



Scheme 2-16: Enantioselective hydrovinylation of styrene in ionic liquid / $scCO_2$ system.

Table 2-9: Hydrovinylation of styrene in IL/scCO$_2$ system.

entry	Ionic liquid	Conversion [%]	3-phenyl-1-butene [%]	Isomer [%]	Oligomers [%]	e.e. (*R*) [%]
1	[EMIM][BTA]	69.9	65.3	0.75	3.8	53.4
2	[EMIM][BF$_4$]	39.6	38.9	0.67	--	34.2
3	[EMIM]-[Al{OC(CF$_3$)$_2$Ph}$_4$]	90.5	87.5	0.73	2.27	78.2
4	[EMIM][BARF]^a	100	63.8	26.2	1	89.4
5	[EMIM][AlCl$_4$]	95.0	83.6	11.5	--	65.0
6	[4-MBP][BTA]	70.5	69.7	0.88	--	58.4
7	[4-MBP][BF$_4$]	35.5	34.8	0.73	--	44.2
8	Li[BTA]	24.4	23.8	0.6	--	65.9
9	Na[BF$_4$]	5.0	5.0	--	--	n.d.

Conditions: 2 ml IL; 10 mmol ethene; styrene/Ni = 350/1 CO$_2$ = 15 g; reaction time 1h; temperature 40 °C; a = temperature 25 °C.

Enantioselectivity of the hydrovinylation of styrene in this new system is significantly influenced by the anion of the ionic liquid, as revealed comparing experiments with negligible consecutive isomerization reactions (entry 1-3; Table 2-9). Comparison on the enantioselectivity has to be done between reactions with negligible isomerization because, as previously mentioned, one of the two enantiomers is isomerized with a faster rate by the same chiral nickel catalyst at least in common organic solvents. Thus, very high e.e. has been obtained with [EMIM][BARF] as solvent (89.4%) but in this case this selectivity may be distorted by the consecutive side isomerization reaction (26.2%). The ionic liquid [EMIM][AlCl$_4$] causes an acceptable level of isomerization products and quite a good enantiomeric excess (65%). Finally, the ethyl-methyl imidazolium salt containing a low coordinating aluminum salt (entry 3; Table 2-9) seems to be a better solvent for this reaction: very low level of side isomerization reaction (0.73%) and high enantioselectivity (78.2%) has been obtained. Considering the enantiomeric excess a general trend can be observed being the e.e. decreased in the order [BARF]$^-$ > [Al{OC(CF$_3$)$_2$Ph}$_4$]$^-$ > [AlCl$_4$]$^-$ > [BTA]$^-$ > [BF$_4$]$^-$.

The cation of the ionic liquid also exhibits an interesting influence on the performance of Wilke's catalyst. At comparable conversions, slightly higher enantioselectivities were found in

[4-MBP][BF_4] and [4-MBP][BTA] as compared to the corresponding [EMIM] salts (entries 1/6, 2/7; Table 2-9). This first observation of a cation effect on enantioselective catalysis in ILs may open new ways for catalyst tuning.

High selectivity and activity have been obtained with the Wilke's catalyst in methylene chloride when the reaction mixture is cooled at very low temperatures (-70°C), and if the catalyst is activated with $Et_3Al_2Cl_3$.[103] The ionic liquid-carbon dioxide system instead allows the reaction to be carried out at milder conditions, *e.g.* room temperature, avoiding cooling procedures and the use of flammable chemicals still providing high values of selectivity and activity.

The influence of some reaction conditions has been briefly assessed for the system [EMIM][BTA]/CO_2 because of the easy synthetic availability of this ionic liquid. Increasing the partial pressure of ethylene and decreasing the temperature was found to suppress the consecutive side reaction. 58% conversion of styrene (styrene/Ni = 1000/1) was achieved after 1 hour (TOF = 580 h^{-1}) under 40 bar of ethylene at 0 °C whereby 3-phenyl-1-butene was detected as the only product with 71% e.e. of the (*R*)-isomer. Furthermore, the influence of carbon dioxide has been investigated in the reaction. The presence of compressed carbon dioxide appears to increase significantly the reaction rate but at the same time the enantioselectivity observed was slightly lower (see Table 2-10).

Table 2-10: Influence of the carbon dioxide in the hydrovinylation of styrene in ionic liquids.

Ionic liquid	CO_2 [g]	Conversion [%]	Selectivity [%]	e.e. [%; *R*]	TOF (h^{-1})
[EMIM][BTA]	--	11.0	100	76.4	440
[EMIM][BTA]	9.8	34.0	100	68.6	1360

Reaction conditions: Substrate/Ni = 1000/1; C_2H_4 = 40 bar; reaction time = 15 min; temperature = 0 °C.

With a substrate-catalyst ratio of 1000/1, at 15 minutes of reaction time and at 0 °C, the conversion in absence of CO_2 is 11% and the e.e. 76.4% (*R*) while in the presence of CO_2 the conversion is 34% but the e.e. decreases to 68.6% (*R*). Both reactions were carried out at the same partial pressure of ethylene (40 bar) in order to avoid the side isomerization reaction. The enhanced reactivity of the catalyst in the presence of compressed carbon dioxide is clearly visible comparing the calculated value of turn over frequency in the two experiments, in absence of CO_2 a TOF of 440 h^{-1} has been obtained while under CO_2 pressure the TOF is 1360 h^{-1}.

As previously reported in chapter 2.2.3, carbon dioxide lowers the viscosity of the ionic liquid and increases the conductivity. In particular this has been demonstrated for the ionic liquid [EMIM][BTA] as part of the present work on understanding physical properties of IL/CO_2 systems. Furthermore, a very recent work published in the literature, confirms that conductivity in ionic liquid is increased by carbon dioxide pressure.[101] This result might explain, at least partly, the lower enantioselectivity observed in the hydrovinylation of styrene with the Wilke's catalyst in ionic liquid in the presence of CO_2, according with previous reported studies (see chapter 2.3.1 and Figure 2-17).[112]

A higher reaction rate was obtained performing the reaction in the mixed system IL/CO_2. This can be explained considering a more efficient mass-transfer which is achieved because of the presence of compressed carbon dioxide in the reaction mixture. Carbon dioxide is known to be very soluble in ionic liquids in general. Ethylene (and ethane) can be considered as the second most soluble gas in ionic liquid after carbon dioxide.[117] On the other hand, styrene is not very soluble in [EMIM][BTA], but the presence of CO_2 will probably increase its solubility and enhance the reaction rate.

The reaction profile of the hydrovinylation of styrene has been briefly evaluated, with an on-line GC-MS technique, in order to estimate the activity of the catalyst in this new system. A 250 mL autoclave was charged under argon with a solution of ionic liquid, catalyst and substrate, the reactor was charged with ethylene and carbon dioxide and it was connected to an on-line GC-MS instrument. The reaction was allowed to proceed at room temperature under vigorous stirring while small amounts of the upper carbon dioxide phase were analyzed on-line with regular reaction time intervals. This measurement was performed with the assumption that most of the reactants and products partition into the CO_2 phase (or at least with an equal distribution between the two phases). Selectivity > 99% was obtained. Furthermore, the concentration of ethylene in the reactor can be considered constant during the reaction since it is in larger excess compared to styrene, thus in a first approximation the reaction may be analyzed by pseudo first-order kinetics.

For a generic first-order reaction:

$$R \xrightarrow[K]{} P \quad (4)$$

the corresponding rate equation is written in differential form as:

$$\mathrm{r} = -\frac{d[R]}{dt} = k[R] \quad (5)$$

To obtain the time-dependent concentration of *R* and *P*, the rate equation must be integrated as follow:

$$\int_{[R]_0}^{[R]} \frac{d[R]}{[R]} = \int_0^t -kdt \Rightarrow \ln\left(\frac{[R]}{[R]_0}\right) = -kt \quad (6)$$

The integration limits follow from the consideration that $[R] = [R]_0$ at $t = 0$. Hence, the following equation describing a first-order kinetic is obtained:

$$[R] = [R]_0 e^{-kt} \Rightarrow [P] = [R]_0(1 - e^{-kt}) \quad (7)$$

Thus, plotting ln[*R*] versus time provides a convenient way to verify that the reaction follow first-order kinetics. Such a plot should yield a straight line and the rate constant follow from the slope of the line. The reaction profile obtained with this on-line experiment is shown in Figure 2-20 where ln[Styrene] is plotted versus time. From this result, the hydrovinylation of styrene appears to follow first-order reaction kinetics, with an observed overall rate constant of $K_{\mathrm{obs}} = 0.348\ \mathrm{s}^{-1}$. Most importantly, this indicates that no product inhibition or catalyst deactivation occurs over the whole course of the reaction in this case. Therefore, the IL environment seems suited to stabilize the key intermediates, an important prerequisite for the continuous flow operation discussed later.

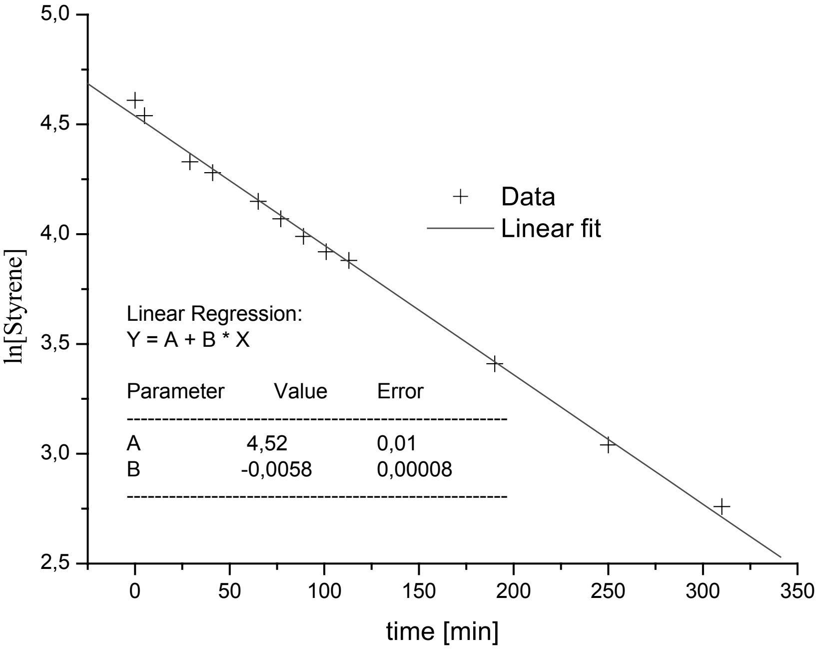


Figure 2-20: On-line monitoring of the hydrovinylation of styrene with the Wilke's catalyst. A stainless steel autoclave ($V = 250$ mL) was charged under argon with a solution of Wilke's catalyst in 10 mL of [EMIM][BTA] and styrene (sub/Ni = 1000/1). The reactor was charged with 50 bar (3 g) of ethylene, 63 g of CO_2 (final pressure at 25 °C 150 bar) and connected with the on-line GC-MS. At regularly interval of time the upper CO_2 phase was analyzed to determine conversion.

The typical distribution of reaction products in the hydrovinylation reaction (styrene, (1-methyl-allyl)-benzene and the *E*/*Z* isomers of (1-methyl-propenyl)-benzene) have been already successfully extracted from the catalyst using supercritical carbon dioxide, as previously described in the literature.[116] Nevertheless, no information was available so far on the extraction of those compounds from ionic liquids with carbon dioxide. It was found that styrene, (1-methyl-allyl)-benzene and the *E*/*Z* isomers of (1-methyl-propenyl)-benzene are quantitatively extracted from [EMIM][BTA] using $scCO_2$ extraction technique. Figure 2-21 shows the typical set-up used for extraction of the reaction products at the end of the hydrovinylation of styrene.

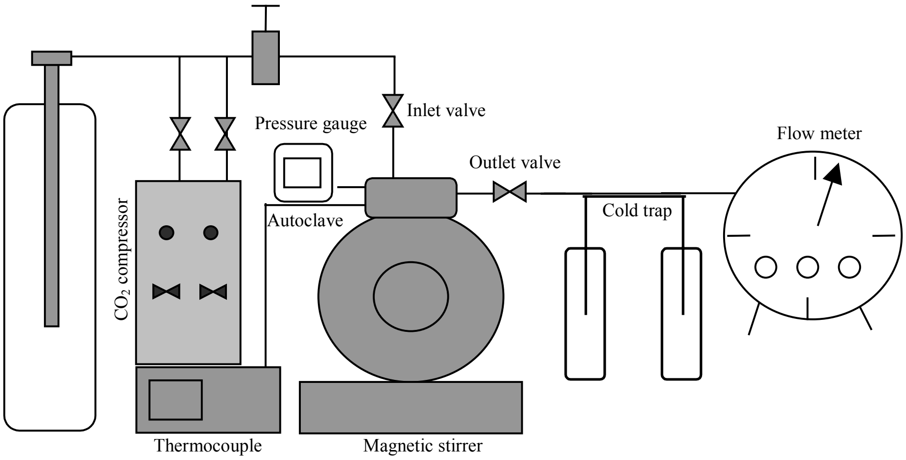


Figure 2-21: Schematic representation of products extraction from ionic liquid with supercritical carbon dioxide. Typical extraction parameters: 150 bar at 40 °C until complete recovery of the products from the reaction vessel.

Unfortunately, all the attempts to recycle the metal catalyst in a batch-wise manner, *e.g.* re-charging the autoclave with fresh styrene at the end of the extraction process, failed. It was speculated that this disappointing result may be mainly related to the instability of the active species in the absence of substrate, a problem that could be easily avoided by operating in a continuous flow system.

Thus, the catalytic system was applied in a continuous operation in which a stream of styrene and ethylene was pushed through a long reactor containing the catalyst dissolved in the ionic liquid by means of compressed carbon dioxide. Reagents should have a sufficient contact time with the metal catalyst during the process in order to guarantee a high value of conversion, considering the rate constant determined from Figure 2-20. Several attempts were made in order to fulfill this requisite.

The input flow of reagents were controlled with a HPLC pump connected to the reactor for the liquid styrene while ethylene was pushed in the reaction mixture by means of a gas dosing unit. Furthermore, the exit flow of reaction products was adjusted together with pressure and temperature in the reactor, exploiting the solvent power of carbon dioxide. Carbon dioxide was allowed to expand into a cold trap (-70°C) where reaction products were collected. Expansion of carbon dioxide at low temperature decreases its solvent power so that a liquid or even solid compound can be isolated in the trap completely free from organic solvent. The product mixture was analyzed *via* GC-MS to determine conversion and enantioselectivity. It is important to note that the outcome of the GC analysis was the only way to understand which of the various reaction parameters (styrene flow, partial pressure of ethylene, CO_2 pressure and temperature) had the greatest effect on efficiency in the process. Besides, only cumulative samples were analyzed meaning that the effect of the various parameters on the reaction was difficult to ascertain. Generally, one can think that decreases in conversion may be caused not only by catalyst decomposition but also because of insufficient availability of ethylene in the reactor. In this last case the dosing of the ethylene gas has to be increased in order to increase the partial pressure of ethylene and consequently catalyst activity. Another drawback, which may originate from the lack of availability of ethylene in the reaction mixture, is the lower selectivity obtained in this case because of the formation of oligomers (reaction of the styrene with its self). Unfortunately, this aspect is not easy to observe, because, generally, carbon dioxide does not extract high molecular weight products (oligomers in this case) from the reaction mixture at the same extend of low molecular weight products (1-methyl-allyl-benzene and 1-methyl-propenyl-benzene typical reaction products here). Therefore, in all experiments which were carried out, temperature and partial pressure of ethylene were adjusted in order to ensure selectivity > 99%. It was verified at the end of every continuous flow experiment that no oligomers remained in the ionic liquid phase.

Furthermore, if the reaction conditions (temperature and overall pressure) are sufficient to have a very fast extraction it can be possible to observe decreasing conversion. In other words, if the percentage of output is much higher than the input, reagents will not have enough contact time with the metal catalyst, thus conversion will be lower. This problem may be solved through decreasing the density of carbon dioxide by changing the overall pressure and temperature of the reactor.

Several technical problems were encountered during the set up of the continuous flow, some of which are very common while working with high pressure techniques. Needle valves, fittings, connections, capillaries and back pressure regulators have to be properly fixed to avoid leakage. During the reaction/extraction it can happen that needle valves get blocked because of the condensation of products. This problem is extremely important because it may lead to an uncontrolled growth of pressure, which may cause explosive pressure spikes. Another technical problem may derive from the cold trap. It can happen, especially for highly volatile compounds, that one cold trap is not sufficient to entrap all reaction products. This problem is easily overcome connecting more cold traps in series. It is extremely important to ensure a very good mass balance in each experiment (the overall inlet moles of substrate must equal the overall moles of reaction products). The most important technical problem encountered in the work presented here was that the CO_2 stream could mechanically push some ionic liquid out from the reactor when introduced from the bottom (see Figure 2-22). A long thin stainless steel capillary, which allows the bubbling of reagents in the catalytic ionic liquid solution, was used in order to avoid this drawback. A fine bubbling of the carbon dioxide solution was realized using a very fine filter connected at the end of the long capillary. Thus, with this solution, no ionic liquids have been detected in the cold trap (see Figure 2-23).

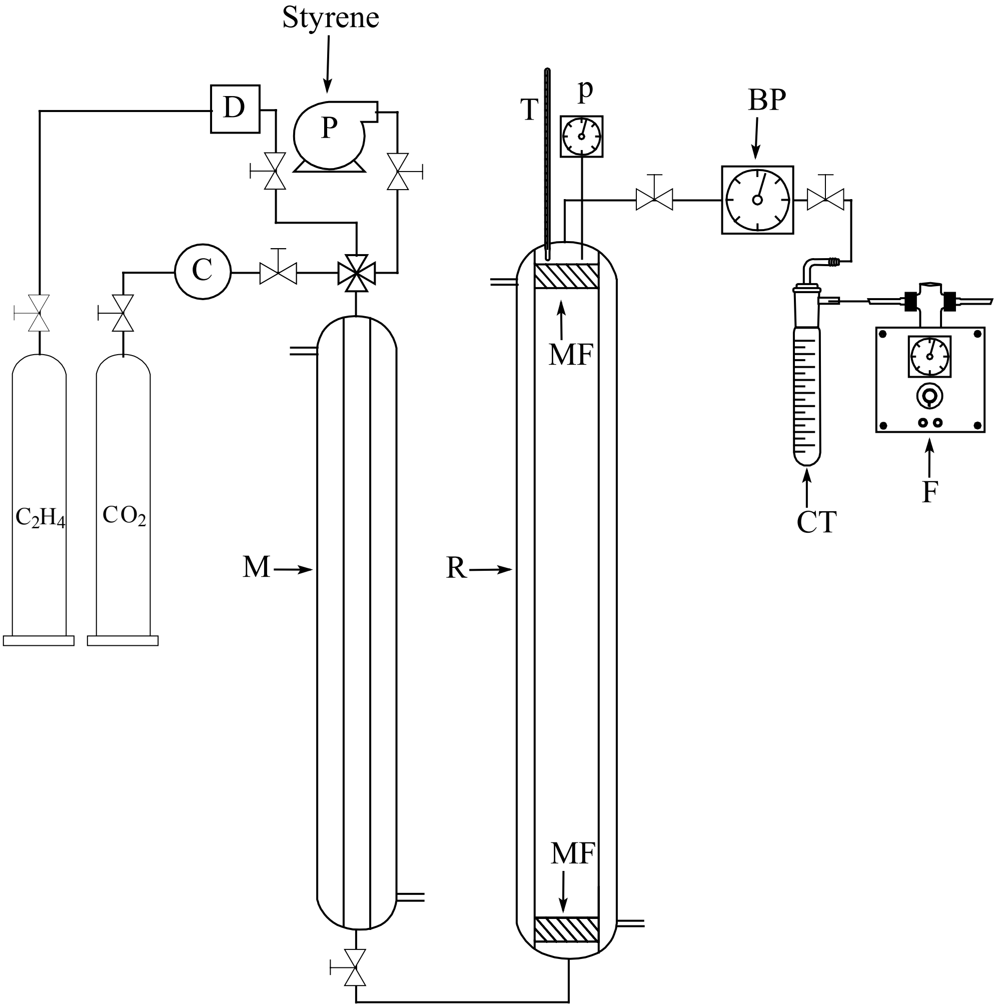


Figure 2-22: Schematic view of the continuous flow reaction apparatus which has been used for the hydrovinylation of styrene. The parts are labeled as follows : *C* = Compressor; *CT* = Cold Trap; *D* = Dosimeter; *BP* = Back pressure regulator; *F* = Flowmeter; *M* = Mixer; *MF* = Metal Filter; *P* = HPLC Pump; *p* = pressure transducer; *R* = Reactor; *T* = Thermocouple.

One of the continuous flow apparatus for homogeneous catalysis in IL/CO_2 systems is depicted schematically in Figure 2-22. The ionic catalytic solution is placed into the reactor R where it is in intimate contact with the continuous reaction phase entering from the bottom through a metal filter. The reaction phase is made up in the mixer from a pulsed flow of ethylene and a continuous flow of styrene and compressed carbon dioxide.

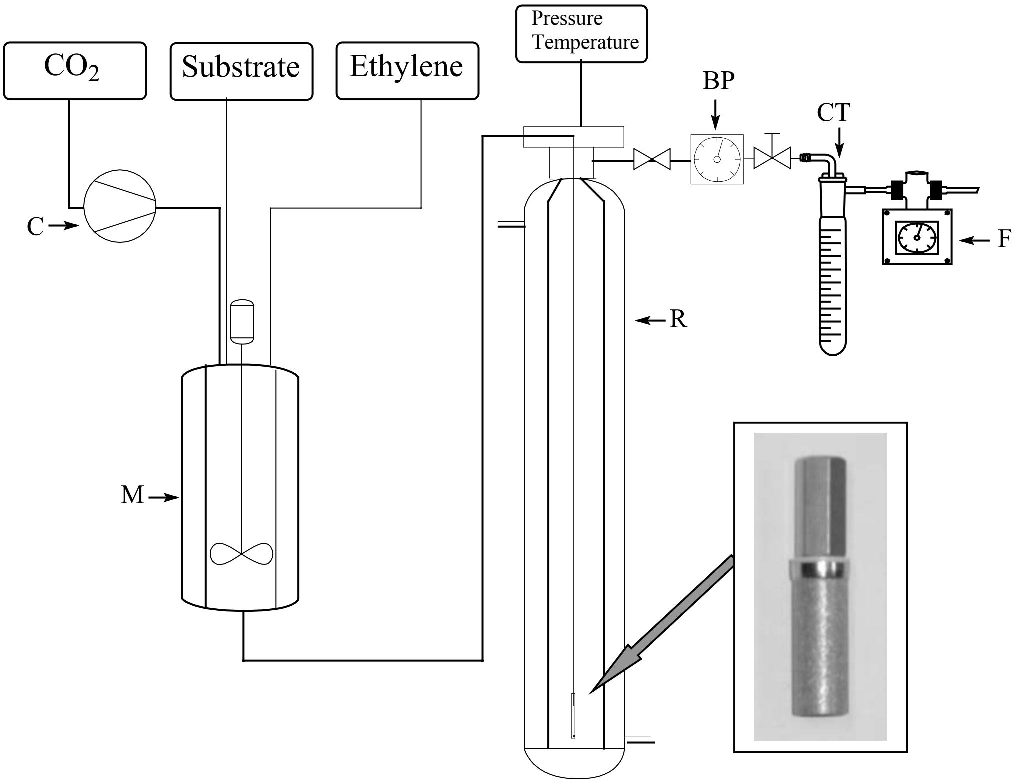


Figure 2-23: Schematic view of the continuous flow reaction apparatus modified with a stainless steel capillary. The parts are labeled as follows : *C* = Compressor; *CT* = Cold Trap; *BP* = Back pressure regulator; *F* = Flowmeter; *M* = Mixer; *MF* = Metal Filter; *R* = Reactor.

The reactor described in Figure 2-23 has been successfully applied in the hydrovinylation reaction of styrene. The use of the metal filter attached at the end of the long capillary is a good way to keep all the ionic liquid in the reactor during the entire process.

Figure 2-24 shows the results of a lifetime study for the Wilke's catalyst dissolved, activated and immobilized in the system [EMIM][BTA]/CO_2 by this straightforward technique. The catalyst shows a remarkable stable activity over 61 hours and enantioselectivity dropped only slightly over the long reaction period. Analysis to determine nickel leaching showed a fairly low nickel content varying from 1.64 ppm and 2.44 ppm for some selected samples.

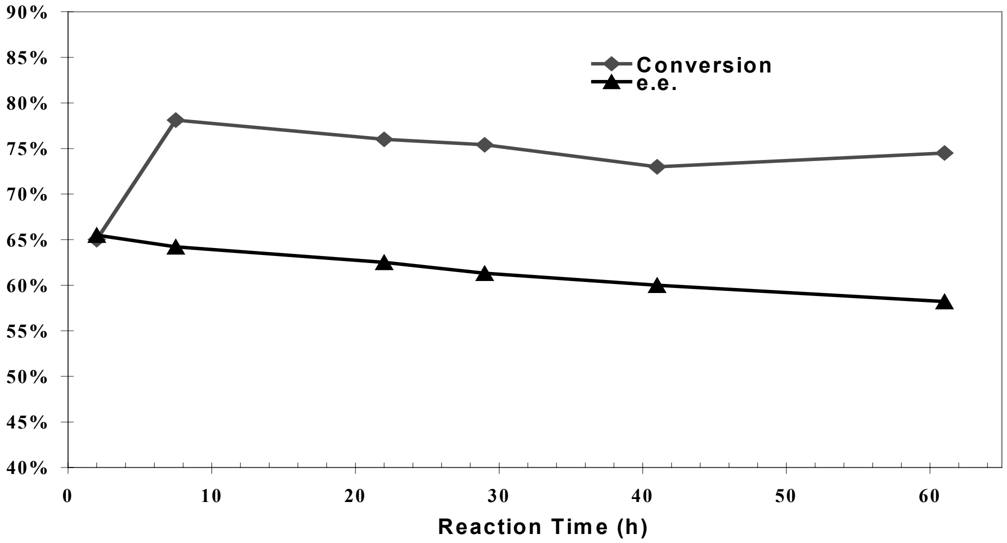


Figure 2-24: Lifetime study for the Wilke's catalyst in the continuous flow hydrovinylation of styrene. Conditions: The reactor was filled under argon atmosphere with 0.19 mmol of Wilke's catalyst dissolved in 39 ml of [EMIM][BTA] and cooled to 0 °C. The reactor pressure was maintained constant at 80 bar by a continuos flow of compressed CO_2 (the exit flow was adjusted between 1 and 0.1 L/min of STP (standard temperature and pressure) carbon dioxide. The reaction was then allowed to proceed with a constant styrene flow of 0.01 mL/min and 1 ml pulses of C_2H_4 (90 bar) every 0.5 min.

The ionic liquid-carbon dioxide system was further investigated changing the aryl substrate after a lapse of time in a continuous flow manner pursuing the aim to have the same batch of catalyst be able to catalyze the transformation of different aryl derivatives. In order to verify this possibility, a smaller continuous flow reactor was built using a 20 mL autoclave connected with compressors for CO_2 and ethylene and HPLC pump for the substrates: 1-isobutyl-4-vinyl-benzene and 1-chloro-4-vinyl-benzene. The reaction was allowed to proceed at 0 °C, with a total pressure of 80 bar, under a continuous flow of carbon dioxide (2.5 L of CO_2 min^{-1}), ethylene (2 mL min^{-1}), and the substrate 1-isobutyl-4-vinyl-benzene (0.01 mL min^{-1}). The products were collected into the cold trap letting carbon dioxide expand through it. Unfortunately, some problems in the mass-balance were encountered. Acting on the carbon dioxide density (the overall pressure in the reactor was increased), and extending the extraction process (no input of substrate) to 12 hours, resulted finally in extraction of almost the theoretical amount of the product mixture. Subsequently, 1-chloro-4-vinyl-benzene was introduced into the reaction mixture and a new mixture of products was isolated in the cold trap. Very poor conversion was obtained for the 1-chloro-4-vinyl-benzene, whereas the smaller amount of 1-isobutyl-4-vinyl-benzene still present in the mixture showed conversion up to 68%. At the end of the process 96% of the product mixture was recovered, albeit with very small conversion of the chloro-substituted starting material.

Table 2-11: Continuous flow hydrovinylation of different substrates.

Entry	Substrate	Reaction time	Conversion [%]	e.e. [%] (*R*)
1	1-isobutyl-4-vinyl-benzene	2 h	52.2 %	66.4 %
2	1-isobutyl-4-vinyl-benzene	4 h	34.3 %	61.0 %
3	--	12 h (no input substrate)	56.9 %	64.3 %
4	1-chloro-4-vinyl-benzene	20 h	1.5 %	--
5	1-chloro-4-vinyl-benzene	22 h	1.1 %	--
6	1-chloro-4-vinyl-benzene	24 h	0 %	--

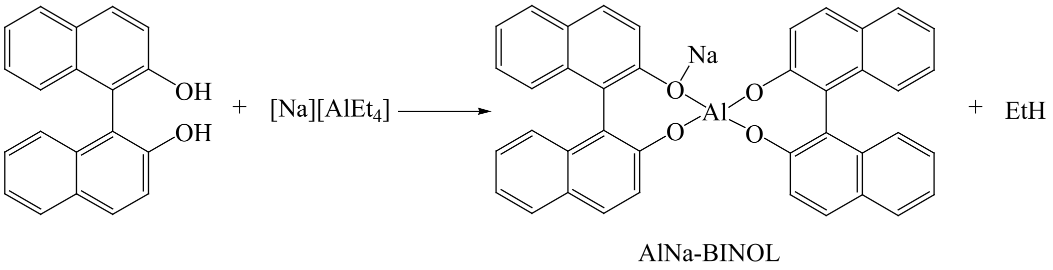
This surprising lack of reactivity of 1-chloro-4-vinyl-benzene was also confirmed in some batch experiments (only 13.6 % of conversion has been obtained in one hour at optimized reaction conditions). For some reason, it appears to be related to the ionic liquid, since the same substrate in pure CO_2 has been quantitatively converted in 1-chloro-4-(1-methyl-allyl)-benzene with 80% of enantioselectivity.[116]

2.3.3 Low coordinating chiral aluminum salts as co-catalyst in the hydrovinylation reaction.

In the past years, heterobimetallic complexes have been introduced for catalytic carbon-carbon bond forming reactions.[118] Particularly, complexes consisting of a rare earth metal center, an alkali metal center (Li, Na, K) and 2,2'dihydroxy-1,1'-binaphthyl (BINOL) have been used in asymmetric reactions. LaLi-BINOL complex is effective in asymmetric nitroaldol reactions, LaNa-BINOL is a very efficient catalyst for asymmetric Michael reactions and AlLi-BINOL has been shown to be a very active catalyst for asymmetric tandem Michael-aldol reactions.[119] Those compounds are believed to behave as Lewis acid (the aluminum center) and as Brønsted base (the alkali naphthoxide moiety) at the same time.

As previously mentioned regarding the mechanism of the hydrovinylation reaction, a weak Lewis-acid interaction is needed in order to begin the catalytic cycle. This activation step in the case of the reaction in ionic liquids is most likely made possible through the anion of the IL. Therefore, designing an ionic liquid containing a chiral anion might lead to an interaction with the catalytic active species and, in the best case, influence the selectivity of the reaction. As a first step towards this goal both enantiomers of AlNa-BINOL have been synthesized here and used as co-catalyst in the hydrovinylation of styrene in common organic solvents. Naturally, the following steps should be the synthesis of chiral ionic liquid based on those BINOL salts and the investigation of their potentiality as applied in the hydrovinylation reaction.

This part of the discussion will focus solely on the preparation of chiral aluminum salts based on the 2,2'-dihydroxy-1,1'-binaphthyl framework. These chiral aluminum salts were tested as chloride abstracting agents in the hydrovinylation of styrene with both achiral and chiral catalysts.



Scheme 2-17: Synthesis of the AlNa-BINOL salt.

The synthetic pathway involves the reaction of (*S*)- or (*R*)-BINOL with [Na][AlEt$_4$] in a molecular ratio of 2:1.[120] The course of the reaction can be followed *via* the formation of bubbles of ethane, see Scheme 2-17. The synthesis was straightforward and gave, with high yield and purity, the desired salts as a white powder. Both enantiomers were readily synthesized, isolated and characterized with NMR technique (^{1}H, ^{13}C) and mass spectroscopy. Successively, the two enantiomeric salts were tested as co-catalysts in the hydrovinylation of styrene with a variety of nickel complexes. Results obtained with this new methodology are depicted in Table 2-12.

Table 2-12: Activation of nickel complexes with chiral AlNa-BINOL.

Entry	System	Reaction Condition	Conversion [%]	3-phenyl-1-butene [%]	e.e. [%]
1	AlNa-(*R*)-BINOL / $[Ni(\eta^3\text{-}C_4H_7)(PCy_3)Cl]$	15 h / 40 °C	36.0	11.0	8.3 (S)
2	AlNa-(*R*)-BINOL / $[Ni(\eta^3\text{-}C_4H_7)(PCy_3)Cl]$	65 h / 25 °C	14.3	14.3	8.4 (S)
3	AlNa-(*S*)-BINOL / $[Ni(\eta^3\text{-}C_4H_7)(PCy_3)Cl]$	48 h / 25 °C	26.8	26.8	5.7 (R)
4	AlNa-(*R*)-BINOL / $[Ni(\eta^3\text{-}C_3H_5)(PPh_3)Br]$	42 h / 25 °C	22.1	22.1	3.2 (S)
5	AlNa-(*R*)-BINOL / Wilke's catalyst	66 h / 25 °C	1.3	1.3	52.3 (R)
6	AlNa-(*S*)-BINOL / Wilke's catalyst	41 h / 25 °C	--	--	--

Conditions: styrene = 3 mmol, 0.03 mmol of the nickel catalyst AlNa-BINOL 0.1 mmol, solvent = 2 mL CH_2Cl_2, ethene = 40 bar.

This new catalytic system appears to have low reactivity and an increase in temperature leads to a significant amount of side products (entry 1; Table 2-12). The optimal reaction conditions were found to be at room temperature, but as a drawback, even for prolonged reaction time, only very low conversion was obtained. Nevertheless, a small but significant enantiomeric excess was observed using achiral nickel phosphine catalysts. The enantioselectivity was observed to be opposite to the configuration of the BINOL moiety in the aluminum salts: the (*R*)- compound leads to (*S*)-3-phenyl-1-butene and *vice versa* (entry 2-3; Table 2-12). Interestingly, the system combined with the triphenyl phosphine ligand gave lower enantioselectivity. Unfortunately, the chiral Wilke's catalyst complex was not activated (entry 4-6; Table 2-12) and matched/mismatched effects could not be studied. Despite the low value of enantiomeric excess which has been observed, these results represent the first example of enantioselective hydrovinylation of styrene catalyzed with an achiral catalyst and a chiral co-catalyst, and may ultimately open the way to future applications for fine tuning of catalytic systems.

2.4 Enantioselective iridium catalyzed hydrogenation

2.4.1 Background

The enantioselective hydrogenation of imines provides an attractive route to enantiomerically enriched chiral secondary amines which is successfully applied in the industrial production of metolachlor.[121] This important molecule is the active ingredient of Dual®, one of the most widely used grass herbicides with a production of about 20.000 tons per year. Metolachlor has two chiral elements, a chiral axis (atropisomerism, due to the rotation around the C_{Ar}-N axis) and a stereogenic carbon atom, leading to 4 different stereoisomers (see Figure 2-25).[122]

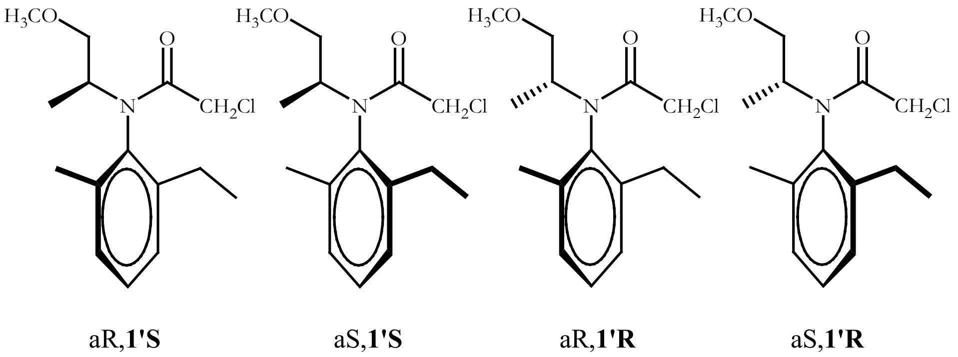
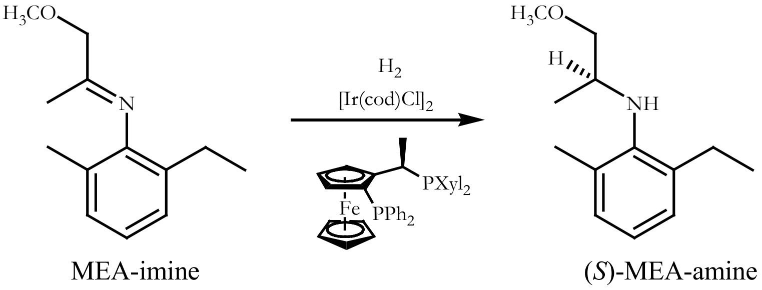


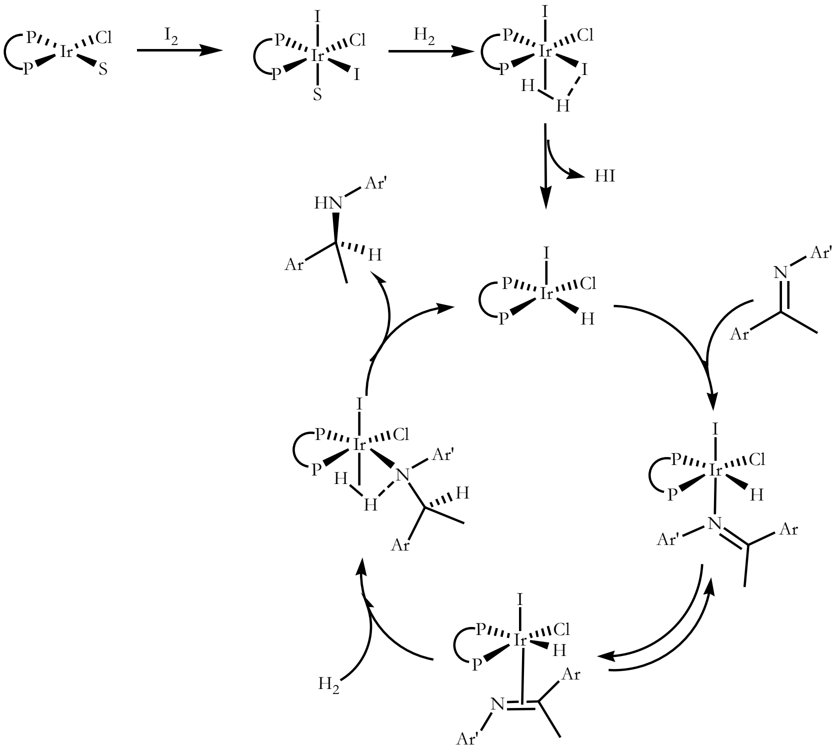
Figure 2-25: Possible stereoisomers of metolachlor.

The stereochemistry of the active compounds was found to be αR,**1'S** and αS,**1'S**.[122] In 1976 metolachlor was commercialized as a mixture of all 4 stereoisomers and the synthetic approach involved the palladium catalyzed reduction of (2-ethyl-6-methyl-phenyl)-(2-methoxy-1-methyl-ethylidene)-amine (MEA-imine) in aqueous methoxyacetone with traces of sulphuric acid, followed by chloroacetylation.[123] After 21 years of intensive research, metolachlor was commercialized as Dual Magnum® containing approximately 90% of the (**1'S**) enantiomers.[121,124] Today the enantioselective hydrogenation of the MEA-imine using a chiral iridium-xyliphos complex is the largest enantioselective catalytic process known.[125]



Scheme 2-18: Enantioselective hydrogenation of the (2-ethyl-6-methyl-phenyl)-(2-methoxy-1-methyl-ethylidene)-amine (MEA imine) with iridium-xyliphos.

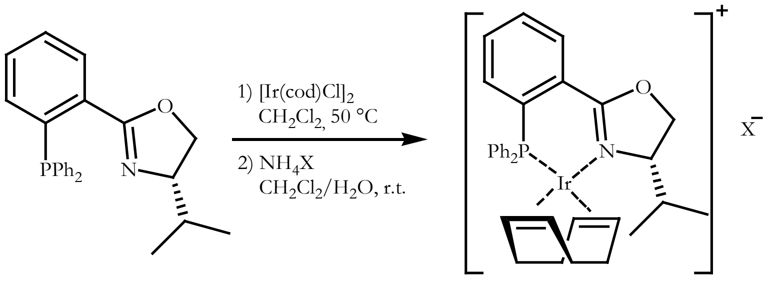
Despite these impressive achievements, only a few detailed studies concerning the mechanism of the homogeneous imine hydrogenation have been reported to date.[126] A generalization seems to be rather difficult to obtain because of two main reasons. First, different catalysts are effective and probably act *via* different mechanisms. Second, the effect of certain additives (especially iodide and acid/base) may be a promoter in one case or a deactivator in another one.[126,127] A generally accepted mechanism is depicted in Scheme 2-19, where the catalytic cycle begins with a Ir(III) hydride species which, in the Novartis process, is generated by an oxidative addition of I_2 to an Ir(I) species. The Ir(III) species coordinates the imine via the lone pair of the nitrogen atom in a η^1-manner. An η^1-η^2 migration leads to two diastereomeric π-coordinated species. The following step is the insertion into the Ir-H bond to give the corresponding iridium amide complexes. The last step is the hydrogenolysis of the Ir-N bond and the formation of a new iridium hydride species, presumably via heterolytic splitting of the H_2 bond. In contrast with the rhodium catalyzed reduction of carbon-carbon double bonds, where the catalytic cycle most probably involves Rh(I) and Rh(III) species, the imine hydrogenation encompasses only Ir(III) species.[128] As mentioned, this simple catalytic cycle does not explain either the enhancement of enantioselectivity observed by addition of iodide or the rate increment obtained with acid, which are crucial in the commercially used Ir-xyliphos catalyzed hydrogenation of imines.[125]



Scheme 2-19: Postulated catalytic cycle for the iridium-diphosphine catalyzed hydrogenation of imines; S = solvent or substrate.

Innovative methodologies for immobilization and efficient recycling of organometallic catalysts are also finding increasing interest in the development of viable homogeneously catalyzed enantioselective hydrogenation of imines. In this contest, a very efficient immobilized version of the xyliphos ligand was synthesized and applied in the enantioselective hydrogenation of C-N double bonds, using silica as solid support.[129] A variety of iridium complexes were immobilized with this technique and the recovery of the metal catalyst was possible merely *via* filtration. Most significantly, an extremely high TOF and TON was obtained (20.000 h^{-1} and >100.000 respectively).

Remarkable progress has been made in the last 10 years toward the discovery of novel efficient catalysts for reduction of C-N double bonds. In particular, Pfaltz and co-workers discovered that enantiopure cationic iridium phosphanodihydrooxazole complexes yield high levels of asymmetric induction in the hydrogenation of prochiral *N*-alkyl and *N*-aryl imines[130] as well as in hydrogenation of carbon-carbon double bonds.[131] The preparation of the (phosphanodihydrooxazole)Ir^I complex Ir[X] has been described as a two-step synthesis (see Scheme 2-20). The structural characteristic of the P-N ligand allows an easy modification of the framework by introducing alkyl and aryl groups both in the phenyl ring and in the dihydrooxazole moiety of the molecule. Furthermore, the chloride anion exchange reaction to isolate the active catalytic precursor, can offer further tuning of the system. In common organic solvents, replacing of PF_6^- anion by other counterions such as $[SbF_6]^-$, $[BPh_4]^-$ or $[BF_4]^-$ had no significant effect on the imine and C-C double bonds hydrogenation reactions.[130,131c] However, weakly coordinating BARF type anions had instead a dramatic effect on the activity of the catalyst in the enantioselective hydrogenation of unfunctionalized tri- and tetra-substituted olefins in common organic solvents, although with a minor effect on the enantioselectivity.[131c] This interesting anion effect has been recently studied by PGSE and ^1H, ^{19}F-HOESY NMR techniques.[132] In contrast to earlier findings with Ir-diphosphane complexes, addition of iodide causes a decrease in enantiomeric excess with catalyst of type Ir[X].



Ir[X]

Scheme 2-20: Synthesis of the (phosphanodihydrooxazole)iridium catalyst Ir[X].

Phosphanodihydrooxazole iridium complexes Ir[X] have been shown to be effectively used as homogeneous catalysts for the hydrogenation of imines in $scCO_2$ upon appropriate modification of the ligand and the counterion.[133] To gain solubility in supercritical carbon dioxide some CO_2-philic groups have to be attached in the ligand or in the anion. For example the CO_2-philic counterion, BARF may be used. If the phosphanodihydrooxazole iridium complexes are modified to adjust them to the specific properties of the reaction medium, the observed selectivity is comparable to that in organic solvents. Thus, phosphanodihydrooxazole iridium complexes with several anions were tested with CO_2-philic groups in the ligand or without. The anion effect in such medium was also observed. The complexes containing $[PF_6]^-$ as counterion leads to quantitative conversion with poor enantioselectivities (up to 37%) while the complexes containing $[BPh_4]^-$ leads to considerably higher e.e. (up to 70%), although with lower activity in the case of the CO_2-philic unmodified ligand. Finally, the complexes containing the BARF anion, leads to high activity and selectivity in $scCO_2$ (> 99% conversion, 81% e.e.) independently of the presence of the CO_2-philic groups in the ligand.[133]

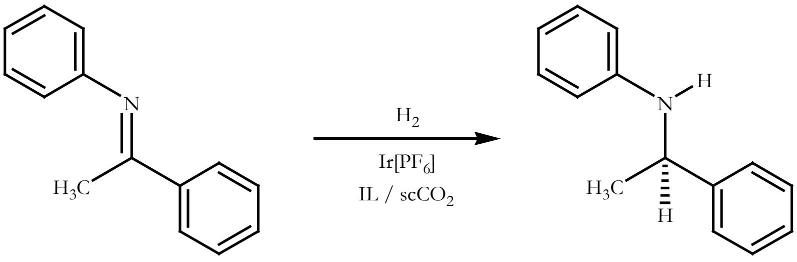
Moreover, the catalyst showed a remarkable enhanced efficiency beyond arguments related to gas availability (see chapter 2.2.1). Thus, the reaction is ~20 time faster in $scCO_2$ as compared with CH_2Cl_2. The CESS procedure allowed catalyst and product separation, but an efficient immobilization of the complex was not possible owing to noticeable deactivation during the recycling process.

The increasing interest toward novel strategies for catalyst immobilization and recycling methodologies aspire to the idea of performing the enantioselective imine hydrogenation in the biphasic system ionic liquid-carbon dioxide. No examples have been reported in the literature so far on this topic, although asymmetric hydrogenation of tiglic acid with Ru-BINAP complexes and recycling with carbon dioxide has been reported.[38] Since ionic liquids are generally able to dissolve polar compounds and charged metal catalysts, it is expected that complex Ir[X] will show a rather good solubility in this media without the need to modify its structure. On the other hand, unmodified complex Ir[X] is not soluble in carbon dioxide; therefore, in IL/CO_2 biphasic systems, all of the catalyst should remain in the lower ionic phase. The results obtained in the enantioselective imine hydrogenation in biphasic system IL/CO_2 with complex $Ir[PF_6]$ will be discussed in the following chapter.

2.4.2 Enantioselective hydrogenation of N-(1-phenylethylidene) aniline in IL/CO_2

The hydrogenation of N-(1-phenylethylidene)aniline to give (*R*)-phenyl-(1-phenylethyl)-amine was used as a benchmark reaction (see Scheme 2-21). In a typical experiment, the appropriate ionic liquid (2.0 ml), the iridium complex ($3 \cdot 10^{-3}$ mmol) and the substrate (sub./Ir = 500/1) were loaded under argon in a window-equipped stainless steel autoclave. The reactor was then pressurized with H_2 and with the desired amount of CO_2 (see Table 2-13) and heated to 40°C for a standard reaction time of 22 hours. The products were collected for offline GC and HPLC analysis from screening experiments by extraction of the IL phase with hexane after cooling and venting, or alternatively isolated by CO_2 extraction as described below. Results are summarized in Table 2-13.

The ionic liquid [EMIM][BTA] was used to assess the influence of CO_2 on the hydrogenation process using $Ir[PF_6]$ as the catalyst precursor (entry 1-3; Table 2-13). Most notably, conversion was only marginal under 30 bar of hydrogen in the absence of CO_2. Significant conversion required the use of hydrogen pressures as high as 100 bar. However, quantitative formation of the hydrogenation product was observed at partial pressure of 30 bar in the presence of 8.9 g of CO_2, under otherwise identical conditions. The extraordinary enhancement of the hydrogen availability in [EMIM][BTA], which has been proved with high pressure NMR measurements (see chapter 2.2.3), can explain the lack of reactivity of the iridium catalyst Ir[PF_6] in the absence of carbon dioxide. However, the availability of molecular hydrogen in the reaction mixture may be sufficient to complete the reaction, at comparable reaction time, with the ionic liquid [4MBP][BTA], see Table 2-13, entry 4 and 5.



Scheme 2-21: Enatioselective imine hydrogenation with the phosphanodihydrooxazole iridium catalyst Ir[PF_6] in IL/CO_2 system.

Table 2-13: Enantioselective hydrogenation of N-(1-phenylethylidene)aniline with different IL/scCO_2 systems.

entry	IL	T [°C]	H_2 [bar]	CO_2 [g]	Conversion %	e.e. (*R*) %
1	[EMIM][BTA][a]	40	30	--	2.7	--
2	[EMIM][BTA]	40	30	8.9	100	56.2
3	[EMIM][BTA][b]	40	100	--	96.7	57.5
4	[4MBP][BTA]	40	30	--	100	53.0
5	[4MBP][BTA]	40	30	9.8	100	52.0
6	[PMIM][PF_6]	40	35	7.5	100	61.0
7	[PMIM][PF_6]	25	30	8.0	100	65.4
8	[BMIM][BF_4]	40	30	7.6	92.2	30.2
9	[EMIM][BARF]	40	30	8.9	100	78.2
10	[EMIM][BARF]	0	30	10.0	53.6	76.4
11	[PMIM][PF_6][c]	40	30	8.6	100	62.3
12	[PMIM][PF_6][d]	40	30	9.2	100	63.5

Conditions: reaction time 22 hours, substrate/Ir = 500/1.a = 2.8% of hydrolysis of the C-N double bound was observed; b = 2a/Ir = 100/1; c = Ir[Cl] isolated; d = in situ protocol.

As previously mentioned, the performance of the cationic catalyst Ir[X] may be in some cases influenced by the choice of the counterion. In order to exploit this tuning effect in conventional solvents, the synthesis of individual catalyst precursors Ir[X] is necessary. Using ILs as a catalyst support creates the opportunity to use the same precursor and introduce the variation of X^- with the choice of the IL.

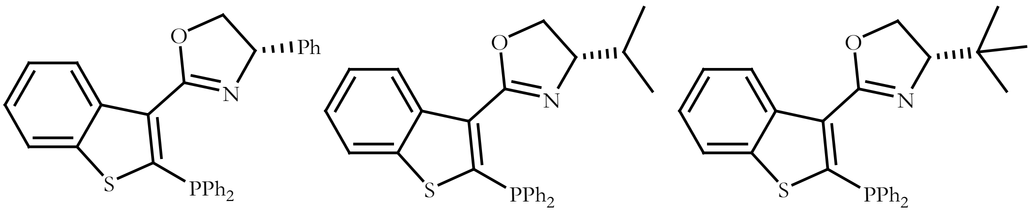
The hydrogenation of the prochiral imine of the acetophenone was clearly influenced by the anion of the ionic liquid, and enantioselectivity increases in the order $[BARF]^-$ > $[PF_6]^-$ > $[BTA]^-$ > $[BF_4]^-$ with decreasing of the coordinating ability of the counterion X^- (entry 9, 6, 2, 8; Table 2-13). The performance varied only marginally as a function of the cation (entry 2,4; Table 2-13). While variation on the temperature did not influence the selectivity, it quite notably altered the rate of the reaction (entry 9-10; table Table 2-13).

A major issue dealing with ionic liquid as solvents is their purification from chloride anions because the general synthetic route usually involves an anion exchange reaction starting from a chloride salt (see chapter 2.2.2). For this reason, the first attempts to perform the reaction in the homemade ionic liquid $[BMIM][BF_4]$ and [EMIM][BARF] were unsuccessful. This has been attributed to traces of chloride anions present in this ionic liquid, which poisoned the iridium catalyst $Ir[PF_6]$. This could be solved by washing with aqueous solution of $AgNO_3$. All ionic liquids tested were able to activate the catalyst after this pre-treatment in order to remove possible chloride anions.

Despite of the adverse effect of larger concentration of Cl^- ions, an *in situ* protocol is possible for the imine hydrogenation. The anion exchange with the IL allows the use of an *in situ* catalyst formed directly from the air stable precursors $[Ir(cod)(Cl)]_2$ and P-N ligand with the appropriate molar ration. The metal complex $[Ir(cod)(Cl)]_2$ and the P-N ligand are not very soluble in the ionic liquid and simple mixing in the IL is not possible. However, an *in situ* protocol is possible by dissolving the desired amount of metal precursor and the P-N ligand in a mixture 25/75 (vol/vol) of CH_2Cl_2 with the appropriate ionic liquid. The organic solvent has to be completely removed under high vacuum before carrying out the hydrogenation reaction. Almost identical results are observed with the *in situ* protocol in $[PMIM][PF_6]$ as compared to the isolated complex in the same IL (entry 12; Table 2-13). The chloride iridium complex Ir[Cl], obtained by simple mixing the precursor and the ligand in CH_2Cl_2 and removing the solvent under vacuum, can also be dissolved successfully in the ionic liquid $[PMIM][PF_6]$, and the hydrogenation reaction is then possible as previously described (entry 11; Table

2-13). The direct use of the chloride precursor would not be possible in a conventional solvent due to the poisoning effect of chloride anions.[130]

The easy *in situ* protocol mentioned above opens a smooth synthetic way to test a variety of P-N ligands in the enantioselective hydrogenation of the N-(1-phenylethylidene)aniline. In order to verify this, a series of ligands recently introduced by the group of Cozzi was investigated.[134] All catalytic solutions were prepared as mentioned before dissolving the ligand and $[Ir(cod)Cl]_2$ (ligand/metal = 1:1) in a mixture of ionic liquid and CH_2Cl_2, the organic solvent was removed by vacuum and the ionic liquid solution transferred in to a 10 mL stainless steel reactor. After charging the substrate, H_2 and CO_2, the reaction was allowed to proceed at 40 °C; the results are indicated in Figure 2-26. The catalyst showed a high activity with all ligands tested, and quantitative conversion was obtained within a reaction time of 22 hours. The enantioselectivity varies between 55% and 68% and the enantiomer (*R*) was obtained as the major isomer. In conventional organic solvent (CH_2Cl_2) the isolated iridium complexes with BARF as counterion give respectively 46, 86 and 76% enantioselectivity.[134]



[BMIM][PF_6]
Conversion > 99%
e.e. = 58% (*R*)

in CH_2Cl_2, BARF
as counterion
Conversion > 99%
e.e. = 46% (*R*)

[BMIM][PF_6]
Conversion > 99%
e.e. = 55% (*R*)

in CH_2Cl_2, BARF
as counterion
Conversion > 99%
e.e. = 86% (*R*)

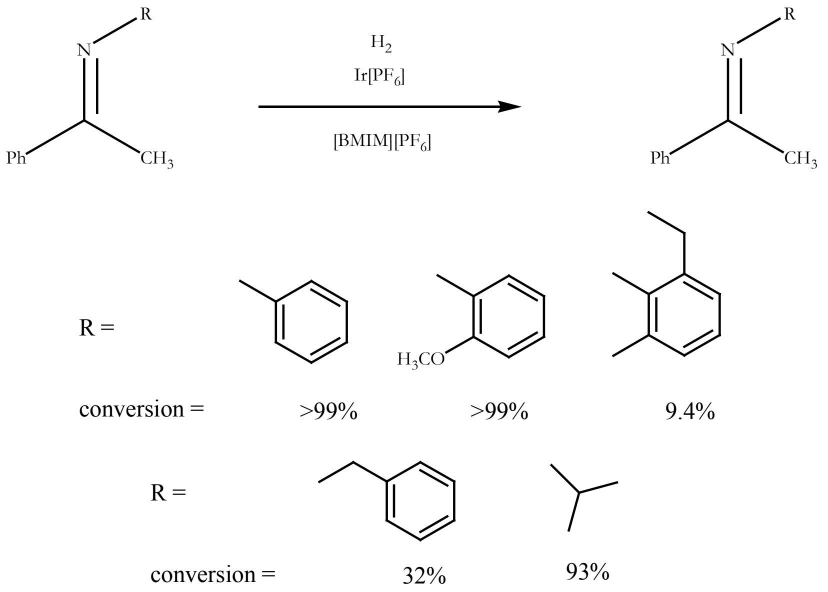
[PMIM][PF_6]
Conversion = > 99%
e.e. = 68% (*R*)

in CH_2Cl_2, BARF
as counterion
Conversion > 99%
e.e. = 76% (*R*)

Figure 2-26: Enantioselective hydrogenation with different P-N ligands.

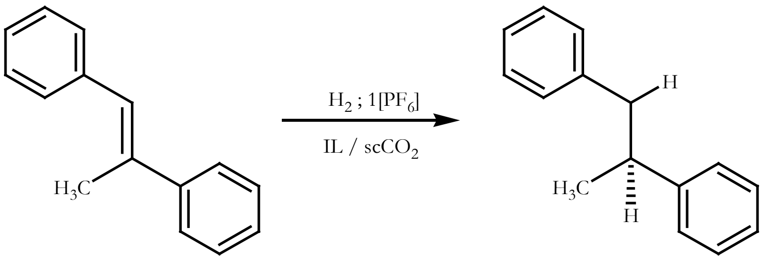
2.4.3 Hydrogenation of other substrates

The substrate scope of Ir[PF_6] was tested in the system [BMIM][PF_6]/CO_2. As seen from Scheme 2-22, the scope and limitations are largely parallel to those observed in conventional solvent systems and $scCO_2$ indicating that the principal mechanistic pathway remains similar in all cases. Imines formed from substituted anilines are readily reduced unless the steric bulk of the *ortho* substituents becomes too large. The [1-(2-methoxy-phenyl)-ethylidene]-phenyl-amine give quantitative conversion and an enantiomeric excess up to 34% (*R*). Changing the aryl group at nitrogen for a benzyl substituent leads to a sharp decrease in conversion, similar to the situation in $scCO_2$. On the other hand, the isopropyl substituted imine is readily hydrogenated. Attempts to analyze the enantiomeric excess by GC and HPLC methods were unsuccessful up to know. The substrate 5-methyl-3,4-dihydro-2*H*-pyrrole is not hydrogenated with catalyst Ir[PF_6] under any of the conditions available so far, which was not surprising, because the hydrogenation of cyclic imine is an intrinsic limitation of the iridium catalyst Ir[PF_6]. Further studies on the substrate scope considering imine hydrogenation, are still under investigation.



Scheme 2-22: Substrate scope of the iridium catalyst Ir[PF_6] in the ionic liquid [BMIM][PF_6]

In order to further investigate the reactivity of the catalyst Ir[PF_6] in ionic liquid carbon dioxide media, the hydrogenation of unsaturated C-C bonds was tested. The phosphanodihydrooxazole-iridium catalyst Ir[PF_6], has been shown to be a very active and selective catalyst for this unfunctionalized olefin in common organic solvent. The test reaction considered here was the enantioselective hydrogenation of α-methyl stilbene (see Scheme 2-23), which was typically carried out in a stainless steel autoclave at several reaction conditions as indicated in Table 2-14.



Scheme 2-23: Enantioselective hydrogenation of α-methyl stilbene in the catalyst Ir[PF$_6$] in ionic liquid-carbon dioxide.

Unfortunately, the reaction in ionic liquid either alone or in combination with carbon dioxide did not result in any significant conversion. Prolonged reaction time or increasing the temperature did not yield any further improvement. Attempts to perform the reaction in pure carbon dioxide or with an anhydrous ionic liquid (in the presence of molecular sieves) yielded no better result. This class of iridium catalyst has been studied by Crabtree who observed the formation of stable hydride-bridged iridium trimers as a deactivation pathway in the hydrogenation of C-C hindered double bonds.[135] The source of the deactivation of the iridium phosphanodihydrooxazole catalyst Ir[PF$_6$] in the system IL/CO$_2$ is not yet known.

Table 2-14: Results of the hydrogenation of C-C double bonds with catalyst Ir[PF$_6$] in various solvents systems.

Entry	Solvent	Sub/Cat	time / T	H$_2$/Total [bar]	Conversion [%]
1	[PMIM][PF$_6$]/CO$_2$	250/1	22h/40°C	50/130	--
2	[BMIM][BTA]/CO$_2$	200/1	22h/40°C	50/130	8.8
3	[BMIM][BTA]/CO$_2$	200/1	72h/60°C	150	1.5
4	[BMIM][BTA]/CO$_2$	200/1	72h/60°C	50/130	2.0
5	[PMIM][PF$_6$]/CO$_2$	25/1	120h/25°C	50/130	--
6	CH$_2$Cl$_2$	25/1	25h/25°C	40	80.2
7	CO$_2$	25/1	26h/25°C	40/130	7.3
8	[PMIM][PF$_6$]/mol. sieves/CO$_2$	25/1	24h/40°C	40/130	3.3

2.4.4 Catalyst recycling and continuous flow processing

The recycling of the iridium catalyst Ir[PF_6] in the system IL/CO_2 was investigated. Carbon dioxide can potentially be used to extract the product of the hydrogenation reaction from the catalytic solution by flowing it at certain value of pressure and temperature through the autoclave, phenyl-(1-phenyl-ethyl)-amine is isolated in a solvent free manner into a cold trap as a white crystalline compounds. Subsequently, the reactor can be charged again with another batch of imine for the successive hydrogenation reaction. As shown in Figure 2-27, the iridium catalyst Ir[PF_6] showed remarkable activity and stability for more than 7 cycles, the conversion maintained above 95% in all the runs and the enantiomeric excess constantly around 63%. The extraction of the amine was carried out using a constant pressure of 160 bar at 45 °C and an exit flow of around 800 cm^3 min^{-1} of CO_2. In the course of 7 runs, 97.5% of the product was recovered in the cold trap, thus sufficiently closing the mass balance. All samples extracted were analyzed *via* ICP measurement to assure the iridium content. From this analysis, the iridium content was below the detection limit of the instrument indicating that upon 7 cycles there was no significant leaching of metal. The total turnover achieved was 3000 and, the catalyst in its active form showed a stable activity over a time-scale of several weeks.

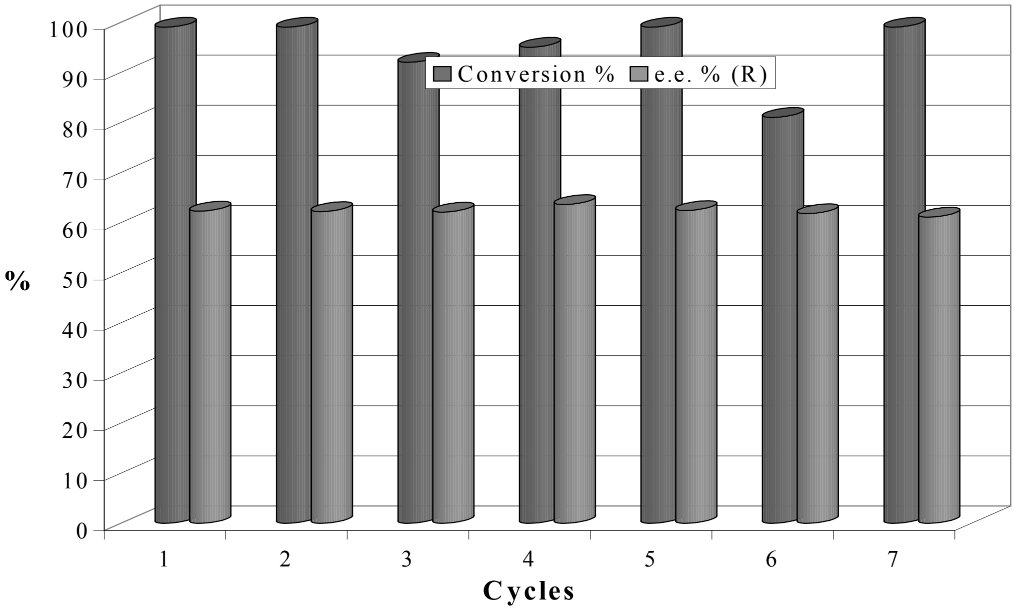


Figure 2-27: Catalyst recycling using the system [BMIM][PF_6]/scCO_2.

To fully exploit the potentiality of this long-term stability of the iridium catalyst several attempts of continuous flow hydrogenation have been performed. However, the test substrate is a solid (melting point ~ 40 °C), so the use of a HPLC pump to push the substrate in the catalytic solution is not possible without expensive and complicated modifications to the system. In order to overcome this drawback, two stainless steel reactors (windows-equipped), with a volume of 20 mL, were connected in series and a stream of carbon dioxide and hydrogen were pushed through it. Ideally, a saturated imine solution of carbon dioxide should move from the first to the second reactor that contains the catalytic solution (see Figure 2-28) dissolved in [EMIM][PF_6] ($5\cdot10^{-3}$ mmol mL^{-1}). The flow of CO_2 and H_2 goes through the first autoclave, which has a temperature of 50 °C, to the second one in which temperature and pressure were changed in order to effect the extraction of the product from the catalytic solution. Table 2-15 shows the results of these experiments.

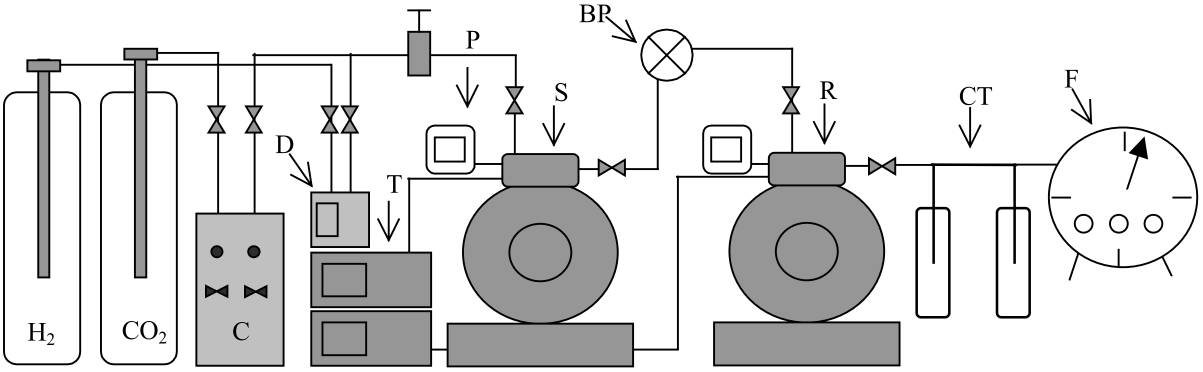


Figure 2-28: Scheme of the system used for the continuous flow hydrogenation of imine with IL/CO_2 system. Legend: C = CO_2 compressor; D = H_2 dosing unit; T = Thermocouple; P = Pressure Gauge; BP = Back Pressure regulator; S = Reservoir of substrate; R = Reactor; CT = Cold Traps; F = Flow meter.

Table 2-15: Continuous flow hydrogenation of N-(1-phenylethylidene)aniline in ionic liquid/$scCO_2$.

entry	P/T reactor	Out [mg]	time [h]	Conversion [%]	CO_2 flow [l/h]
1	175 bar 45 °C	5.5	3.5	39.1	67
2	190 bar 35 °C	7.9	6.5	30.1	109
3	200 bar 35 °C	17	8.5	26.2	129
4	200 bar 35 °C	63.1	22.5	25.3	184
5	110 bar 40 °C	54.5	30.5	26.9	152

As shown in Table 2-15, the system has fairly low activity, with conversion never exceeding 40% over the entire reaction time. Unfortunately, the biggest limitation of this set up arises from a technical problem related to the difficulty of handling the solid substrate. It was indeed possible to estimate that all substrate charged (2.2 g; 11.3 mmol) was moved out from the first autoclave in 6 hours leading to an approximated substrate flow of 0.4 g h^{-1}. Compared to this value, the product collected in the cold trap was in every cases extremely low although varying the pressure and temperature in the reactor causes increasing of recovered compounds. At the end of the experiment, the ionic liquid was extracted with pentane several time until all compounds was recovered. Thus, 0.55 g were recovered from the residue IL while only 148 mg were collected in the cold trap. This means that, only 31% of the substrate charged in the first autoclave reached effectively the catalytic solution. The remaining substrate was found to be condensed along capillaries and in the mechanism of the back pressure regulator despite the fact that the entire system was warmed to 40 °C. At the end of the process, only 27% of the effective amount of substrate that reached the reactor was efficiently extracted in the cold traps.

Mainly because of those technical problems, continuous flow hydrogenation of N-(1-phenylethylidene)aniline has not been completely successful so far. The low conversion observed may be due to insufficient residence-time, not optimized flow rate *etc*.

2.5 Summary

In this chapter a novel biphasic system consisting of ionic liquid and compressed or supercritical carbon dioxide was tested in two synthetically important metal catalyzed reactions. The combination of non-volatile ILs with non-hazardous CO_2 represents a particularly attractive approach to environmentally benign processes. In addition to the use of CO_2 alone, the IL provides the potential to activate and tune the organometallic catalyst. This has been successfully demonstrated in both reactions: hydrovinylation of styrene and hydrogenation of imine, in particular N-(1-phenylethylidene)aniline. Furthermore, some physical properties of the system IL/CO_2 were investigated. It was shown that the conductivity of the IL [EMIM][BTA] increases with carbon dioxide pressure. This has been related to the slight decrease in enantioselectivity observed in the hydrovinylation of styrene in this media. Hydrogen solubility has been measured in [EMIM][BTA] *via* high pressure NMR technique. A very low hydrogen solubility/availability in the ionic liquid tested is most probably responsible for the lack of reactivity with the catalyst Ir[PF_6] in absence of carbon dioxide. However, in the biphasic system IL/CO_2, hydrogen solubility was found to substantially increase, allowing for efficient hydrogenation reaction. Thus, in order to evaluate catalyst activity or even somehow predict selectivity, it is also important to consider the physical-chemical properties of the ionic liquid-carbon dioxide media.

The Wilke's catalyst was activated and tuned in all ionic liquids tested, and the activity and the selectivity of the catalyst strongly dependent on the anion of the IL. The biphasic system IL/CO_2 has been successfully applied in a continuous flow manner for the hydrovinylation of styrene. In this case the catalyst showed stable activity and selectivity up to 60 hours. With this system, reaction and product separation was possible without exposing the catalyst to a variation of temperature, pressure or substrate concentration.

The imine hydrogenation reaction has also been tested here and successfully applied with a batch-wise recycling methodology. Noteworthy, iridium leaching was below the detection limit, and no metal was found in the isolated product. Furthermore, catalyst performance is tuned by the anion in the ionic liquid, and higher enantiomeric excess was obtained with ionic liquids containing low coordinating anions. So far, the system could not be successfully applied for the enantioselective hydrogenation of C-C double bonds. For imine hydrogenation, an easy synthetic protocol which allows the formation of the active catalytic precursor directly in the ionic liquid was developed. This permits a straightforward method for testing other chiral P-N ligands.

This new system for catalyst immobilization is open to further improvement through the molecular design of the ionic solvent or the catalyst (chiral ionic liquids, stable catalytic complexes *etc.*). At the same time, reaction engineering in order to maximize residence time, use of electronic devices which permit a very accurate control of the flows, use of on-line analytical methods *etc* are of fundamental importance for detailed optimizations and a broad application of this new technology.

3 Catalysis with PEG modified ligands and compressed carbon dioxide

3.1 Background

As already introduced in chapter 2.2.1, supercritical fluids are substances heated above their critical temperature T_c and compressed above their critical pressure P_c.[6a] Carbon dioxide is the most widely used supercritical fluid by far; it has mild critical data, it is non-toxic, non-flammable and can be easily handled.[6a,29b] Density, solvent power, dielectric constant, miscibility with other compounds and heat capacity are some of the most important characteristics of carbon dioxide that can be tuned by variation of pressure and temperature.[6a] These unique properties open the way to novel strategies for catalyst immobilization using carbon dioxide alone or in combination with other solvent system. During the reaction stage reagents and catalyst need to be in intimate contact but, at the same time, a maximum of discrimination should be obtained in the separation stage.[20] Catalyst immobilization involving supercritical fluids encompasses three different approaches.

- Solid-supercritical fluid: the catalyst is anchored to a solid organic or inorganic support and it is in contact with reagents dissolved in carbon dioxide.
- Liquid-supercritical fluid: the catalyst is dissolved in a liquid phase insoluble with the carbon dioxide phase, reagents and products are in the supercritical phase. Alternatively, in the inverted system, the catalyst containing the CO_2-philic group is dissolved in carbon dioxide, while reagents and products are in the liquid phase.
- Supercritical fluid: the tunable properties of the fluid are used to control catalyst, reagents and products solubility. It is referred to such process as CESS (*c*atalysis and *e*xtraction using *s*upercritical *s*olution).

The application of supercritical carbon dioxide in a continuous flow fixed bed reactor was successfully developed by Poliakoff and co-workers. The use of immobilized homogeneous catalysts were applied to hydrogenation,[11a,136] Friedel-Crafts alkylation[137] and etherification[138] reactions using catalyst supported on polysiloxane. Furthermore, the Rh-complex of *N*-(3-trimethoxysilyl-*n*-propyl)-4,5-bis(diphenylphosphino)phenoxazine immobilized on silica was successfully applied in the hydroformylation of 1-octene in a continuous flow manner.[139] The system showed high selectivity and reactivity over 30 hours continuously.

The combination of non-volatile ionic liquids with carbon dioxide has been described in the previous chapter and it surely offers an intriguing alternative strategy for catalyst immobilization.[38-40] An organometallic catalyst, not soluble in $scCO_2$, is dissolved in the ionic liquid, while the supercritical fluid is used as a mobile phase to transport reagents and products even in a continuous fashion.[41-42] This methodology was successfully applied in the hydrovinylation of styrene and in the hydroformylation of 1-dodecene.[41-42]

Another intriguing combination is offered by the use of poly(ethylene glycol) (PEG) with carbon dioxide in a liquid/supercritical biphasic system. PEG has been tested extensively and it is approved for use in food. High molecular weight PEGs are waxy solids and become expanded low viscosity liquids under CO_2 pressure. These molten PEGs are capable of dissolving organic compounds including metal catalysts. Recently, Jessop and coworkers demonstrated that PEG 900 and PEG 1500 may be efficiently used as solvent for the hydrogenation of styrene, catalyzed by the Wilkinson's complex, under CO_2 pressure. Reaction products can be isolated from the polymer using supercritical CO_2 extraction technique with fairly low rhodium leaching. PEG residues may be found in the extracted product if the molecular weight of the polymer is not sufficiently high.[36]

The CESS methodology was efficiently applied, for example, in the hydroformylation of styrene and its derivatives using the highly fluorinated ligands modified complex (*R*,*S*)-3-H^2F^6-BINAPHOS.[30] A more general application of this procedure presents some limitations: the modification of the catalyst is expensive and it will not necessarily lead to a homogeneous system during the reaction under CO_2 pressure, which is beneficial for higher reaction rates. For other examples on catalyst recycling with carbon dioxide, refer to chapter 2.2.1.

This chapter introduces, for the first time, the combination of poly(ethylene glycol) derived rhodium complexes with carbon dioxide as an efficient method for catalyst recycling. A rhodium catalyst containing phosphine ligands with PEG tails will be designed and synthesized to be soluble in the substrate of the reaction. No other organic solvents will be used to carry out the reaction. Furthermore, the PEG-ligand should lead to a metal complex insoluble in carbon dioxide. Thus, the catalyst/products separation can be performed by pressurizing the autoclave with carbon dioxide at the end of the reaction. In this way, a homogeneous reaction mixture will be converted into a solid/supercritical CO_2 biphasic system during the recycling stage of the process. This approach can not be framed in one of the previously mentioned methodologies of catalyst immobilization involving supercritical fluids. The reaction is indeed intended to be performed in the absence of carbon dioxide that will be used only for extraction of products. The only previous example reported in the literature concerns the hydroformylation of 1-octene using a rhodium catalyst modified with phosphines ligands having long alkane chains.[37] This leads to a metal complex insoluble in CO_2 and the separation of the product mixture from the catalytic solution is performed by flushing the supercritical fluid through the reactor vessel and decompressing it into a cold trap or another reactor. The authors also used carbon dioxide as a solvent for the reaction. However, the reaction is slow with a turn over frequency less than 70-80 h^{-1}.[37]

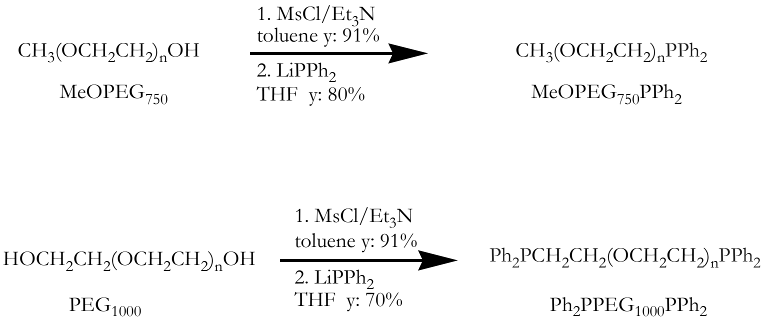
Evidently, switching between a homogeneous system during the reaction, to a heterogeneous at the end of the transformation, thus allowing an easy separation of the catalyst from the products, is one of the most desirable approaches to the field of biphasic catalysis.[20] The combination of PEG-ligands and supercritical carbon dioxide that will be follow discussed, propose a new way to such approach for biphasic catalysis.

3.2 Synthesis of PEG-modified phosphines and their application as ligands in solvent-free hydroformylation

It is well established that poly(ethylene glycol) (PEG) of high molecular weight is not soluble in supercritical carbon dioxide. Furthermore, CO_2 pressure can decrease the melting point and viscosity of PEG of a certain molecular weight so that it can be used as solvent for catalytic purposes.[36] On the other hand, poly(ethylene glycol) moieties attached to phosphorous ligands are commonly used to modify metal catalysts.[26] Several synthetic methodologies are indeed available to prepare and characterize this class of ligands which are for example successfully applied in biphasic catalytic reactions. Nevertheless, no information is available to date on the phase behavior of PEG modified ligands and carbon dioxide. It is expected that metal complexes modified with such polymeric groups will lead to carbon dioxide insoluble compounds, depending on the length and number of the PEG chains. Thus, quantitative precipitation of a PEG modified metal catalyst may be caused by pressurizing the reaction vessel with carbon dioxide, leading to an alternative way for catalyst recovery. Some reported PEG modified catalysts contain very long poly(ethylene glycol) chains with a molecular weight of around 2000. Those catalysts are solids and need organic solvents to carry out the reaction. The objective of the following chapter was to design and synthesize a simple phosphine ligand with a defined number of poly(ethylene glycol) chains of various lengths. This metal complex must be insoluble in carbon dioxide and, at the same time, soluble in the substrates of the reaction since no other organic solvents will be added during the reaction. The hydroformylation of medium to long chain olefins have been chosen as bench-mark reaction. Thus, the designed ligands should be miscible in 1-octene, 1-tetradecene *etc* so that the reaction can be performed using only carbon dioxide as solvent in the entire process.

Poly(ethylene glycol) of moderate chains lengths (average molecular weigh 750-1000) have been introduced for this purpose to synthesize monodentate triphenyl phosphine ligands analogous to TPP (triphenyl phosphine).

This project was carried out in collaboration with Dr. J. Jang[#] who synthesized the two ligands, in high yields and purity, as low melting colorless to pale yellow waxy substances.



Scheme 3-1: Synthetic approach to the poly(ethylene glycol) derived ligands.

The characterization of the ligands $MeOPEG_{750}PPh_2$ and $Ph_2PPEG_{1000}PPh_2$ was performed by ^{31}P and ^{13}C NMR spectroscopy. The ^{31}P NMR chemical shifts are nearly identical for both ligands, and the NMR characterizations are in accordance with data reported in the literature for similar ligands.[140] A detailed description of the synthetic methods as well as a full characterization by NMR technique is reported in the experimental section (chapter 5).

The PEG modified ligands $MeOPEG_{750}PPh_2$ and $Ph_2PPEG_{1000}PPh_2$ were tested in homogeneous catalysis, particularly in the hydroformylation of olefins under solvent-less conditions. The catalyst precursor was formed in situ by preparing a solution of the substrate 1-octene, $[Rh(CO)_2(acac)]$ and the ligand $MeOPEG_{750}PPh_2$ (P/Rh = 5/1). A series of reactions were performed in a completely solvent-free manner with a constant pressure (50 bar of syngas) and reaction time (two hours) varying other reaction parameters (see Scheme 3-2).

The system showed a temperature dependent activity, thus higher reaction rates and selectivity toward 1-nonanal were obtained at 70 °C (Table 3-1, entry 3, 5-8). At 50 °C and 60 °C the reaction proceeded at a lower rate but with slightly increased selectivity toward 1-nonanal (entry 1-2), whereas higher temperature lead to lower selectivity due to isomerization of 1-octene and the relative aldehydes formed (entry 4).

The substrate/catalyst ratio was varied in order to assess the activity of the system, which illustrated a reasonably high turn over frequency around 1700 h^{-1}. The system is very selective toward aldehydes and does not lead to a significant amount of isomerization for temperatures lower than 90 °C. This screening suggests that the PEG-phosphine complex has roughly the

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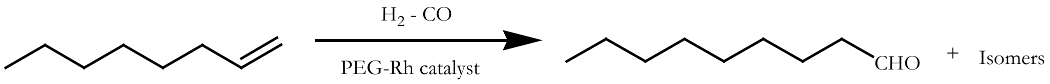
[#] Postdoctoral research associate in the group of Prof. W. Leitner 2002-2003.

same activity and selectivity of the analogous triphenylphosphine or alkyl-diphenylphosphine rhodium complex.



Scheme 3-2: Solvent free rhodium catalyzed hydroformylation of 1-octene.

Table 3-1: Activity and selectivity of the $MeOPEG_{750}PPh_2/[Rh(CO)_2(acac)]$ catalyst in the hydroformylation of 1-octene at different reaction conditions.

Entry	Temperature [°C]	Rh loading [%]	Conversion§ [%]	Selectivity n-nonanal [%]	L/B#	Side products$ [%]
1	50	0.1	7.7	73.4	2.8	<0.1
2	60*	0.5	56.1	75.2	3.0	<0.1
3	70	0.1	>99	71.4	2.5	<0.1
4	90	0.09	>99	57.9	1.9	11.6
5	70	0.05	96.1	71.5	2.5	<0.1
6	70	0.03	96.2	71.3	2.5	<0.1
7	70	0.02	84.8	71.5	2.5	<0.1
8	70	0.01	34.0	71.4	2.5	<0.1

*reaction time 3 hours; §conversion is calculated considering the unreacted 1-octene; #L/B = n-nonanal / overall branched aldehydes; $side products = C-8 isomers + octane + internal aldehydes.

In such a solvent free system the activity of the PEG-rhodium complex is influenced by its miscibility with the substrate. If the substrate and the PEG-catalyst lead to a complete homogeneous system, higher reaction rates are expected to be observed.

The experimental results obtained confirmed these expectations. The rhodium complex with ligand $MeOPEG_{750}PPh_2$ shows very high activity for each substrate tested under optimized conditions (Table 3-2, entry 1-4; 6). No solubility problems were encountered in this case. It has to be specified that the substrates 1-decene and 1-tetradecene were of technical grade purity (94% of the terminal olefin in the case of 1-decene; 92% in the case of 1-tetradecene). Nevertheless, quantitative conversion of the terminal olefin was obtained and none of the internal olefins present in the reaction mixtures were hydroformylated. Thus, reasonable selectivity toward the linear aldehyde was obtained (around 72%) in both cases. Furthermore, the internal double bound in the trans-4-octene was not hydroformylated at optimized reaction conditions. Therefore, the PEG-modified catalyst shows a fairly good regioselectivity toward terminal olefins for reaction carried out at 70°C.

Table 3-2: Hydroformylation of various substrates with the $MeOPEG_{750}PPh_2$/[$Rh(CO)_2(acac)$] catalyst.

Entry	Substrate	Conversion[§] [%]	Aldehyde yield[#] [%]	L/B
1	1-octene	> 99	> 99	2.5
2	1-decene	> 99	95.3	2.5
3	1-tetradecene	> 99	90.0	2.4
4	2-hex-5-enyl-oxirane	> 99	98.3	2.3
5	1,1-diphenyl ethene[†]	--	--	--
6	styrene	98.3	98.3	10/90
7	trans-4-octene	--	--	--

Reaction conditions: sub/cat = 2000/1; T = 70 °C; P = 50 bar syn gas ($CO/H_2 = 1$); t = 2 hours. [§]Conversion is calculated considering the unreacted terminal olefin; [#]L/B = terminal aldehyde / overall branched aldehydes; † conversion up to 35.9 % has been observed after 10 days at 100 °C.

Table 3-3: Hydroformylation of various substrates with the $Ph_2PPEG_{1000}PPh_2$/[$Rh(CO)_2(acac)$] catalyst.

Entry	Substrate	Conversion[§] [%]	Aldehyde yield[#] [%]	L/B
1	1-octene	98.3	98.3	2.2
2	1-decene	56.6	53.2	2.8
3	1-tetradecene	7.5	6.9	2.3
4	Styrene	> 99	> 99	10/90

Reaction conditions: sub/cat = 2000/1; T = 70 °C; P = 50 bar syn gas ($CO/H_2 = 1$); t = 2 hours. [§]Conversion is calculated considering the unreacted terminal olefin; [#]L/B = terminal aldehyde / overall branched aldehydes.

On the other hand, the rhodium complex modified with ligand $Ph_2PPEG_{1000}PPh_2$ has a lower solubility in some of the olefins tested, especially in 1-decene and 1-tetradecene. Lower activity has been observed in the hydroformylation of these substrates at comparable reaction conditions (Table 3-2 and Table 3-3). The system $MeOPEG_{750}PPh_2$/[$Rh(CO)_2(acac)$] showed almost the same activity and selectivity with all the linear olefins tested, and selectivity of up to 71% toward the linear aldehyde was observed (see Table 3-2, entry 1-4). Moreover, the 2-hex-5-enyl-oxirane, which represents an important substrate for further functionalization,[141] has also been hydroformylated with high yield and selectivity with the reaction unaffected by the presence of the epoxyde functional group (Table 3-2, entry 4). The hydroformylation of a particularly stericly hindered olefin such as 1,1-diphenyl ethene (entry 5; table 3.2-2) did not work at the same reaction conditions. Conversion up to 35.9% (61% of aldehydes, 100% selectivity toward the linear product) was achieved at more harsh conditions (100 °C, 10 days, 50 bar CO/H_2, sub/cat = 300/1) according to previously reported data on the hydroformylation of this substrate.[142] The reaction mixture consisted of 11.6% of the hydrogenated 1,1-diphenyl ethane and 2.3% of the 3,3-diphenyl-propan-1-ol derived from the reduction of the linear aldehyde. Noteworthy, this reaction mixture was efficiently extracted with CO_2 extraction technique (extraction conditions: temperature = 45°C; pressure 80 to 130 bar; total amount of CO_2 = 220 L). The $Ph_2PPEG_{1000}PPh_2/[Rh(CO)_2(acac)]$ catalyst despite of a lower activity in the hydroformylation of 1-decene and 1-tetradecene showed a comparable selectivity toward the linear aldehyde, up to 75%. These catalytic systems have comparable activity and selectivity in the hydroformylation of 1-octene and styrene, and the catalysts are completely soluble with the reactants.

3.3 Batch-wise recycling of the PEG-catalyst

The phase behavior of the PEG-modified catalyst and supercritical carbon dioxide was explored. For this purpose, a 20 mL autoclave was charged with 1.3 g of ligand $MeOPEG_{750}PPh_2$ and pressurized with carbon dioxide at several temperatures. Looking through the thick-walled window, it was assured that the compound does not dissolve in the liquid or supercritical CO_2, but remains in the bottom of the reactor even at high density carbon dioxide (200 bar; 35 °C; d = 0.876 g/mL). The supercritical carbon dioxide remains as a colorless phase in all experiments, while the ligand, a pale yellow viscous oil, can be observed in the bottom of the autoclave. To further investigate the solubility of this ligand in carbon dioxide, all the volatile compounds were vented through a cold trap and the autoclave flushed with fresh CO_2 for three times at 200 bar and 35 °C. The contents of the trap was analyzed by ^{31}P NMR and no peak of phosphorous was detected indicating that the charged ligand was not extracted out from the reactor, according to the detention limit of the NMR. The efficiency of the catalyst separation (ligand $MeOPEG_{750}PPh_2/[Rh(CO)_2(acac)]$) with carbon dioxide was further investigated at reaction conditions, where the presence of reagents and products can clearly influence the phase behavior. The hydroformylation reactions of 1-octene was performed at different amounts (densities) of carbon dioxide. The results clearly indicate (see Table 3-4) how the increased amount of carbon dioxide, in the same reactor volume, leads to decreased activity of the catalytic system. This behavior is so effective that it leads to a complete switch off for the reaction, and no conversion was observed at 130 bar of total pressure.

Table 3-4: Hydroformylation of 1-octene at various CO_2 densities.

Entry	System	ΔP (bar)	Conversion§ [%]	n-nonanal [%]
1	CO/H_2	--	100	71.4
2	$CO/H_2 + CO_2$ (7.9 g)	50	66.4	69.7
3	$CO/H_2 + CO_2$ (12.8 g)	77	--	--

Conditions: $[Rh(CO)_2(acac)]$ = 0.01 mmol; ligand $MeOPEG_{750}PPh_2$ = 0.05 mmol; 1-octene = 10 mmol; CO/H_2 = 50 bar; reaction time = 2 hours; temperature = 70 °C; reactor volume ≅ 18 mL; ΔP = (total pressure at room temperature) - (CO/H_2 pressure); §Conversion is calculated considering the unreacted terminal olefin.

Upon pressurizing of the reaction mixture with CO_2, the PEG-catalyst precipitated on the bottom of the autoclave (Figure 3-1), therefore the heterogeneous catalytic mixture obtained has a much lower reactivity. This *"phase switch"* is a function of the carbon dioxide density in the reactor and can be quantitative if it is high enough to bring all substrate in the upper supercritical phase, thus separating it from the catalyst. This particular phase behavior indicates the effective possibility to use carbon dioxide for an efficient recycling of the PEG-metal catalyst.

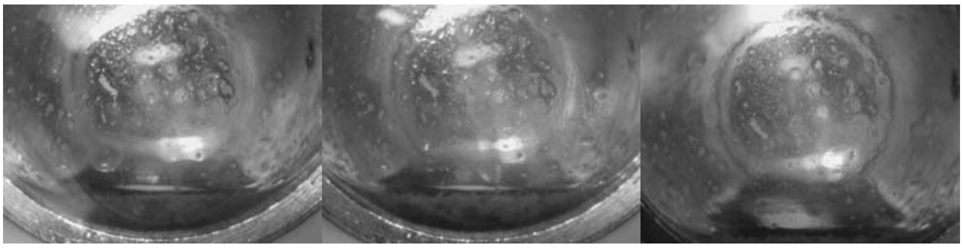


Figure 3-1: Precipitation of the PEG-catalyst with carbon dioxide. The PEG-catalyst is scattered in the window of the autoclave (yellow dots).

The catalyst system $MeOPEG_{750}PPh_2$/[$Rh(CO)_2(acac)$] was successfully tested in a series of batch-wise recycling experiments. A 20 mL stainless steel reactor was charged under argon atmosphere with 0.02 mmol of [$Rh(CO)_2(acac)$] and the ligand $MeOPEG_{750}PPh_2$ (P/Rh = 5/1). The reactor was then charged under argon atmosphere with 10 mmol of 1-octene and the hydroformylation was allowed to proceed at the optimized reaction conditions (70 °C; *syn-gas* = 50 bar), for a convenient longer reaction time (12 hours). At the end of the reaction the autoclave was cooled to 50 °C, pressurized with carbon dioxide, and the extraction process was allowed to proceed venting the CO_2 trough a double cold trap (-70 °C). The extraction was visually observed through the glass window of the autoclave and carried out until no liquid product remained in the reactor and only the catalyst, a yellow viscous oil, was left in the bottom of the reactor. The conditions of the extraction were adjusted time to time and maintained around 150 - 160 bar at 45 - 50 °C. In the initial stage of the extraction, the organic phase expands due to the dissolving carbon dioxide (see chapter 2.2.1). In this stage, two phases are present at the same time: a liquid phase containing mostly the PEG-catalyst, the dissolved carbon dioxide, and the organic reaction products (mainly aldehydes), and an upper phase containing mostly carbon dioxide and reaction products, but not the catalyst. The upper phase is expanded in a cold trap, as previously mentioned, allowing the isolation of the reaction products as a colorless liquid. In the reaction vessel, the level of the expanded liquid decreases during the extraction. The extraction stage may be visually monitored and optimized for example by varying the pressure and temperature of carbon dioxide. If in the initial stage of the extraction process, the level of the liquid is left to increase until it reaches the top of the reactor, the liquid colored phase, containing the metal catalyst, will come out from the reactor causing leaching. The steps of the catalytic process using the PEG modified rhodium complex and carbon dioxide are illustrated in Figure 3-2. At the end of the extraction process the autoclave was charged under argon with another batch of 1-octene and the reaction allowed to proceed at the same reaction conditions. Results and detailed extraction conditions are illustrated in Table 3-5.

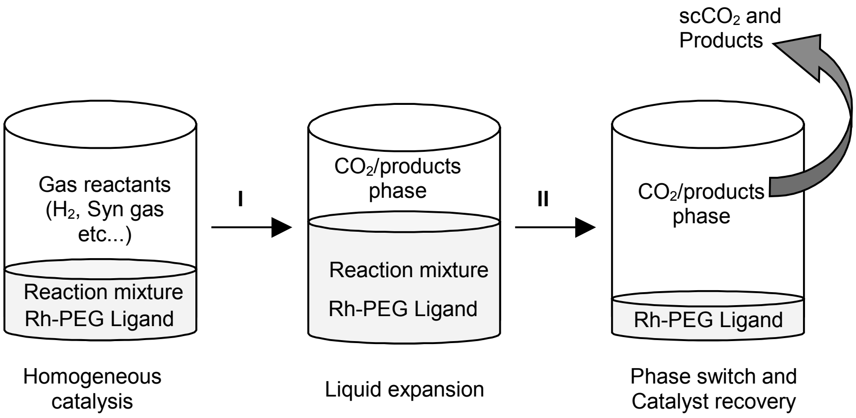


Figure 3-2: Catalytic process using the combination of PEG-modified ligands and $scCO_2$: homogeneous reaction and phase switch with carbon dioxide. **I**: The reaction vessel is pressurized with carbon dioxide and the extraction process starts; CO_2 causes the expansion of the organic mixture. **II**: Pressure and temperature are adjusted during the extraction process until complete recovery of the products: a quantitative phase switch is obtained.

As expected, the density of carbon dioxide is a fundamental factor for the extraction process: with high density carbon dioxide, products are quantitatively extracted very smoothly, while with low densities, more carbon dioxide is generally needed. A technical problem during the extraction may arise from difficulties in controlling the exit valve, and from an insufficient number of cold traps. Nevertheless, almost quantitative recovery of products was obtained at the end of each extraction. The system showed stable activity and selectivity for 6 cycles although small amount of isomerization of 1-octene to internal olefins occurred. Conversion was higher than 99% and the selectivity around 71%.

Table 3-5: Hydroformylation of 1-octene: recycling with supercritical carbon dioxide.

Entry	Conversion§ [%]	L/B#	C-8 isomers$ [%]	Recovered [%]	Extraction conditions (CO_2 density / amount)
1	98	2.5	1.7	91	0.7 g/mL / 40 liters
2	>99	2.5	1.6	97	0.2 g/mL / 355 liters
3	>99	2.4	1.8	91	0.35 g/mL / 173 liters
4	>99	2.3	2.5	93	0.3 g/mL / 271 liters
5	>99	2.4	1.7	92	0.3 g/mL / 231 liters
6	>99	2.3	2.4	103	0.3 g/mL / 171 liters

Reaction conditions: $[Rh(CO)_2(acac)]$ = 0.01 mmol; ligand $MeOPEG_{750}PPh_2$ = 0.05 mmol; 1-octene = 10 mmol; CO/H_2 = 50 bar of constant pressure; temperature = 70 °C; Reaction time = 12 hours; §Conversion is calculated considering the unreacted terminal olefin; $internal olefins has been found as only side products of these reactions; #L/B = n-nonanal / overall branched aldehydes

The results obtained with the PEG modified rhodium catalyst were compared with the analogous triphenylphosphine ligand. The TPP ligand has a low solubility in CO_2[143] thus, in order to perform homogeneous reactions in supercritical carbon dioxide, it needs to be modified with CO_2-philic groups (see chapter 2.2.1). Accordingly, one may think to use this commercially available ligand to perform the hydroformylation reaction and recover the catalyst with CO_2 extraction, as previously described for the PEG variant. Thus, a comparison experiment was needed: the hydroformylation of 1-octene was performed in the same way as previously described and the recycling was carried out using supercritical carbon dioxide (see Table 3-6).

Table 3-6: Hydroformylation and batch-wise recycling using TPP as ligand.

Run	1-Octene [%]	C-8 Isomers [%]	Branched [%]	n-nonanal [%]	L/B
1	1.7	0.4	24.1	73.8	3.1
2	1.9	8.6	43.1	46.4	1.1
3	1.5	5.0	35.7	57.8	1.6

Selectivity of the reaction dropped dramatically within three cycles due to isomerization and the subsequent formation of internal aldehydes the major side reaction. These data suggest that a significant part of the catalytic reaction occurred at phosphine free rhodium carbonyl complexes. Rhodium and phosphorous leaching measurements indicated that within 3 cycle 1.3% of the metal and 2% of the ligand have been extracted during the recycling. The values do not fully explain such a dramatic decrease of selectivity observed after only the first cycle. Nevertheless, recycling of the catalyst using the simple rhodium TPP modified complex and carbon dioxide seem to be impractical. Modification of the metal complex with PEG chains is necessary to achieve an efficient process.

3.4 Multipurpose cartridge of catalyst for a variety of substrates and reactions

Since stable activity and selectivity was observed in the hydroformylation of 1-octene with the PEG modified catalyst, it was attempted to develop a multifunctional cartridge of catalyst to perform the hydroformylation of a range of different substrates. The catalyst system has already been tested with a variety of olefins and it was shown to have high activity and fairly good selectivity toward the linear aldehyde (except in the case of styrene where the selectivity is mostly the branched product). Analogous to the previously described recycling experiment, a 20 mL autoclave was charged with $[Rh(CO)_2(acac)]$ and ligand $MeOPEG_{750}PPh_2$ (P/Rh = 5/1). The reactor was then charged under argon with 1-octene (sub/Rh = 2000/1), which was selected as the starting substrate. The reaction was allowed to proceed at the usual reaction conditions (70 °C, 2 hours). At the end of the reaction, the products were extracted with compressed carbon dioxide and the reactor charged again with another batch of 1-octene. The third cycle was performed in the same catalytic solution changing the substrate to 1-tetradecene and the reaction performed at the same conditions. The extraction was carried out as usual, with a slightly modification of pressure and temperature due to lower volatility of the aldehydes in this case. The products were isolated in a pure form into the cold trap without cross-contamination with the preceding substrate. Table 3-7 shows more in details the variety of substrates used in this experiment. A total of 9 cycles were performed changing the substrates respectively from 1-octene to 1-tetradecene to 1-epoxy-7-octene to styrene, and finally back to 1-octene obtaining exactly the same reactivity and selectivity obtained in the first run with the fresh catalytic solution. In all cases, the products were isolated quantitatively in the cold traps modifying the extraction condition depending on the substrate.

Table 3-7: Hydroformylation of different substrates: extraction conditions.

Run	Substrate	Recovered product	CO_2 condition for extraction	
			P from → to (bar) / T (°C)	CO_2 (L)
1	1-octene	87.0 %	80→96 / 45	130
2	1-octene	92.7 %	85→95 / 45	140
3	1-tetradecene	99.8 %	120→130 / 45	188
4	1-tetraecene	100 %	120→140 / 45	200
5	1-epoxy-7-octene	100 %	90→100 / 45	120
6	1-epoxy-7-octene	100 %	95→105 / 45	130
7	Styrene	91.0 %	86→95 / 45	115
8	Styrene	91.0 %	88→100 / 45	120
9	1-octene	86.2 %	80→100 / 45	100

Furthermore, high activity was achieved in each catalytic cycle with the conversion of the olefin always higher than 99% except in the last hydroformylation of 1-octene in which it was 94%. Selectivity toward the linear aldehyde depended on the substrate, for 1-octene was 73.6%, for 1-tetradecene 70.6%, for 1-epoxy-7-octene 68.9% and in the case of the hydroformylation of styrene selectivity was reversed to 90% of the branched aldehyde. Selectivities obtained were in accordance with the previous values obtained in batch experiments (see Table 3-2). In the entire process, no relevant side products (isomerization and internal branched aldehydes) were observed. Figure 3-3 shows graphically the results obtained with this experiment. All sample collected were analyzed for rhodium and phosphorus contents. At the end of the process, a total of only 1.2% of rhodium and 2.4% of phosphorus was leached in the reaction products and a total turnover number of *circa* 9000 has been obtained.

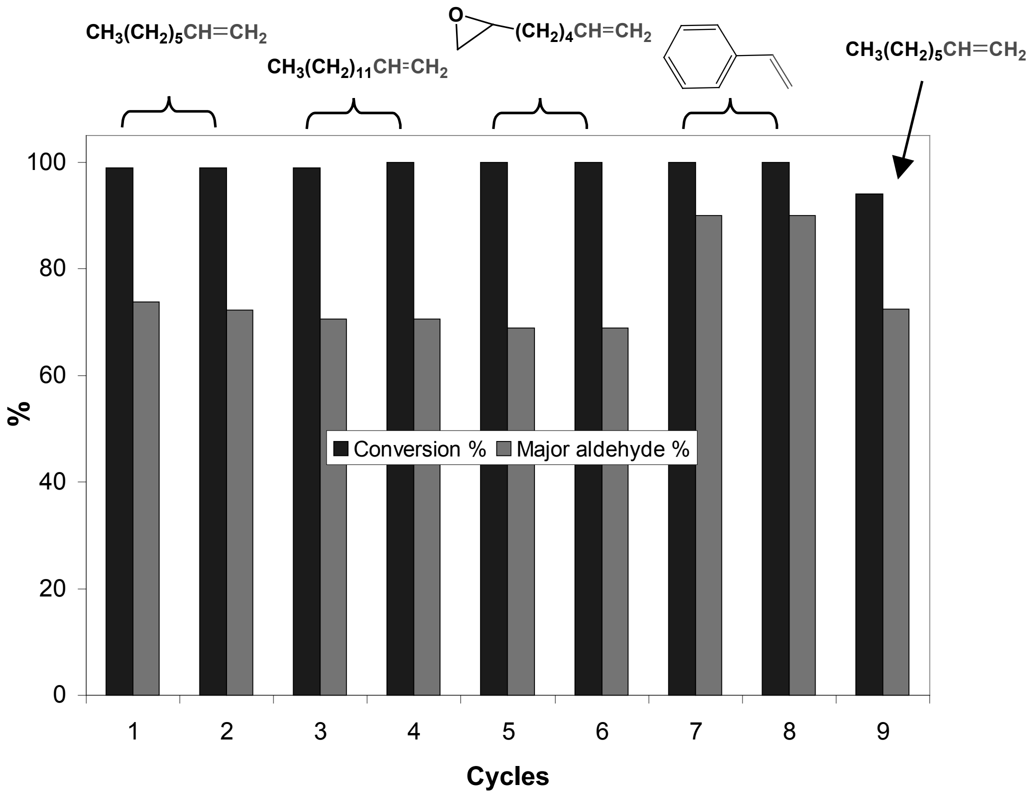


Figure 3-3: Batch-wise recycling experiment with a variety of substrates. The values of conversion and selectivity toward the major aldehyde are indicated (linear terminal aldehyde in all cases except for the hydroformylation of styrene where the major aldehyde is the 2-phenyl-propionaldehyde).

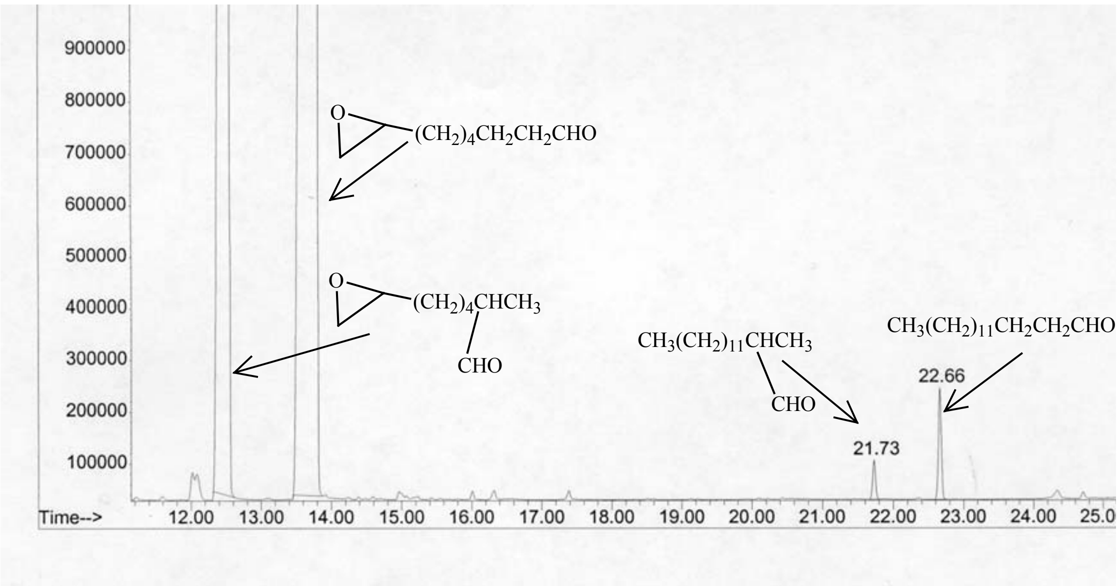


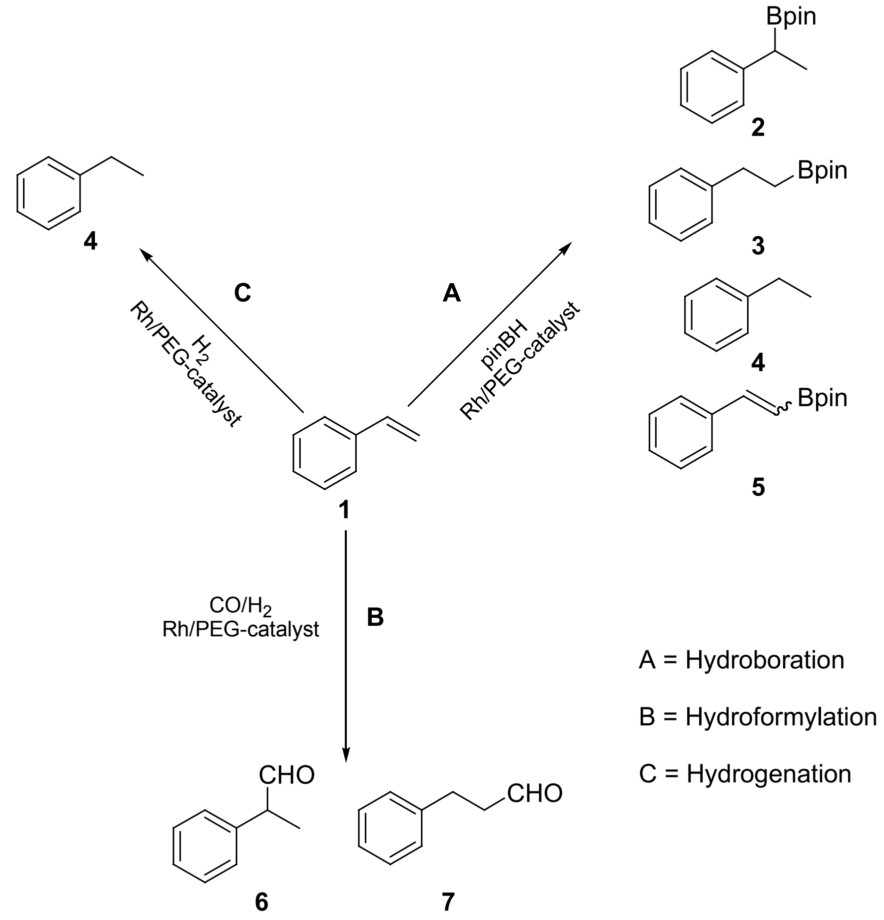
Figure 3-4: Illustrative chromatogram for the hydroformylation of different consecutive substrates. The cross contamination arising from the previous reaction (substrate = 1-tetradecene) is negligible.

A major challenge was to apply the system to a range of consecutive different reactions using the same batch of catalyst each cycle. It is indeed known that phosphine carbonyl hydride rhodium(I) complexes, the catalytic active species in the hydroformylation reaction, may be an intermediate of several other catalytic reactions. Restricting the attention in functionalization of double bonds reactions, the PEG-catalyst was tested in the hydrogenation and hydroboration of styrene. Hydrogenation is a well known and exstensively studied reaction as a powerful tool for the preparation of chiral chemical compounds.[144] Hydroboration, the addition of a hydrogen atom and a borane group to a double bond, leads to organoboranes, and are extremely important intermediates for the synthesis of a variety of compounds such as alkanes, alcohols, acids, chloro or iodo compounds.[145] Typically, the hydroboration reaction is carried out using catecholborane or pinacolborane and an olefin. The organoboranes obtained normally undergo an oxidative work-up with H_2O_2 and an aqueous solution of sodium hydroxide leading to alcohol.[146] This time-consuming step can be alternatively avoided and the isolated organoboranes can be directly analyzed via GC-MS technique. The poly(ethylene glycol) system combined with carbon dioxide was, so far, successfully applied in the hydroformylation of a variety of substrates in a solvent free manner. Furthermore, it was successfully recycled without any significant cross-contamination between the different substrates. Hence, the metal complex is efficiently precipitated and isolate in the bottom of the autoclave after the extraction process, and ready to be tested for another reaction type.

The first results were obtained alternating the hydroformylation of styrene with the hydrogenation of styrene using the same batch of catalyst. A 20 mL stainless steel reactor was charged under argon with a solution of $[Rh(CO)_2(acac)]$ (0.01 mmol) and the ligand $MeOPEG_{750}PPh_2$ (0.05 mmol) in styrene (10 mmol). The reactor was pressurized with 50 bar of syngas and the reaction allowed to proceed for 12 hours at 70 °C. The aldehydes were extracted with supercritical carbon dioxide (90-95 bar at 45 °C), isolated in the cold trap and analyzed by GC-MS. As expected, conversion higher than 99% and selectivity toward the branched aldehyde of 89.6% were obtained. Subsequently the reactor was re-charged with styrene (10 mmol) and pressurized with H_2 up to 50 bar. The reaction was allowed to proceed for 12 hours, and the products were extracted again with $scCO_2$ (85-90 bar at 45 °C). Ethyl benzene was the only product isolated containing less than 1% of aldehydes from the preceding reaction. This small cross contamination can be easily avoided simply extending the extraction time before re-charging the autoclave with another batch of substrate.

Furthermore, with the same catalyst/ligand/substrate ratios, a different experiment was performed this time changing from the hydrogenation reaction of styrene to the hydroformylation of the same substrate, and paying attention to isolate more efficiently the products of the reaction in the extraction process. Noteworthy, the same activity and selectivity were obtained and no cross contamination was observed. Only in the case of the hydrogenation of the styrene, the high volatility of the ethyl-benzene caused a loss of *circa* 50% of the product from the cold traps, due to insufficient cooling. Thus, the extraction process can be adapted for each compound. In summary, the PEG-complex was successfully applied as a catalyst cartridge, at least in the hydrogenation/hydroformylation reactions.

The system was subsequently tested in three different reactions, one after the other, and back to the starting reaction to assure that the catalyst still has the same selectivity as in the beginning of the experiment. The reactions sequence chosen was hydroboration, hydroformylation, hydrogenation and again back to hydroboration of styrene.



Scheme 3-3: Different reactions applied with the system Rh-PEG-ligand $MeOPEG_{750}PPh_2/scCO_2$. After completion of each reaction all the volatile compounds were extracted with carbon dioxide and the reactor charged for the consecutive reaction.

The hydroboration of styrene was initially performed in a solvent free manner in a batch experiment. After some screening, pinacolborane (pinBH) was found to be preferred as borylation agent over catecholborane under these conditions. The PEG-catalyst showed a good activity and selectivity at the reaction conditions tested (**1**/cat = 1000/1, $MeOPEG_{750}PPh_2/Rh = 5$, reaction time = 12 hours, T = 25 °C), 86.3% of the branched organoborane **2** and less than 9% of side products were obtained (ethyl-benzene **4** and the 4,4,5,5-tetramethyl-2-styryl-[1,3,2]dioxaborolane **5**). The rhodium complex containing TPP at comparable reaction conditions gives 61.1% of selectivity toward the branched organoborane and a substantial amount of side products **4** and **5** (30%). In the same reaction the PEG ligand gave higher selectivity. As depicted in Scheme 3-3, the hydroboration of styrene was followed by the hydroformylation of styrene, hydrogenation and back to the hydroboration, recycling the metal catalyst each time with supercritical carbon dioxide. The reactions were carried out in a 20 mL stainless steel reactor equipped with a window, at different temperatures and pressure, using for each run a styrene/rhodium ratio equal to 1000. The extraction process can be adjusted for each reaction mixture and visually controlled through the autoclave window.

The hydroboration of the styrene was carried out at room temperature for 3 hours and the products extracted with supercritical carbon dioxide (A: 60 to 100 bar at 45 °C). Afterwards, the hydroformylation of styrene was carried out (B: 70 °C for 2 hours, 50 bar syngas) and product extracted with CO_2 (100 bar at 45 °C). Hydrogenation was carried out as third reaction (C: 50 °C for 2 hours, 50 bar H_2) and products extracted as usual (80 bar at 45°C). The first hydroboration led to conversion of 87% with a selectivity toward the branched product **2** of 84%. The hydroformylation reaction gave complete conversion with a selectivity of 90% for the 2-phenyl-propionaldehyde **6**, while the hydrogenation gave 100% conversion to ethylbenzene **4**. Going back to the hydroboration reaction, the conversion was 89% with a selectivity of 83% to the product **2**, supporting the fact that the same rhodium catalyst cartridge could be used in the three reactions.

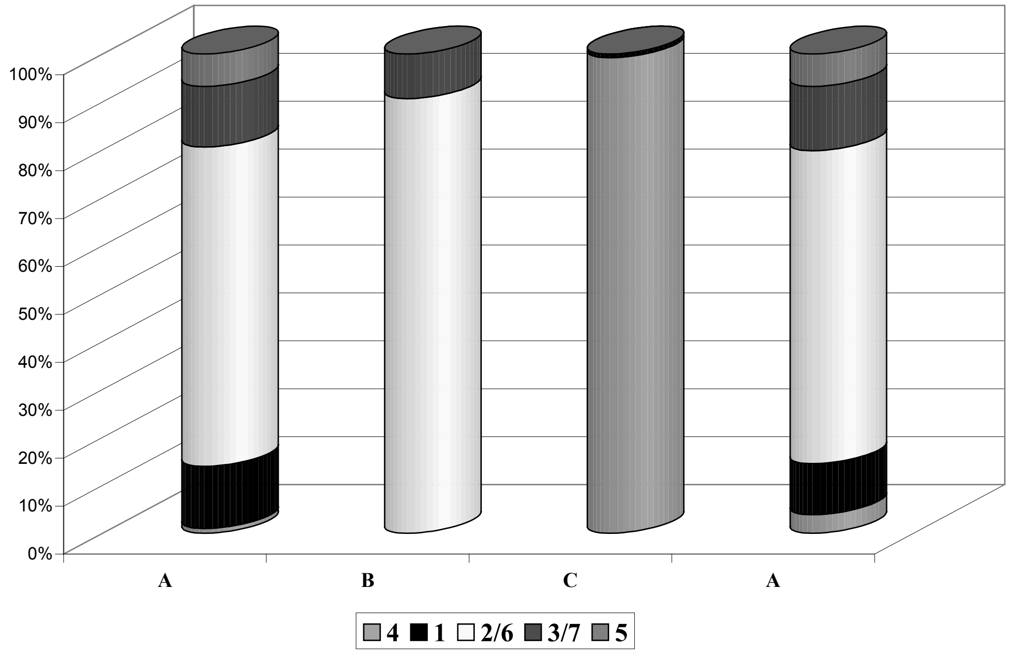


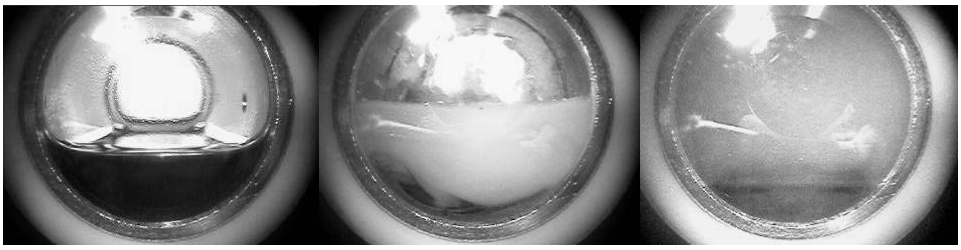
Figure 3-5: Series of consecutive reactions using the same catalytic solution; the extraction is performed with scCO_2. ([$Rh(CO)_2(acac)$] = 0.01 mmol; ligand $MeOPEG_{750}PPh_2$ = 0.05 mmol; styrene = 10 mmol; Reaction **A**: Pinacolborane = 10 mmol bar; time = 3 hours; temp. = 25 °C; Reaction **B**: CO/H_2 = 50 bar, time 2 hours, temp. 70 °C; Reaction **C**: H_2 = 50 bar; time 2 hours, temp. = 50 °C).

As shown in Figure 3-5, the catalyst proved to give the same activity and selectivity observed in the batch reactions. Furthermore, same selectivity and activity has been observed within the entire process: the same results were obtained in the first and last hydroboration reaction. Most notable, the catalyst has been shown to be unaffected from the broad variations in the reaction conditions (temperature, pressure, different gases etc), thus attesting to a good stability of this PEG modified complex.

3.5 Summary

In summary, the efficient combination of carbon dioxide and poly(ethylene glycol) derived ligands led to a novel recycling methodology in which the switching between a homogeneous and heterogeneous system is possible by tuning the carbon dioxide pressure. Supercritical carbon dioxide is the only solvent used in the process, the reaction can be performed by dissolving the complex in the substrate. Furthermore, the tunable properties of

CO_2 are used during the extraction process to induce the selective separation of the metal complex from the reaction mixture. Products are isolated in a solvent free manner after decompressing the carbon dioxide into a cold trap while the catalyst remains in the reactor. This system was applied to the hydroformylation of alkenes showing a general high activity and selectivity. Furthermore, the catalyst was recycled several times without any loss of activity and selectivity in the case of the hydroformylation of 1-octene. The following picture shows the stages of the catalytic/recycling process.



I **II** **III**

I first the reaction is allowed to proceed in a solvent free manner, the catalyst is dissolved directly in the substrate;

II at the end of the reaction the stainless steel autoclave is charged with carbon dioxide, the poly(ethylene glycol) modified rhodium catalyst start to precipitate while substrate and products are soluble in the carbon dioxide phase. Furthermore, expansion of the organic phase volume is observed because of dissolution of CO_2 into it;

III once the extraction process has been quantitatively carried out, the yellow viscous liquid rhodium catalyst is left in the reactor which can be charged again for another batch.

The PEG system was also applied to the hydroformylation of a variety of substrates recycling the same catalyst. Furthermore, the efficiency of the system has been tested changing consecutively the reaction with the same batch of rhodium catalyst.

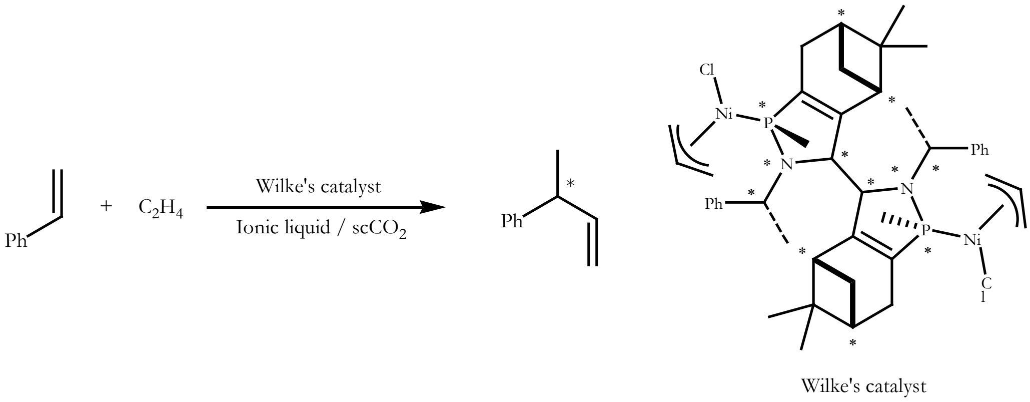
By combining PEG ligands and carbon dioxide, it is possible to have a multifunctional cartridge of rhodium catalyst, which may be used for a variety of different substrates and reactions.

4 Conclusion

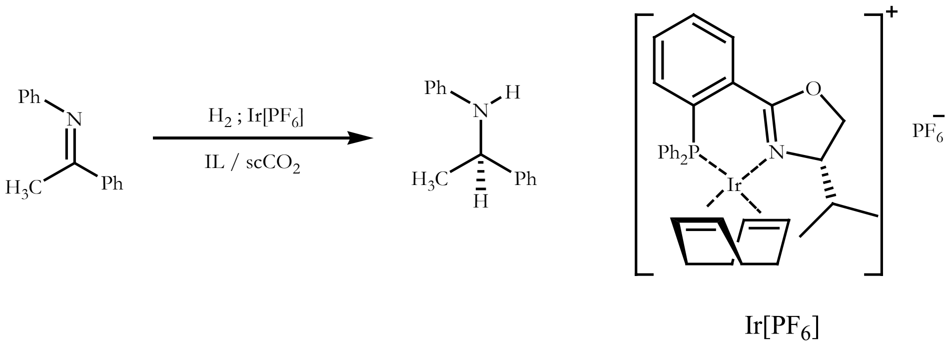
The quest for new strategies toward immobilization and recycling of organometallic complexes is an important area of modern catalysis research.[20] The high cost of the noble metal catalysts and the sophisticated ligand systems represent a major limit for a broader application in industrial processes, although very high values of selectivity and activity are usually obtained. Recyclability of catalysts is a key issue of sustainable development in chemistry.[1] Moreover, organic solvents are used in large quantity in chemical reactions and represent a considerable source of waste: they are usually all volatile, and some are toxic and carcinogenic. Research in the field of *green chemistry* is indeed focused on the replacement of organic solvents with solvent-free processes or with benign alternative reaction media.[1]

The work presented in this thesis was mainly focused on new strategies for multiphase catalysis. Compressed or supercritical carbon dioxide[6a] was used in combination with ionic liquids[14a] and poly(ethylene glycol) modified rhodium complexes.[26] Here one of the first examples of metal catalyzed reactions in a biphasic system made of ionic liquids and carbon dioxide was presented.[42] Furthermore, the first example of the combination of poly(ethylene glycol) ligands and carbon dioxide was also shown.

The combination of non volatile ionic liquids with carbon dioxide was successfully applied in two important metal catalyzed reactions: hydrovinylation of styrene and imine hydrogenation (see Scheme 4-1 and Scheme 4-2).



Scheme 4-1: Enantioselective hydrovinylation of styrene in Ionic liquid/CO_2 system.



Scheme 4-2: Enantioselective imine hydrogenation in IL/CO_2 system.

The unique properties of this new biphasic system, allowed an efficient immobilization of both metal catalysts used: Wilke's catalyst for the hydrovinylation and Ir[PF_6] for the hydrogenation reaction. Both catalytic systems were found to be activated in the ionic liquid used. Furthermore, activity and selectivity can be related in both cases to the nature of the anions of the ionic liquid. Higher enantiomeric excesses are found with ionic liquids containing low coordinating anions. Among them [BARF] and [Al{OC(CF_3)$_2$Ph}$_4$] were introduced here for the first time as anions of ionic liquids. Table 4-1 and Table 4-2 summarize the most significant results obtained in the hydrovinylation of styrene and hydrogenation of the imine from acetophenone. As shown, the largest variations in term of selectivity and enantiomeric excess are obtained as function of the anion of the ionic liquid.

Table 4-1: Hydrovinylation of styrene in IL/$scCO_2$ system, selected results. Selectivity toward 3-phenyl-1-butene is indicated.

entry	Ionic liquid	Conversion [%]	Selectivity [%]	e.e. (*R*) [%]
1	[EMIM][BTA]	69.9	93.4	53.4
2	[EMIM][Al{OC(CF_3)$_2$Ph}$_4$]	90.5	96.7	78.2
3	[EMIM][BARF]	100	63.8	89.4
4	[EMIM][$AlCl_4$]	95.0	88.0	65.0
5	[4-MBP][BTA]	70.5	98.9	58.4

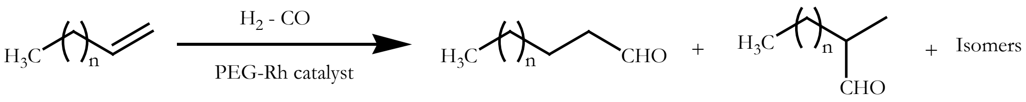
Table 4-2: Enantioselective hydrogenation of N-(1-phenylethylidene)aniline, selected results. Selectivity in all reactions = 100%.

entry	Ionic liquid	Conversion [%]	e.e. (*R*) [%]
1	[EMIM][BTA]	100	56.2
2	[4MBP][BTA]	100	52.0
3	[PMIM][PF_6]	100	65.4
4	[BMIM][BF_4]	92.2	30.2
5	[EMIM][BARF]	100	78.2

Moreover, some physical-chemical properties of the biphasic system IL/CO_2 were investigated with high pressure techniques. Conductivity of the ionic liquid [EMIM][BTA] is increased by the effect of the carbon dioxide pressure. This aspect, according to previous studies on the enantioselective hydrovinylation with the Wilke's catalyst, may be responsible for the slightly lower value of enantioselectivity observed in the hydrovinylation of styrene in IL/CO_2 system as compared to the ionic liquid alone. Furthermore, solubility of molecular hydrogen was investigated with high pressure NMR techniques. Hydrogen solubility is below the detection limit of the NMR at pressure of 30 bar. Pressurizing with carbon dioxide at room temperature causes a very high enhancement of hydrogen solubility. This may be responsible for the dramatic increase in activity of catalyst Ir[PF_6] at 30 bar of hydrogen in [EMIM][BTA] in the presence of carbon dioxide.

The efficiency of the biphasic system IL/CO_2 allowed a continuous flow reaction where reagents and products were constantly pushed through the ionic liquid solution containing the catalyst. This system was successfully applied with the Wilke's catalyst for the continuous flow hydrovinylation of styrene. Products were collected in a cold trap solvent and metal free.[42] No volatile organic solvent is used during the entire process, thus decreasing the environmental impact of the system. The iridium catalyst Ir[PF_6] was immobilized and recycled in a batch wise procedure for 7 cycles without any loss of activity and selectivity. ICP measurements indicated that the iridium content in the extracted sample was lower then the detection limit. Furthermore, the system allowed an efficient in situ formation of the catalyst by mixing the air stable [Ir(cod)Cl]$_2$ and P-N ligand. This methodology allows an easy way for testing a variety of phosphine-nitrogen mixed ligands and offers the possibility to further improve the system by choosing the right combination of ionic liquid and ligand.

The second part of the thesis presented the combination of poly(ethylene glycol) modified ligands with supercritical carbon dioxide. Two ligands derived from poly(ethylene glycol) monomethylether 750 and poly(ethylene glycol) 1000 were applied in the hydroformylation of olefins in a solvent free manner.



Scheme 4-3: Hydroformylation of olefin with PEG modified rhodium catalysts.

High activity and selectivity up to 75% of linear aldehyde was obtained with a variety of olefinic substrates. The phase behavior of the PEG ligands $MeOPEG_{750}PPh_2$ and $Ph_2PPEG_{1000}PPh_2$ with carbon dioxide allowed the *switching off* of the reaction by simply pressurizing the autoclave with CO_2. Thus, the hydroformylation of 1-octene, for example, can be carried out by dissolving the metal precursor and ligand in the substrate, and all products are extracted out from the reaction vessel with carbon dioxide. The PEG modified rhodium complex is precipitated in the bottom of the reactor by pressurizing with carbon dioxide. This approach toward multiphase catalysis does not allow a continuous flow system where reagents and products are constantly pushed through the reactor, but permit a very efficient separation of the metal catalyst from the reaction mixture. Thus, the same batch of catalyst can be used to successively carry out the hydroformylation of different substrates without significant cross contamination. Rhodium and phosphorous leaching were estimated *via* ICP measurements being around 1% and 2% respectively after 9 cycles. Moreover, the same catalyst can be used for different consecutive reactions: the rhodium modified catalyst with ligand $MeOPEG_{750}PPh_2$, was used to perform hydroformylation, hydrogenation and hydroboration of styrene. Reaction products were extracted and isolated each time with carbon dioxide (see Figure 4-1).

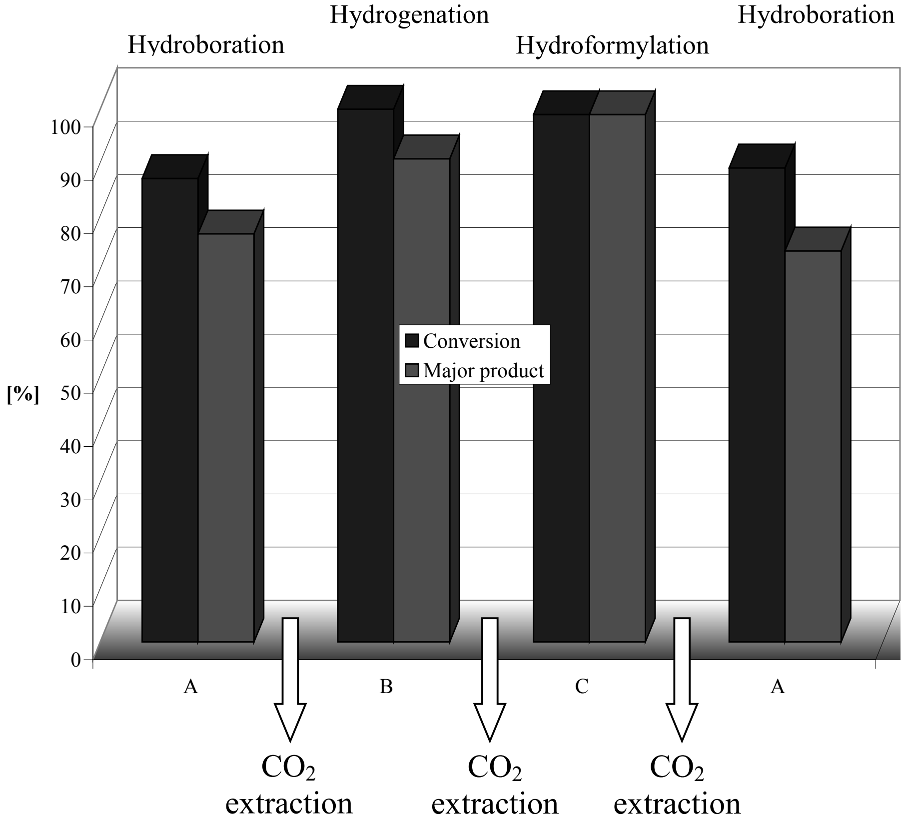


Figure 4-1: PEG-modified catalyst cartridge for different reactions, A: Hydroboration of styrene, B: Hydroformylation of styrene, C: Hydrogenation of styrene.

The two new systems for multiphase catalysis presented here may certainly offer alternative approaches toward catalyst recycling with a large potential for further development. The ionic liquid itself does not act as an "innocent" solvent, but can influence activity and selectivity of the reaction opening the way to an effective fine tuning of the metal complex. An example would be the use of a chiral ionic liquid, either with chiral anion and/or cation, in order to influence the enantioselectivity of the reaction. Further details on the physicochemical properties of this new biphasic system are still needed in order to fully exploit all its possible advantages. For a general reaction, the phase behavior of reactants and products in the IL/CO_2 system would be highly desirable even before starting a continuous flow investigation. Continuous flow processes are not possible with the PEG approach, where on the contrary the presence of carbon dioxide allows the precipitation of the catalyst. However, this methodology gives a very easy and efficient way for product separation, which may be easily applied to more selective metal catalysts because of the easily modifiable ligand framework. Therefore, further exploration of both methods seems highly promising for scientific and practical reasons.

5 Experimental section

General: All reactions and manipulations were performed under an atmosphere of dry argon by using standard Schlenk and glovebox techniques. Solvents were purchased from Aldrich and Acros, dried and purified according to standard methodologies.[147] All gases (CH_2CH_2, H_2, CO, CO_2) were used without further purification. The Wilke's catalyst and the ligand were available in the library of catalysts of the Max-Planck-Institute. The phosphanodihydrooxazole-iridium catalyst Ir[PF_6] and the ligands were kindly donated by Prof. Pfaltz (University of Basel). The other P-N ligands were donated by Prof. Cozzi (University of Bologna). All the ionic liquids used were synthesized and purified according to literature procedures[68] or purchased from Solvent Innovation GmbH[14b] and purified prior to use as described in literature.[68] ^{1}H-NMR, ^{13}C-NMR, ^{19}F -NMR and ^{31}P-NMR spectra were recorded in deuterated solvents with a Bruker AMX 300, DPX-300 and AC 200 spectrometer. Chemical shifts of the NMR spectra are referenced internally to $SiMe_4$ via the resonance of the solvents (^{1}H and ^{13}C) or externally to H_3PO_4 (^{31}P). GC-MS were performed with a HP-MASS 5973 equipped with RTX-1 (30 m) or with Ivadex 5 (25 m) columns and with a HP 6890 GC equipped with a Ivadex 5 (25 m) + BPX-70 (30 m) column, following different programming as:

(start oven temperature/hold min (ramp (X °C/min) final oven temperature/hold min). Mass spectroscopy was performed with a Finnigan MAT SSQ 7000 (EI). HPLC analysis were performed with a JASCO PU-2080 equipped with a MD-2010 detector and a CHIRACEL OD-H column.

All the manipulation of the high pressure experiment were handle with suitable equipment and under rigorous safety conditions.

5.1 Batch wise hydrovinylation of styrene

In a typical experiment, a stainless steel high pressure reactor (V = 10 mL) equipped with thick-wall glass windows, a PTFE stirring bar and a thermocouple was charged with 2 mL of ionic liquid and 0.3 g (10 mmol) of ethene. A dosing unit containing 0.3 mL of a styrene solution of Wilke's catalyst (styrene/Ni = 350/1) was connected to the reactor through a ball valve and pressurized with CO_2 (7 g). The reactor was filled through another valve with

CO_2 (9 g). The reaction mixture was then warmed to 40 °C, while the dosing unit was heated to 60 °C. Opening the ball valve started the reaction which was allowed to proceed for 1 hour. After venting off the volatile compounds through a cold trap, the IL was extracted with pentane and the combined extract and trap contents were analyzed by a GC-MS equipped with a RTX-1 (30 m) column with the following programming (60/5 200(5 °C/min) 200/5 2min iso 280) the retention times were: styrene = 5.5 min, 3-phenyl-1-butene = 9.6 min, 2-phenyl-1-butene = 9.8 min. MS (70 eV, EI): *m/z* (%) Styrene = 104(100) [M^+], 77(20) [$C_6H_5^+$], 3-phenyl-1-butene = 132(21) [M^+], 117(100) [M^+- CH_3], 77(15) [$C_6H_5^+$], 2-phenyl-1-butene 132(15) [M^+], 117(100) [M^+- CH_3], 77(24) [$C_6H_5^+$].

The enantiomeric excess was determined with a HP 6890 GC equipped with a Ivadex 5 (25 m) + BPX-70 (30 m) column using H_2 as carrier gas. With the following programming (60 (2 °C/min) 180 15min iso 300) the retention time are: (*R*)-3-phenyl-1-butene = 17.25 min., (*S*)-3-phenyl-1-butene = 17.51 min.

5.2 On-line monitoring of the hydrovinylation of styrene

A stainless steel autoclave (V = 250 mL) was charged under argon with a solution of Wilke's catalyst (0.0212 mmol) in 10 mL of [EMIM][BTA] and 4.55 g (0.044 mol) of styrene (sub/Ni = 1000/1). The reactor was charged with 50 bar (3 g) of ethylene, 63 g of CO_2 (total pressure at 25 °C, 150 bar) and connected to the on-line GC-MS, the reaction was allowed to proceed at 25 °C. At defined intervals of time, small samples (loop volume of 1µl) were taken automatically of the upper CO_2 phase and analyzed to determine the conversion.[120] At the end of the reaction the remaining products were extracted quantitatively from the ionic liquid phase using 185 liters of CO_2. The extraction was performed with compressed carbon dioxide at 25 °C and 130 bar and the collected products in the cold trap analyzed as previously described.

5.3 Continuous flow hydrovinylation of styrene

The reactor was filled under argon atmosphere with 0.166 g (0.19 mmol) of Wilke's catalyst dissolved in 39 ml of [EMIM][BTA] and cooled to 0 °C. The reactor pressure was maintained constant at 80 bar by a continuos flow of compressed CO_2 (the exit flow was adjusted between 1 and 0.1 L min^{-1} of CO_2). The reaction was then allowed to proceed with a constant styrene flow of 0.01 mL min^{-1} and 1 mL pulses of C_2H_4 (90 bar) every 0.5 min. Several sample were collected over a period of 61 hours. Conversion and e.e. were determined as previously described.

5.4 Continuous flow hydrovinylation with various substrates

A 20 mL autoclave was filled under argon with a solution of 0.0653 g of Wilke's catalyst in 25 mL of [EMIM][BTA] and cooled at 0 °C. The reactor pressure was maintained at constant pressure of 80 bar by a continuos flow of compressed CO_2 (the exit flow was adjusted to about 2.5 L min^{-1} and the ethylene input was 1 mL pulses of C_2H_4 (90 bar) every 0.5 min). The substrate flow was 0.01 mL min^{-1}. After 12 hour the second substrate was introduced in the reactor with a flow of 0.01 mL min^{-1}. Products were analyzed as previously described: 1-isobutyl-4-vinyl-benzene = 16.6 min.; 1-isobutyl-4-(1-methyl-allyl)-benzene = 19.5 min.; 1-chloro-4-vinyl-benzene = 11.7 min.; 1-chloro-4-(1-methyl-allyl)-benzene = 15.4 min. MS (70 eV, EI): *m/z* (%): 1-isobutyl-4-vinyl-benzene = 160(84) [M^+], 117(100) [M^+- $CH(CH_3)_2$], 77(15) [$C_6H_5^+$], 1-isobutyl-4-(1-methyl-allyl)-benzene 188(66) [M^+], 173(18) [M^+- CH_3], 145(100) [M^+- $CH(CH_3)_2$], 131(100) [M^+- $CH_2CH(CH_3)_2$], 77(16) [$C_6H_5^+$], 1-chloro-4-vinyl-benzene 138(100) [M^+], 103(60) [M^+- Cl], 77(40) [$C_6H_5^+$], 1-chloro-4-(1-methyl-allyl)-benzene 166(14) [M^+], 151(25) [M^+- CH_3], 131(48) [M^+- Cl], 116(100) [$C_9H_8^+$]77(12) [$C_6H_5^+$].

5.5 Synthesis and characterization of aluminum salts

Synthesis of AlNa-BINOL salts: In a typical experiment a suspension of 2.83 g (9.88 mmol) of (*R*)-BINOL (or (*S*)-BINOL) and 0.82 g (4.9 mmol) of [Na][AlEt$_4$] in 60 mL of dry toluene was stirred at room temperature for 12 hours. The product was filtrated under argon and washed with toluene (3x20 mL). A white powder was obtained, yield: 98%. ^{1}H NMR (300 MHz, THF$_{d8}$): δ = 6.97-7.37 (m, 20H, arom. CH), 7.77-7.91 (m, 4H, arom. CH). ^{13}C NMR (75 MHz, THF$_{d8}$): δ = 118.9, 124.0, 124.9, 126.2, 127.9, 128.0, 128.3, 129.1, 129.5, 129.8, 135.0, 154.2 (arom. CH and C). MS (70 eV, EI): *m/z* (%) 595(100) [M$^+$ - Na], 285(100) [$C_{20}H_{13}O_2^+$].

Synthesis of the [Na][Al{OC(CF$_3$)$_2$Ph}$_4$]: To a suspension of 1.70 g (0.01 mol) of [Al(Et)$_4$][Na] in 50 mL of dry toluene was added at room temperature a solution of 10 g (0.04 mol) of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol in 20 mL of toluene. The reaction was allowed to proceed for 4 hours at 110 °C. The solvent was removed under vacuum and the white oil obtained was re-crystallized from dry n-hexan. A white powder was isolated (5.05 g - 50% yield). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.26-7.42 (m, 3H, arom. CH), 7.66-7.74 (m, 2H, arom. CH). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 129.1, 124.7 (q. ^{1}J(C-F) = 290), 133.2, 127.8, 128.7, 130.1 (arom. CH and C). ^{19}F NMR (282 MHz, CD_2Cl_2) δ = - 75.5.

5.6 Hydrovinylation of styrene with chiral aluminum salts as co-catalyst

In a typical experiment, a stainless steel high pressure reactor (*V* = 10 mL) equipped with thick-wall glass windows, a PTFE stirring bar and a thermocouple was charged with 3 mmol of styrene, 0.03 mmol of nickel catalyst and 0.1 mmol of the aluminum salt in 2 mL of CH_2Cl_2. The reactor was then charged with 40 bar of ethene. The reaction was allowed to proceed at the reaction conditions listed in Table 2-12 and the product analyzed as previously described.

5.7 Synthesis of the imine substrates

All substrate were synthesized according to standard procedures[130] and the purity was checked by NMR. ***N*-(1-Phenylethylidene)aniline**: Isolated as a pale yellow solid, 73% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 6.78-6.83 (m, 2H, arom. CH), 7.07-7.13 (m, 1H, arom. CH), 7.33-7.39 (m, 2H, arom. CH), 7.43-7.50 (m, 3H, arom. CH), 7.96-8.01 (m, 2H, arom. CH). ^{13}C NMR (75 MHz, CDCl3): δ = 17.3 (CH_3), 119.3, 123.2, 127.1, 128.3, 129.9, 130.4 (arom. CH), 139.4, 151.7 (arom. C), 165.5 (C=N); MS (70 eV, EI): *m/z* (%) 195(55) [M^+], 180(100) [$(M-CH_3)^+$], 118(11) [$(M-C_6H_5)^+$], 77(61) [$C_6H_5^+$].

***N*-(1-Phenylethylidene)benzylamine**: Isolated as a white solid, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, CH_3 (major isomer)), 2.37 (t, *J* = 1.13 Hz, 3H, CH_3 (minor isomer)), 4.43 (s, 2H, H_2CPh (minor isomer)), 4.73 (s, 2H, H_2CPh (major isomer)), 7.14-7.46 (m, 8 arom. CH), 7.83-7.89 (m, 2 arom. CH); (Z)/(E) isomer ratio 13/1; ^{13}C NMR (75 MHz, CDCl3): δ = 15.7 (CH_3), 55.6 (CH_2), 126.5, 126.7, 127.6, 128.1, 128.3, 129.6 (arom. CH), 140.5, 141.0 (arom. C), 165.9 (C=N);); MS (70 eV, EI): *m/z* (%) 209(14) [M^+], 194(2) [$(M-CH_3)^+$], 91(100) [$C_7H_7^+$].

(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine: Isolated as a dark yellow viscous liquid, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3), 6.79-6.83 (m, 1 arom. CH), 6.95-7.02 (m, 2 arom. CH), 7.07-7.14 (m, 1 arom. CH), 7.45-7.49 (m, 3 arom. CH), 8.02-8.06 (m, 1 arom. CH); ^{13}C NMR (75 MHz, CDCl3): δ = 17.7 (CH_3), 55.5 (OCH_3), 111.4, 120.5, 120.7, 124.0, 126.8, 127.2, 127.8, 128.2, 130.3, (arom. CH), 139.3, 140.5, 148.8 (arom. C), 166.9 (C=N); MS (70 eV, EI): *m/z* (%) 225(66) [M^+], 210(100) [$(M-CH_3)^+$], 194(15) [$(M-OCH_3)$], 77(31) [$C_6H_5^+$].

Isopropyl-(1-phenyl-ethylidene)-amine: Isolated as a colorless liquid, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6 Hz, 6H, CH_3), 2.27 (s, 3H, CH_3), 3.88 (m, *J* = 6 Hz, 1H, CH), 7.36-7.45 (m, 3 arom. CH), 7.74-7.81 (m, 2 arom. CH); ^{13}C NMR (75 MHz, CDCl3): δ = 15.1 (CH_3 isopropyl), 23.5 (CH_3), 51.1 (CH), 125.6, 126.6, 128.1, 128.4, 129.1

(arom. CH), 141.8 (arom. C), 162.3 (C=N); MS (70 eV, EI): *m/z* (%) 161(21) [M^+], 146(55) [$(M\text{-}CH_3)^+$], 103(100) [$C_7H_5N^+$], 77(58) [$C_6H_5^+$].

(2-Ethyl-6-methyl-phenyl)-(1-phenyl-ethylidene)-amine: Isolated as pale yellow liquid, 58 % yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.5 Hz, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.20-2.40 (m, 2H, CH_2), 6.84-6.89 (t, 1 arom. CH), 6.96-7.01 (t, 2 arom. CH), 7.34-7.42 (m, 3 arom. CH), 7.92-7.98 (m, 2 arom. CH); ^{13}C NMR (75 MHz, CDCl3): δ = 13.8 (CH_3 ethyl), 17.5 (CH_2 ethyl), 17.9 (ortho CH_3), 24.6 (CH_3), 122.8, 125.4, 125.9, 127.0, 127.8, 128.4, 130.4, 131.8, (arom. CH), 139.1, 148,5 (arom. C), 164.9 (C=N). MS (70 eV, EI): *m/z* (%) 237(36) [M^+], 222(100) [$(M\text{-}CH_3)^+$], 207(22) [$(M\text{-}CH_2CH_3)^+$], 77(21) [$C_6H_5^+$].

5.8 Hydrogenation of N-(1-Phenylethylidene)aniline and other imine substrates

In a typical experiment a 10 mL window equipped stainless steel reactor, was charged under argon atmosphere with 2 mL of IL, 1.5 mmol of N-(1-phenylethylidene)aniline and 0.003 mmol of catalyst Ir[PF_6]. The reactor was pressurized with 30 bar of hydrogen and with 8.5 g of CO_2 (corresponding to a total pressure of 150 bar at room temperature). The reactor was warmed up to 40 °C and the reaction was allowed to proceed for 22 hours. After that time all the volatile were vented out through a cold trap at -70 °C. The IL was recovered from the autoclave and extracted several time with n-hexane until complete recovering of the reaction product. The content of the cold trap and the extracted phase were collected and analyzed by GC-MS and HPLC. GC-MS (RTX-1 (30 m) column) programming (50/5 200(10 °C/min) 280(15°C/min) 280 5min iso 280) the retention times were: phenyl-(1-phenyl-ethyl)-amine = 18.3 min, N-(1-phenylethylidene)aniline = 18.6 min. MS (70 eV, EI): *m/z* (%) **3** 197(56) [M^+], 182(100) [$M\text{-}CH_3^+$], 77(44) [$C_6H_5^+$].

All other substrates were hydrogenated following the same procedure. Reaction products were characterized similarly as reported above.

5.9 Batch-wise recycling of hydrogenation catalyst

A 20 mL windows equipped stainless steel autoclave was charged, under argon atmosphere, with 3.2 mL of [BMIM][PF_6], 0.01 mmol of the catalyst Ir[PF_6] and 4.45 mmol of the substrate N-(1-phenylethylidene)aniline. The reactor was pressurized with 40 bar of hydrogen and with 13.7 g of CO_2 (total pressure = 145 bar at 22 °C). The reaction was allowed to proceed at 40 °C for 3 hours. All the reaction products were extracted with CO_2 at 160 bar and 45 °C. The extraction time was 3 hours with an exit flow around 700-800 L min^{-1}. After the extraction the reactor was charged again with the same amount of substrate, hydrogen and CO_2 for the successive reaction.

5.10 High pressure NMR investigation

A 5 mm high-pressure sapphire NMR tube (V = 0.9 mL) was charged, under argon atmosphere, with [EMIM][BTA] 0.5 mL and one drop of C_6D_6 (as lock solvent). The NMR tube was pressurized at room temperature with 30 bar of H_2. After careful shaking ^{1}H NMR measurements were performed. CO_2 was added on top to the same sample (total pressure of 120 bar) and after shacking ^{1}H NMR measurements were performed. The measurements were executed at 25 °C. In all spectra it was checked by double measurements that H_2 reached its equilibrium solubility.

5.11 Continuous flow hydrogenation of imine

Two 20 mL autoclaves were connected in series through a manual back pressure regulator (see figure Figure 2-28), the first was charged with 2.2 g (0.011 mol) of substrate N-(1-phenylethylidene)aniline and the second with 5 ml of [BMIM][PF_6] and 23.8 mg (0.03

mmol) of iridium catalyst Ir[PF_6]. The first autoclave was pressurized with H_2 and CO_2 at 50 °C. Pressure and temperature were adjusted in the second autoclave. A flow rate of substrate from the first to the second autoclave, was estimated to be 6 mg min^{-1} with the constant flow of circa 2 L min^{-1} of CO_2. The product were condensed into a cold trap and analyzed with GC-MS as described.

5.12 Hydrogenation of α-methyl stilbene

In a typical experiment a stainless steel reactor (V = 10 mL) was charged under argon atmosphere with 1 mg (1.2 μmol) of catalyst Ir[PF_6], 58 mg (0.3 mmol) of α-methyl stilbene and 2 mL of [PMIM][PF_6]. The reactor was pressurized with 50 bar of H_2 (~ 0.1 g) and with additional 6 g of CO_2. The reactor was warmed up to 40 °C and the reaction was allowed to proceed for 22 hours. After the previously described work-up the products were analyzed by GC-MS.

5.13 Hydrogenation with other P-N ligands

The hydrogenation using other P-N ligands complexes were performed using the *in-situ* protocol. In a typical experiment 0.03 mmol of the selected ligand and 0.015 mmol of $[Ir(cod)Cl]_2$ were dissolved in a mixture of 2 mL of ionic liquid and 0.5 mL of CH_2Cl_2 and stirred for 3 hours at 50 °C. This solution was transferred in the autoclave and the organic solvent was removed under vacuum, the substrate N-(1-phenylethylidene)aniline was added to the mixture and the autoclave was charged with H_2 and CO_2 (40 bar / 6 g). The reaction was allowed to proceed for 22 hours at 40 °C. The products were analyzed as previously described.

5.14 Preparation of ligand $MeOPEG_{750}PPh_2$ (average mw 918 g mol^{-1})

Synthesis of $MeOPEG_{750}OMs$: 30 g of $MeOPEG_{750}$ (0.04 mole) and 4.1 g of triethylamine (0.041 mol) were dissolved in 150 ml of toluene. The solution was cooled in an ice-water bath and then 4.6 g methanesulfonyl chloride (0.04 mol) dissolved in 10 mL of CH_2Cl_2 was added drop-wise (10 min) under stirring. The reaction mixture was stirred overnight at room temperature. The resulted solid was filtered and washed with 2x30 mL of toluene. The filtrate was evaporated to give 30.3 g of the corresponding $CH_3OCH_2CH_2(OCH_2CH_2)_mOMs$, yield 91.5%. ^{1}H-NMR ($CDCl_3$) δ ppm: 3.08 s (3H), 3.37 s (3H), 3.54-4.37 m (70H). $^{13}C\{^1H\}$-NMR δ(ppm): 39.02 s, 60.32 s, 70.30 s, 70.60 s, 71.85-73.22 m.

Synthesis of $MeOPEG_{750}PPh_2$: 30 g (0.037 mol) of $MeOPEG_{750}OMs$, was dissolved in 100 mL THF and then was added to a solution of $LiPPh_2$ (0.05 mol) in THF in 2 hours while cooled at 0 °C. The reaction mixture was stirred overnight. To this mixture a solution 30 mL water and 1.0 mL acetic acid was added and the resulted aqueous solution was separated and washed with 20 ml of THF. The combined organic phase was dried under vacuum and the residue was dissolved in 80 mL of toluene and filtrated. The toluene solution was extracted with water (2x60 mL) and the aqueous solution was washed with 30 mL of pentane. After evaporating the aqueous solution gives 27.2 g of $MeOPEG_{750}PPh_2$ (yield 80.9%). ^{1}H-NMR (CD_3OD) δ ppm: 2.40 t (2H), 3.38 s (3H), 3.54-3.65 m (71H), 7.35-7.48 m (10H). $^{13}C\{^1H\}$-NMR δ ppm: 29.96 d (J_{CP}= 13Hz), 69.65 d (J_{CP} = 23 Hz), 59.24 s, 71.3-71.7 m, 129.7 s, 129.86 d (J_{CP}= 12Hz), 133.89 d (J_{CP} = 19Hz), 139.9 d (J_{CP} = 13Hz). $^{31}P\{^1H\}$ NMR δ: -21.1 ppm.

5.15 Preparation of $Ph_2PPEG_{1000}PPh_2$ (average mw 1336 g mol^{-1})

Synthesis of $MsOPEG_{1000}OMs$: 20 g of PEG_{1000} (0.02 mol) and 4.1 g of triethylamine (0.041 mol) were dissolved in 150 ml of toluene. The solution was cooled in an ice-water bath and then 4.6 g of methanesulfonyl chloride (0.04 mol) in 10 ml of CH_2Cl_2 was added drop-wise within 30 minutes under stirring. The reaction mixture was stirred at room temperature overnight. The resulted solid was filtered and washed with toluene (2x30 ml). The filtrate was evaporated to give 24.5 g of the corresponding $MsOPEG_{1000}OMs$, (yield 91.7 %). ^{1}H-NMR ($CDCl_3$) δ(ppm): 3.09 s (6H), 3.65-3.69 m (90H); $^{13}C\{^1H\}$-NMR δ ppm: 39.85 s, 71.13 s, 71.42 s, 72.3-73.0 m.

Synthesis of $Ph_2PPEG_{1000}PPh_2$: 24.5 g of $MsOPEG_{1000}OMs$ (0.02 mol), was dissolved in 60 ml of THF and then was added to a solution of $LiPPh_2$ (0.05 mol) in THF in 2 hours at 0 °C. After the usual work-up as mentioned above 17.2 g of $Ph_2PPEG_{1000}PPh_2$ (yield 70.2%) were obtained. ^{1}H-NMR (CD_3OD) δ ppm: 2.32 m (4H), 3.54 m (85H), 7.33 m (19.3H); $^{13}C\{^1H\}$-NMR δ ppm: 29.99 d (J_{CP} = 13Hz), 69.70 d, (J_{CP}= 23Hz), 71.3-71.7 m, 129.7 s, 129.86 d (J_{CP} = 12Hz), 133.93 d (J_{CP} = 20Hz), 140.03 d (J_{CP} = 13Hz). $^{31}P\{^1H\}$- NMR δ: -21.0ppm.

5.16 Catalytic hydroformylation using ligand $MeOPEG_{750}PPh_2$: general procedure

[$Rh(CO)_2(acac)$] (28 mg; 0.11 mmol) and the ligand $MeOPEG_{750}PPh_2$ (505 mg; 0.55 mmol) were dissolved in 11 mL of freshly distilled CH_2Cl_2. 1 mL of this solution was transferred under argon in a stainless steel 20 mL autoclave and the solvent was removed under high vacuum. The autoclave was subsequently charged under argon with the exact amount of substrate to reach the desiderated ratio with the catalyst (e.g. 1.12 g of 1-octene; 0.01 mol). Alternatively, the catalytic solution can be also prepared dissolving the rhodium precursor and the ligand in the substrate (1-octene).

The reactor was warmed up to 70°C and pressurized with 50 bar of syn gas (CO/H_2 = 1/1). The reaction was allowed to proceed for two hours, after that all the volatile compounds were vented off and the products analyzed by GC-MS after separation from the catalyst either with $scCO_2$ or by filtration through a small column charged with silica. The products has been identified with the following programming 80 8°C/min 300. 1-octene = 2.6 min, octene isomers = 2.68-2.82 min, 2-nonanal = 7.14 min, 1-nonanal = 8.27 min.

5.17 Catalytic hydroformylation using ligand $PPh_2PEG_{1000}PPh_2$: general procedure

$[Rh(CO)_2(acac)]$ (28 mg; 0.11 mmol) and the ligand $Ph_2PPEG_{1000}PPh_2$ (588 mg; 0.44 mmol) were dissolved in 11 mL of a freshly distilled CH_2Cl_2. 1 mL of this solution was transferred under argon in a stainless steel 20 mL autoclave and the solvent was removed under high vacuum. The autoclave was subsequently charged under argon with the exact amount of substrate to reach the desiderated ratio with the catalyst (e.g. 1.12 g of 1-octene; 0.01 mol). The reactor was warmed up to 70°C and pressurized with 50 bar of syn gas (CO/H_2 = 1/1). The reaction was allowed to proceed for six hours after that all the volatile compounds were vented off and the products analyzed by GC-MS after separation from the catalyst either with $scCO_2$ or by filtration through silica.

5.18 Catalytic hydrogenation using ligand $MeOPEG_{750}PPh_2$: general procedure

A 20 mL Schlenk was charged under argon with $[Rh(CO)_2(acac)]$ (3.3 mg; 0.013 mmol) and the ligand $MeOPEG_{750}PPh_2$ (59 mg; 0.064 mmol). Styrene was added to the mixture (1.33 g, 12.7 mmol) and the reaction was allowed to proceed at room temperature for 12 hours. At the end of the reaction the catalyst was recovered by CO_2 extraction and the products analyzed *via* GC-MS.

5.19 Catalytic hydroboration using ligand $MeOPEG_{750}PPh_2$: general procedure

A 20 mL autoclave was charged under argon with 1 mL of a stock solution containing $[Rh(CO)_2(acac)]$ (13.2 mg; 0.05 mmol) and the ligand $MeOPEG_{750}PPh_2$ (248 mg; 0.27 mmol) in 5 mL of dried CH_2Cl_2. The solvent was completely removed under high vacuum and styrene was added to the mixture (1.02 g, 9.8 mmol), the reactor charged with 50 bar of H_2 and the reaction was allowed to proceed at 50 °C for 2 hours. At the end all the volatile compounds were vented out through a cold trap. The products extracted with CO_2 and analyzed *via* GC-MS.

5.20 Recycling experiment with ligand $MeOPEG_{750}PPh_2$: hydroformylation

A 20 mL autoclave containing all the products from the hydroformylation reaction was cooled up to 45 °C, carbon dioxide was bubbled through the homogeneous solution of the catalyst in the product mixtures using a compressor. The gas phase was then passed through a valve into two cold traps (-78 °C) in series for 3 to 4 hours using in average a total amount of 150 liters of CO_2. The extraction process can be monitored by watching inside the reactor by the thick wall window due to the precipitation of the catalyst for a certain pressure of carbon dioxide.

The products were isolated in a solvent free manner and analyzed by GC-MS. The reactor was charged again for the following hydroformylation reaction.

5.21 Recycling experiment with ligand $MeOPEG_{750}PPh_2$: consecutive reactions

A stainless steel reactor (20 mL) was charged under argon with 0.01 mmol of $[Rh(CO)_2(acac)]$ and 0.05 mmol of ligand $MeOPEG_{750}PPh_2$. The autoclave was subsequently charged with 10 mmol of styrene. The hydroformylation was allowed to proceed for 12 hours at 70 °C with a constant pressure of 50 bar of CO/H_2. After the reaction all the products were extracted with CO_2 as described above and analyzed by GC-MS. The reactor was charged again with styrene (10 mmol) and with 50 bar of H_2. The hydrogenation was allowed to proceed for 12 hours at 70 °C. After the reaction all the products were extracted with CO_2 as described above and analyzed by GC-MS. The reactor was charged again with 13 mmol of styrene for the third reaction and with 10 mmol of pinacolborane. The hydroboration reaction was allowed to proceed for 12 hours at room temperature. The product were extracted using CO_2 as described above and the isolated compounds were treated for work-up as described in literature[146] and analyzed by GC-MS. Alternatively the crude product can be also injected in the GC-MS, once the catalyst has been separated from the mixture, following the GC method: 60(5) 5°C/min 300(5). The product were identified having the following GC retention time: Ethyl-benzene = 4.12 min; Styrene = 4.86 min, 4,4,5,5-Tetramethyl-[1,3,2]dioxaborolane (pinacolborane) = 7.90 min; 4,4,5,5-Tetramethyl-2-(1-phenyl-ethyl)-[1,3,2]dioxaborolane (the branched product) = 21.93 min; 4,4,5,5-Tetramethyl-2-phenethyl-[1,3,2]dioxaborolane (the linear product) 23.55 min; 4,4,5,5-Tetramethyl-2-styryl-[1,3,2]dioxaborolane 26.57 min. MS (70 eV, EI): *m/z* (%) ethyl-benzene 106(21) $[M^+]$, 91(100) $[(M\text{-}CH_3)^+]$, 77(7) $[C_6H_5^+]$; styrene 104(100) $[M^+]$, 89(75) $[(M\text{-}CH_3)^+]$, 77(55) $[C_6H_5^+]$; 4,4,5,5-Tetramethyl-2-(1-phenyl-ethyl)-[1,3,2]dioxaborolane 232(29) $[M^+]$, 217(13) $[(M\text{-}CH_3)^+]$, 105(100) $[(M\text{-pinbH})^+]$, 77(9) $[C_6H_5^+]$; 4,4,5,5-Tetramethyl-2-phenethyl-[1,3,2]dioxaborolane 232(6) $[M^+]$ 217(5) $[(M\text{-}CH_3)^+]$, 105(22) $[(M\text{-pinbH})^+]$, 84(100) [?], 77(5) $[C_6H_5^+]$, 4,4,5,5-Tetramethyl-2-styryl-[1,3,2]dioxaborolane 230(22) $[M^+]$ 216(11) $[C_{13}H_{17}BO_2^+]$, 130(100) $[C_9H_{11}B^+]$, 77(14) $[C_6H_5^+]$.

5.22 Recycling experiment with ligand MeOPEG$_{750}$PPh$_2$: hydroformylation of different substrates

A stainless steel reactor (V = 20 mL) was charged under argon with 0.01 mmol of [Rh(CO)$_2$(acac)] and 0.05 mmol of ligand MeOPEG$_{750}$PPh$_2$, the reactor was then charged with 10 mmol of the first substrate (1-octene) and the reaction was allowed to proceed for 2 hours at 70 °C with a constant pressure of 50 bar of CO/H$_2$. All the products were extracted with scCO$_2$ as described above and analyzed by GC-MS. The reactor was then loaded with the subsequently substrate (1-decene, 1-tetradecene *etc*.) and the same procedures as above was followed.

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7 Publications

1. Maurizio Solinas, A. Pfaltz, P. G. Cozzi, W. Leitner, ***Enantioselective Hydrogenation of Imines in Ionic Liquid/Carbon Dioxide Media***, submitted for publication.

2. Maurizio Solinas, J. Jiang, O. Stelzer, W. Leitner, ***Poly(Ethylene Glycol) Modified Phosphine Ligands and supercritical carbon dioxide for Solvent-Free Catalytic Reactions***, manuscript in preparation.

3. Z. Hou, Maurizio Solinas, D. Giunta, N. Theyssen, W. Wiesenhöfer, J. Panten, W. Leitner, ***Biphasic continuous flow olefin metathesis in ionic liquids / scCO*** $_2$, manuscript in preparation.

4. Maurizio Solinas, M. Marchetti, S. Gladiali, ***Hydroformylation of Aryloxy Ethylenes by Rh/BINAPHOS Complex Catalyst Deactivation Path and Application to the Asymmetric Synthesis of 2-Aryloxypropanoic Acids***, submitted for publication.

5. D. Ballivet-Tkatchenko, M. Picquet, Maurizio Solinas, G. Francio, P. Wasserscheid, W. Leitner, ***Acrylate Dimerisation Under Ionic Liquid-Supercritical Carbon Dioxide Conditions,*** *Green Chemistry*, **2003**, *5*(2), 232.

6. Bösmann, G. Francio, E. Janssen, Maurizio Solinas, W. Leitner, P. Wasserscheid, ***Activation, Tuning, and Immobilization of Homogeneous Catalysts in an Ionic Liquid/Compressed CO*** $_2$ ***Continuous-Flow System***, *Angewandte Chemie, International Edition*, **2001**, *40*(14), 2697, (*Very Important Paper*).

8 Curriculum Vitae

Name	Maurizio Solinas
Place of birth	Sassari, Italy
Date of birth	25th January 1975
Nationality	Italian

EDUCATION

1993/1994	Diploma on Industrial Chemistry at the Technical high school of Sassari, Italy.
1999/2000	Degree in Chemistry (organic and analytical field) at the University of Sassari having the vote of 110/110. The experimental thesis with the title "Study on enantioselective hydroformylation of aryl- and aryloxyethenes by rhodium complexes with diphosphorate chelating atropisomeric ligands" has been done at the laboratory of Dr. Mauro Marchetti at the institute for Bio-Molecular chemistry C.N.R. c/o Chemistry department, University of Sassari, Italy.
2000/2004	Ph.D. student in the group of Prof. Walter Leitner (RWTH-Aachen and MPI-Muelheim and der Ruhr) working on "New Strategies for Multiphase Catalysis Using Supercritical Carbon Dioxide". Date of Award 18th June 2004.