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Diploma Thesis

Continuous enantioselective organocatalysis with supported ionic liquid catalysts in supercritical carbon dioxide

Conducted at the

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Abstract

Homogeneous catalysis has numerous attractive features concerning selectivity and activity; however, catalyst, product and solvent removal after the reaction could lead to problems for the applicability in chemical industries. The concept of supported ionic liquid-phases (SILP) allows immobilizing a catalyst dissolved in ionic liquids as a thin layer on a porous solid support material, aiming to combine advantages of homogenous and heterogeneous catalysis. This SILP concept already found applications in gas phase reactions, while the use of a liquid mobile phase remains challenging due to ionic liquid and catalyst leaching. These problems may be overcome in combination with supercritical carbon dioxide ($scCO_2$) as solvent, which shows high solubility in many ionic liquids, whereas ionic liquids typically only show limited solubility in $scCO_2$. Reactants can be efficiently transported to the catalytic sites in the ionic liquid layer and products are afterwards removed from this phase in a continuous-flow methodology.

This thesis focuses on the development of continuous-flow asymmetric Aldol and Mannich reactions in $scCO_2$ relying on supported chiral ionic liquids as catalysts. A set of three different (*L*)-proline-based chiral ionic liquids was selected as organocatalysts for these two reactions, and the impact of operational conditions was investigated. Furthermore, studies on ionic liquid leaching were performed and showed that amino-acid derived ionic liquids can be immobilized as a thin layer on a solid silica support with minimal losses in a continuous flow system relying on $scCO_2$ and acetone as solvent.

Kurzfassung

Die homogene Katalyse hat im Vergleich zur heterogenen Katalyse vielseitige Vorteile bezüglich Selektivität und Aktivität. Jedoch bereitet die Abtrennung der verwendeten Katalysatoren, Produkte und Lösungsmittel oftmals Schwierigkeiten für die Umsetzbarkeit im großtechnischen Maßstab. Das Konzept der "supported ionic liquid phases" (SILP) erlaubt eine Immobilisierung eines homogenen Katalysators, indem dieser in ionischen Flüssigkeiten gelöst und als dünner Film auf einem porösen Trägermaterial aufgetragen wird. Dieses sogenannte SILP-Konzept vereint die Vorzüge der heterogenen und homogenen Katalyse und fand bereits vielseitige Anwendungen für Gasphasenreaktionen. Im Gegensatz dazu stellt die Verwendung von flüssigen mobile Phasen wegen des Verlusts von Katalysator und ionischer Flüssigkeit noch eine Herausforderung dar. Dieses Problem könnte sich durch die Verwendung von superkritischem Kohlendioxid ($scCO_2$) als mobile Phase vermeiden lassen. Superkritisches Kohlendioxid hat eine hohe Löslichkeit in ionischen Flüssigkeiten und bietet die Möglichkeit einer kontinuierliche Reaktionsführung. Die Edukte werden durch die mobile Phase in die ionische Flüssigkeit transportiert, und die erzeugten Produkte können wiederum kontinuierlich durch die mobile Phase abgetrennt werden.

Der Fokus der vorliegenden Arbeit liegt in der Entwicklung eines kontinuierlichen Prozesses mit überkritischem Kohlendioxid und auf Feststoffen immobilisierten chiralen ionischen Flüssigkeiten. Es wurden dabei zwei Reaktionen, eine asymmetrische Aldol-Reaktion und eine asymmetrische Mannich-Reaktion, untersucht. Der Einfluss der Prozessparameter für die kontinuierliche Reaktionsführung wurde für drei verschiedene, auf (*L)*-Prolin basierenden chiralen ionischen Flüssigkeiten als Organokatalysator für die oben genannten Reaktionen geprüft. Außerdem wurde das Ausmaß der Auswaschung der auf Aminosäuren basierenden chiralen ionischen Flüssigkeiten in einem Laufmittelgemisch aus überkritischem Kohlendioxid und Aceton geprüft.

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1 Introduction

Most chemical processes rely on the use of volatile organic solvents, either as reaction medium or during separation and purification steps. Consequently, solvents are an integral part of the chemical industry and used in almost all areas. However, organic solvents have been debated controversially. Many of these commonly used solvents are considered as environmental risk and as a contributor to health issues. In fact, some of these solvents in debate are classified as volatile organic compounds (VOCs). This means that they feature low vapour pressure at room temperature and contribute to ozone and smog formation through free radical air oxidation processes.[1] As a consequence, governmental regulations on solvent usage were put in place, paving the way for greener alternatives.

Subsequently, the field of "Green Chemistry" emerged to provide guidelines for chemists and engineers to design sustainable products and processes. The prevention of waste as well as the use of benign solvents have been identified among the key principles (Figure 1, left). An analysis by Sheldon[2,3] shows that complex synthesis problems (especially for fine chemicals and pharmaceutical compounds) generate more waste than simple operations. A major part of the waste generated is usually linked to solvent disposal and poor reprocessing (Figure 1, right).[4] Solvent choice has therefore become a critical issue in the chemical industry, especially with regard to waste prevention.

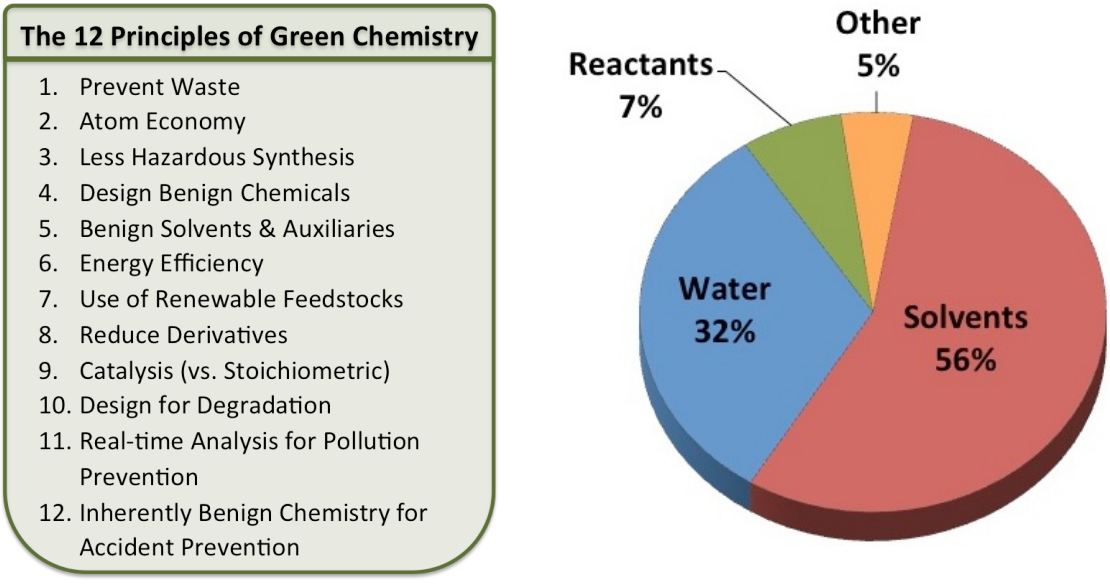


Figure 1: The 12 principles of green chemistry[5] (left). Composition of the raw materials associated with waste generation in the synthesis of pharmaceutical compounds[6] (right).

Another principle of "Green Chemistry" and important aspect concerning sustainable and atom efficient synthesis[5] is the use of catalytic instead of stoichiometric reagents. Ideally, a catalytic transformations should be as selective as possible. This is most frequently achieved by homogeneous catalysis. A wide variety of essential reactions in chemical industry (e.g. hydroformylation, olefin metathesis) are carried out with homogeneous transition metal catalysts, because they satisfy the requirements in terms of activity and selectivity. However, the drawback in such reactions is the insufficient catalyst recovery. The major issue is to separate the active catalyst from the product and simultaneously avoid contamination with catalyst residues. One promising novel approach is the use of liquid-liquid biphasic catalysis. The fundamental idea is that the catalyst is soluble in only one phase, while substrates/products remain in the other phase. As a consequence, catalyst recycling and product isolation is realized by simple phase separation.

In summary, modern synthesis planning should involve not only environmentally benign solvents, but also a re-evaluation of the used synthetic tools with regard to waste prevention.

1.1 Supercritical fluids

In recent years, research on alternative solvents has become very popular in academia and industry to address the principles of "Green Chemistry"[5] as well as engineering demands. One of the most promising examples for innovative solvents are supercritical fluids, which show remarkable opportunities in modern chemistry. According to the IUPAC definition[7] a supercritical fluid (SCF) is defined as a compound, mixture or element above its critical pressure (p_c) and critical temperature (T_c), but below the pressure required to condense it into a solid. At this point the interface between the gas and the liquid phase disappears and the phases get undistinguishable. Consequently supercritical fluids feature unique physical and chemical properties, which are often described as intermediate between those of a gas and a liquid. Table 1 shows the typical order of magnitude for density, viscosity and diffusivity of liquids, gases and SCFs. Comparing density values shows that the SCF behaves more like a liquid. When looking at its viscosity, the SCF behaves more like a gas. With regard to its diffusivity, SCF shows values between the diffusion coefficients of liquids and gases. As a consequence, SCF possess very favourable mass transport characteristics, which is especially interesting for fast reactions where diffusion limits the reaction progress.[8]

Table 1: Orders of magnitude for density and transport properties in the gaseous, SCF and liquid state

Property	Gas	SCF	Liquid
Density [g/cm^3]	10^{-3}	0.3	1
Viscosity [Pa s]	10^{-5}	10^{-4}	10^{-3}
Diffusion coefficient [cm^2/s]	0.1	10^{-3}	5 x 10^{-6}

In the supercritical region only one homogeneous phase exists and it is possible to continuously fine tune physical properties by adjusting temperature and pressure. Most importantly the bulk density of the SCF can be modified near the critical point by variation of these parameters, which directly affects the solvation power.

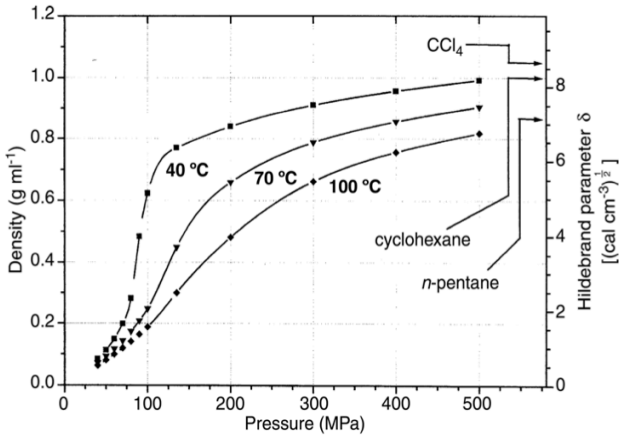


Figure 2: scCO$_2$ - Density dependency with variable pressure and effect on solvation power adapted from P. Jessop and W. Leitner[9]

Figure 2 gives an example of the density dependency at variable pressure for scCO$_2$; while at the critical point density is approximately 0.466 g/cm^3, higher pressure around 30 MPa leads to densities comparable to liquid carbon dioxide. The solvating power is expressed by Hildebrand parameters[10] and directly proportional to the density.[11] This circumstance is frequently utilized for selective extractions of natural products. The decaffeination of green coffee beans with supercritical CO$_2$ that is running world-wide in multi-ton scale is one typical example.[12] Additionally noteworthy is the fact that SCFs have no surface tension. This makes them perfectly suitable to interpenetrate complex matrices and useful for the extraction of compounds from natural resources. Some substances frequently used as SCF are listed in Table 2, together with their critical properties.

Table 2: Critical properties of commonly used SCF

SCF	T_C [°C]	p_C [MPa]
Ammonia (NH_3)	132.4	11.32
Carbon dioxide (CO_2)	31.1	7.38
Argon (Ar)	-122.5	4.86
Ethane (C_2H_6)	32.2	4.87
Ethylene (C_2H_4)	9.3	5.04
Methanol (CH_3OH)	239.4	8.09
Ethanol (C_2H_5OH)	238.9	6.14
Nitrous oxide (N_2O)	36.4	7.25
Sulfur hexafluoride (SF_6)	45.5	3.76
Water (H_2O)	374.0	22.06

1.2 Supercritical carbon dioxide

The most studied SCF is supercritical carbon dioxide ($scCO_2$), as it needs relatively moderate conditions to reach the supercritical state (31.1 °C, 7.38 MPa). Figure 3 illustrates the phase diagram of pure carbon dioxide, with pictures taken to visualize the phase behaviour along the gas-liquid equilibrium curve. In the first picture, next to the triple point, an evident gas-liquid phase boundary is observable. In the sub-supercritical region the meniscus begins to diminish, because gas and liquid densities are getting more similar. In the supercritical region the interface vanishes completely and only one homogeneous phase is recognizable.

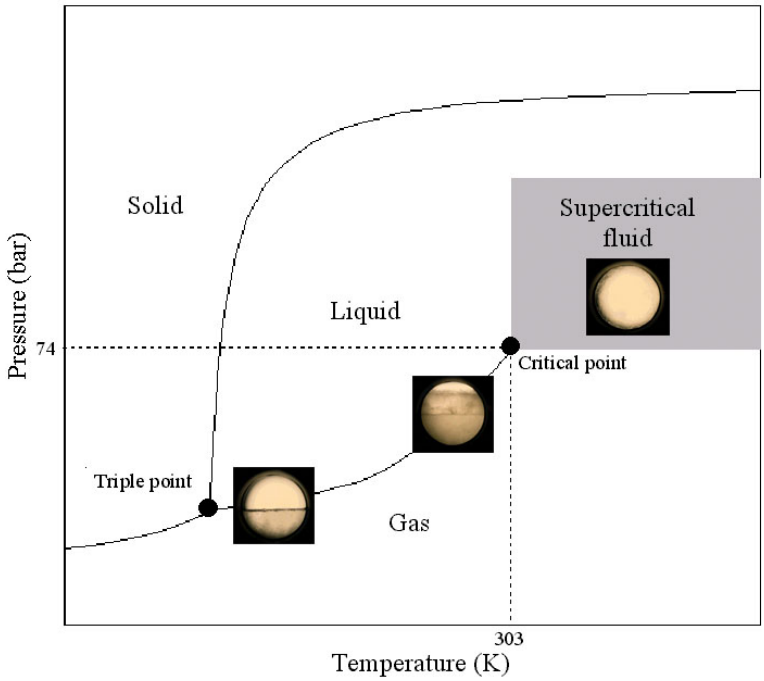


Figure 3: Phase diagram of carbon dioxide adapted from Oakes et. al.[13]

Several publications[8,14,15,16] have appeared in recent years emphasizing the benefits of $scCO_2$ as green solvent. Although CO_2 is considered as a greenhouse gas, its usage as solvent in the chemical industry can be beneficial from an environmental point of view. First of all only already existing CO_2 would be processed with no additional exposure to the environment. Moreover it is possible to use closed loop processes where the spent CO_2 is recycled in its liquid or gas state with no exposure at all. Evidently CO_2 is abundant and available as recycled waste from combustions or ammonia synthesis and because of that inexpensive. Other advantages associated with $scCO_2$ include low acute toxicity and non-flammability, which provides safety under operating conditions. From the process-engineering perspective the easy solvent-product separation through depressurizing is appealing, since it prevents costly solvent removal procedures. Adjustable density (and therefore solvating power) as well as high diffusion rates and low viscosity are other features enriching the list of benefits. While all these arguments favour $scCO_2$ there are still some drawbacks discouraging the industry from adapting $scCO_2$. The investment costs for the equipment are high, because maintaining the desired pressure and temperature is energy demanding. Since carbon dioxide is a very apolar compound often solubility problems arise for polar solutes, which cannot always be controlled over density modification. Usually, these solubility problems can be avoided by adding polar co-solvents (e.g. MeOH, EtOH) to regulate the polarity of $scCO_2$. Table 3 summarizes the advantages and disadvantages when using supercritical carbon dioxide as a solvent replacement.

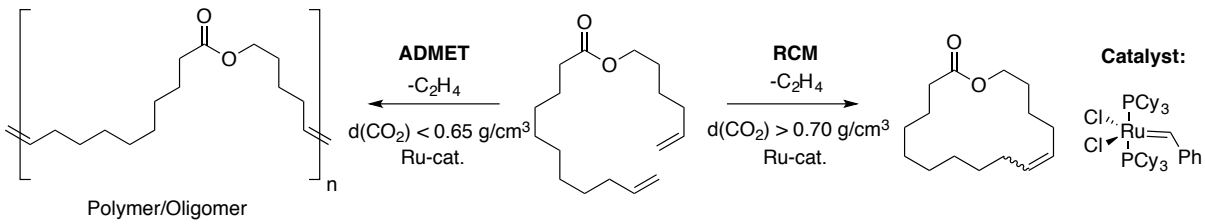
Table 3: Benefits and drawbacks of using $scCO_2$ as solvent

Advantages	Disadvantages
Non-toxic	Needs high pressures
Non-flammable	Energy demanding
Relatively unreactive	Low solubility (without co-solvent)
Inexpensive	
Less solvent residues in product	
Lower environmental impact	
Can be recycled	
Penetrating power of a gas Solvent power of a liquid	
Tuneable solvent	

1.2.1 Potential for synthetic chemistry

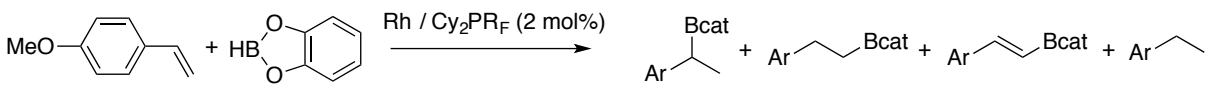
In addition to its advantages as solvent described in the last paragraph, $scCO_2$ can influence parameters such as the reaction rate and selectivity. Especially the tunable nature of $scCO_2$ has the potential for exciting synthetic chemistry applications. Supercritical CO_2 is known[17] for its influence on many reactions, regarding their chemo-, regio-, or stereoselectivity.

The tunability of the density can sometimes be used in order to gain control of the chemical reaction pathway. In 2001 Fürstner et al.[18] illustrated this in a ruthenium catalyzed olefin metathesis for a 16-membered cyclic ester (Scheme 1). In organic solvents ring-closing metathesis (RCM) competes with the oligomerization reaction (acyclic diene metathesis; ADMET), while the latter is favoured at high substrate concentrations. As a consequence, these reactions are frequently carried out in highly diluted solutions. In $scCO_2$, the density can be adjusted by pressure at constant temperature. Above a density of 0.7 g/cm^3 the intramolecular pathway is selectively preferred. At a density below 0.65 g/cm^3 the intermolecular oligomerization reaction is favoured, which makes it possible to gain the polymerization product. In other words the higher density leads to a dilution effect, without the need to change the volume of the reaction.



Scheme 1: Olefin metathesis with reaction pathway depending on density

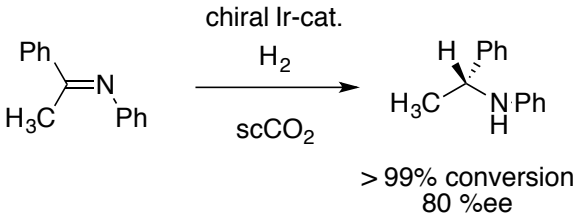
The influence of $scCO_2$ on chemo- and regioselectivity was also demonstrated by Carter and co-workers[19] in the rhodium-catalyzed hydroboration of vinyl arenes (Scheme 2). They showed that the use of THF as a solvent leads to mixtures of all four possible reaction products. Using $scCO_2$ in the same reaction yields exclusively one single isomer.



THF:	32%	34%	17%	17%
$scCO_2$:	100%	---	---	---

Scheme 2: Hydroboration and selectivity comparison in $scCO_2$ and THF

The results obtained by Kainz and co-workers[20] suggest that even higher reaction rates can be obtained by using $scCO_2$. The authors studied an iridium-catalyzed enantioselective hydrogenation of prochiral imines in CH_2Cl_2 and in $scCO_2$ (Scheme 3). The evaluation of the reaction times until complete conversion showed that the reaction is about 20 times faster in $scCO_2$ compared to CH_2Cl_2. Kinetic studies suggested that the difference is linked to a changed reaction profile and not only to better hydrogen gas availability.



Scheme 3: Asymmetric hydrogenation of imines in $scCO_2$ shows a rate enhancement

While the usage of $scCO_2$ in synthesis is still not prevalent, other industry branches have established techniques for the utilization of $scCO_2$ as solvent. The most significant applications for $scCO_2$ have been developed for natural product extractions[21], mainly for food products (coffee[12], tea) and food ingredients (hops aromas, colorants, lipids). Compared to conventional processes using organic solvents it is possible to avoid harmful solvent contaminations. Another example for commercial application of $scCO_2$ is dry cleaning[22] were it functions as a substitute for the potential carcinogenic perchloroethylen.

1.3 Catalysis in liquid-liquid biphasic systems

1.3.1 General considerations on catalysis

Traditionally catalysis is classified into heterogeneous or homogeneous systems depending whether the substrates and catalyst are in the same phase. Each system features different advantages: While heterogeneous catalysis (usually with metals or metal oxides) provides comfortable separation of the catalyst from the substrate, selectivity and activity of the catalyst is usually low. In contrast homogeneous catalysis features higher selectivity and activity, because the molecular catalyst (mostly transition metal catalysts) is easily tunable through appropriate ligand design. However separating the catalyst from the product is problematic. Furthermore industry demand for continuous processes, rather than batch type processes, limits the scope of traditional homogeneous catalysis.

In order to solve this problem, research has focused on possibilities to „heterogenize“ the homogenous catalysts, primarily with the concept of homogeneous liquid-liquid biphasic catalysis or via the immobilization of a solid and inert support material such as silica.[23] Figure 4 illustrates the general workflow for a liquid-liquid biphasic catalysis system. A catalyst is dissolved in phase I (e.g. water, IL, etc.) while the other immiscible phase II (e.g. organic solvent) carries the reagents. The reaction takes place in phase I and the product is accumulated in phase II were it can be removed before new substrate is added. In this ideal scenario the catalyst-carrying phase can be recycled. No cross contamination of the catalyst in phase II occurs and the product is highly soluble in phase II.

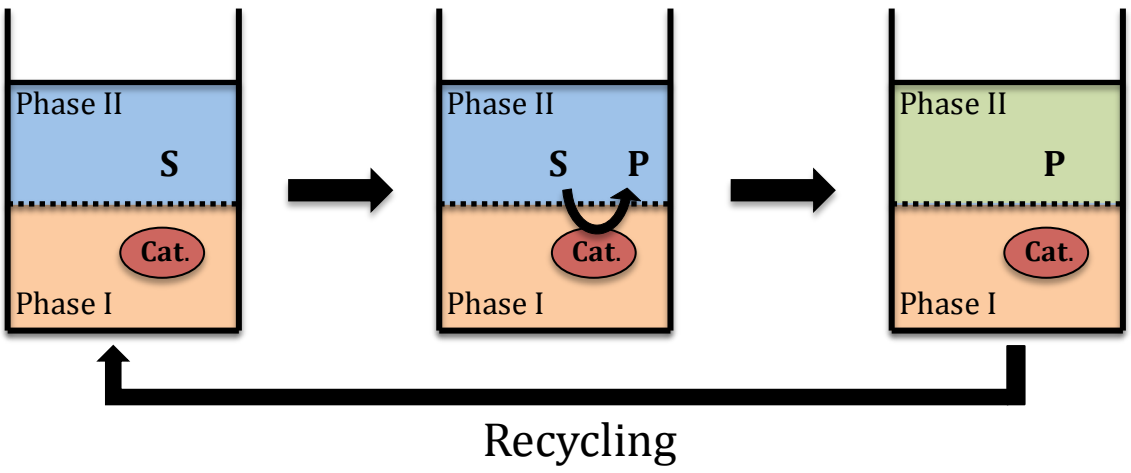


Figure 4: Concept of liquid-liquid biphasic catalysis (Cat.: catalyst; S: substrate; P: product)

1.3.2 Ionic liquids in liquid-liquid biphasic catalysis

A number of options exists for the formation of liquid-liquid biphasic catalysis, and different solvents strategies[24] for biphasic system are currently investigated. The most important ones feature aqueous-organic[25], fluorous-organic[26] or ionic liquid-organic[27] phases. The focus of this chapter is on ionic liquid based biphasic systems.

The term "Ionic Liquids" (ILs) is frequently used for organic salts with a melting point below 100 °C that solely consist of ions. Since the 1990s also the term of room-temperatur ILs (RTIL) has been established in literature.[28] Typically ILs consist of bulky organic cations, such as imidazolium, pyridinium or ammonium in combination with inorganic or organic anions. All these structures have large ions with a conformational flexibility, which leads to small lattice enthalpies and large entropy changes, which favour low melting points.[29] Figure 5 illustrates a variety of different anions and cations that are most commonly used in ILs.

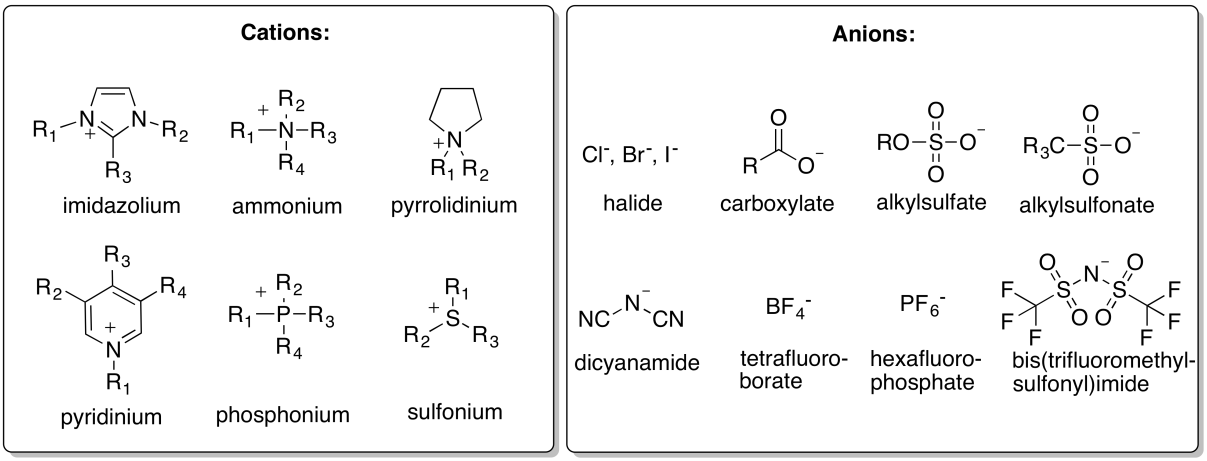
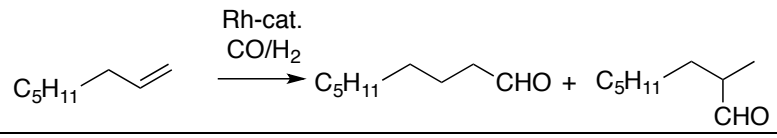
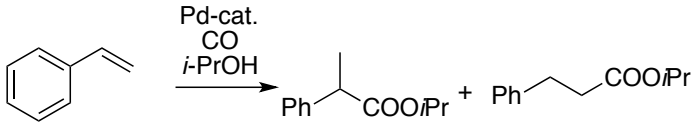
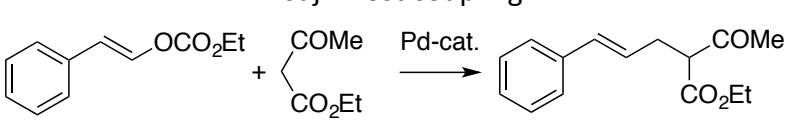
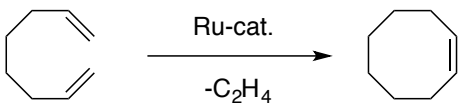


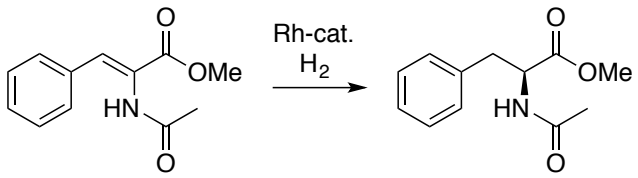
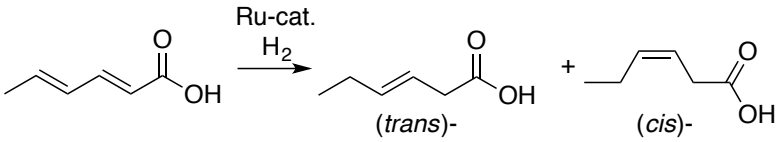
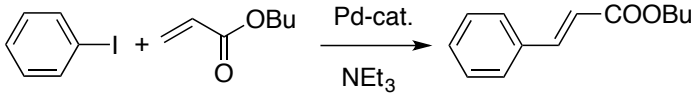
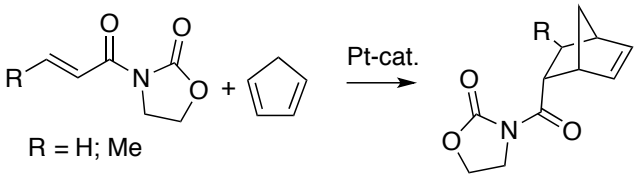
Figure 5: Different cations and anions structures used in ionic liquids

The large number of possible combinations of ions led to the idea of a "designer solvent". The polarity and other solvent properties are synthetically adjustable, depending for example on alkyl chain length, functional groups or perfluorinated carbon substituents. General features[27] for ionic liquids include negligible vapour pressure, non-flammability, high thermal stability and electrical conductivity. For the successful application[30,31] of ionic liquids in biphasic synthesis it is essential that the catalyst (mostly frequently transition metal catalysts) dissolves exclusively in the ionic liquid phase. In the easiest case the substrate is then simply added to the IL phase including the catalyst. The formed product separates as independent second phase, which can be decanted for isolation purpose (e.g. BASF's BASIL™

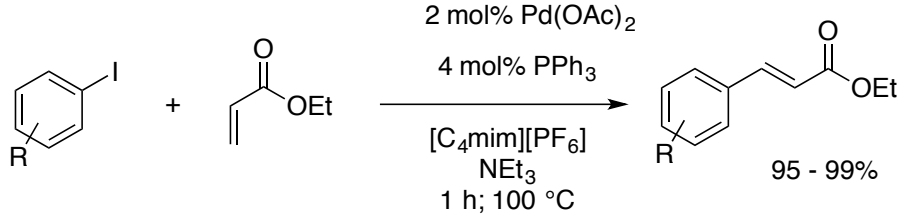
process). Unfortunately, polar products are often quite soluble in the IL phase. Therefore an additional organic solvent phase is needed. Reflecting on the huge choice of available ionic liquids, it is often possible to find appropriate biphasic IL-organic systems, where the substrates are partially miscibility in the IL, but products preferably soluble in the organic phase. In comparison to aqueous-organic systems this tunability of the IL system is an essential improvement compared to conventional solvent combinations such as water/organic solvent. One frequently faced issue in hydroformylation is the low solubility of long chained alkene in the water phase, which leads to low conversions. Solutions for this problem are mainly the use of surfactants or co-solvents (Table 4, entry 1). However, this leads to additional problems in the phase separation process. In case of ionic liquids, this low solubility of higher alkenes is not a problem, since the solvation power of the ionic liquids can be ideally tuned for the desired alkene. Furthermore many ILs have high solubility for transition metal catalysts and therefore no ligand modification is necessary as it would be required for aqueous systems. In any case, the ionic liquid phase with the catalyst can be recycled for further reaction runs, ensuring the overall efficiency of the process and justifying the higher price[32] of the ionic liquid as a solvent.

Table 4: Selected examples for ionic liquid-organic biphasic reactions

Entry	Solvent system	Reaction	Ref.
1	$[C_4mim][PF_6]$ decane	Hydroformylation 	[33]
2	$[C_4mim][BF_4]$ cyclohexane	Alkoxycarbonylation 	[34]
3	$[C_4mim][Cl]$ MeCyH	Tsuji-Trost coupling 	[35]
4	$[C_4mim][PF_6]$ toluene	Ring-closing metathesis 	[36]

Entry	Solvent system	Reaction	Ref.
5	$[C_4mim][BF_4]$ MTBE	Hydrogenation 	[37]
6	$[C_4mim][PF_6]$ MTBE	Hydrogenation 	[38]
7	$[Bu_4N][BF_4]$ toluene	Heck coupling 	[39]
8	$[C_2mim][NTf_2]$ Et_2O	Diels-Alder reaction 	[40]

In some special cases even triphasic systems IL-aqueous-organic are applied – an early example was a Heck coupling reaction reported by Carmichael et al.[41] as illustrated in Scheme 4. The used palladium catalyst ($Pd(OAc)_2$ / PPh_3) dissolves preferentially in the IL phase and extraction was done with cyclohexane and water. The product (*trans*-ethyl cinnamate) was recovered from the organic phase and the salt and by-product triethylammonium iodide was removed in the water phase. The reaction was carried out six times without activity loss of the catalyst with yields over 95%.



Scheme 4: Heck reaction as example for triphasic systems[41]

1.4 Combination of supercritical carbon dioxide and ionic liquids

1.4.1 General aspects on solubility of CO_2 in ionic liquids

While supercritical carbon dioxide has received much attention as green solvent alternative over the past decades, its combination with ionic liquids opens outstanding new possibilities. This derives from the fact that CO_2 is highly soluble in many ionic liquids, whereas the ILs are practically insoluble in CO_2[17,42,43,44]. The solubility of CO_2 in ionic liquids has been extensively studied by different authors[43] focusing on the effect of pressure, temperature, impurities, cation and anion. The general observations conclude an increasing molar solubility with rising pressure and decreasing solubility with ascending temperature. The effect of different anions on the solubility of CO_2 was investigated for the $[C_4mim]^+$ cation.[45] Anions containing fluoroalkyl groups ($[NTf_2]^-$ and $[OTf]^-$) showed higher solubility than nonfluorinated anions like $[NO_3]^-$ or $[DCA]^-$. In contrast, the cation choice seems to have minor effects on the solubility of CO_2. Only small chances were reported with variation of the alky chain length in imidazolium based ionic liquids.

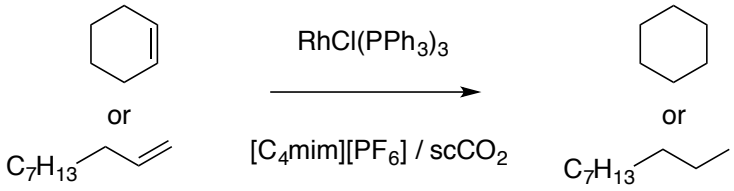
Furthermore, compared to conventional organic solvents the phenomenon of volume expansion ("swelling") with CO_2 in ionic liquids is insignificant.[14] One demonstrative example was reported by Blanchard and co-workers[46] comparing the volume expansion of 1-methyl-imidazole and $[C_4mim][PF_6]$ at 85 bar with CO_2. The ionic liquid expanded only 18%, while the volume of the organic substance increased by 103%.

As a consequence of the low vapour pressure, ionic liquids are basically insoluble in pure $scCO_2$. This makes such biphasic system suitable for extractions and separation processes. However, as soon as polar co-solvents are introduced, it is possible that the solubility of the ionic liquids in the CO_2 phase increases. In 2003 Wu and co-workers[47] investigated the solubility of $[C_4mim][PF_6]$ in $scCO_2$ with ethanol, acetone and *n*-hexane as co-solvent in a flow apparatus. They report the increased solubility of the IL in $scCO_2$ when 15 - 30 mol% of ethanol or acetone was added (120 - 150 bar; 40 - 55 °C). In contrast the addition of *n*-hexane did not show significant changes for the solubility.

1.4.2 Combined ionic liquid - $scCO_2$ biphasic systems in catalysis

Particularly interesting applications have been found in the field of biphasic reaction systems, where the reaction products can be extracted with $scCO_2$ from the ionic liquid phase while keeping the catalytically active species intact. Because of the complete miscibility of $scCO_2$ with many gases (hydrogen, carbon monoxide, etc.), a variety of reactions with gaseous reagents, such as hydrogenations, hydroformylations or oxidations were investigated.

One early example of such a $scCO_2$/IL biphasic system with homogeneous transition metal catalyst in the ionic liquid phase was reported by Liu et al.[48] for the hydrogenation of dec-1-ene and cyclohexene using Wilkinson's catalyst ($RhCl(PPh_3)_3$) in $[C_4mim][PF_6]$.



Scheme 5: Hydrogenation of hexene or dec-1-ene as reported by Liu et al.[48]

They demonstrated high conversion (98% for *n*-decene; 96% for cyclohexene) at 48 bar H_2 pressure and a total pressure of 207 bar. Recycling experiments for dec-1-ene were also conducted. After removal of the $scCO_2$ phase to isolate the product fresh reagents were added to the catalyst-carrying ionic liquid phase. The authors reported that recycling was possible up to four times without any loss of catalytic activity.

Another appealing approach is the usage of $scCO_2$ as transport medium to introduce reagents into the ionic liquid phase and remove formed products under continuous flow conditions. In 2003 Webb and co-workers[49] reported a continuous flow process with IL and $scCO_2$ as carrier medium for reagents and products. They investigated the hydroformylation of 1-dodecene with an in situ generated ionic rhodium catalyst prepared from $[Rh(acac)(CO)_2]$ and $[C_3mim][Ph_2P(3\text{-}C_6H_4SO_3)]$ (Figure 6) dissolved in a thin layer of $[C_8mim][NTf_2]$.

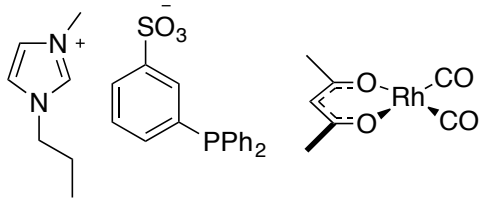


Figure 6: Rhodium catalyst formed in situ from $[Rh(acac)(CO)_2]$ and $[C_3mim][Ph_2P(3\text{-}C_6H_4SO_3)]$

The reaction rates were comparable to commercial systems and catalyst leaching found to be minimal (3.6 µg/mol product). However the selectivity towards the linear aldehyde was lower than desired. The continuous flow system used by Webb et al. is presented in Figure 7.

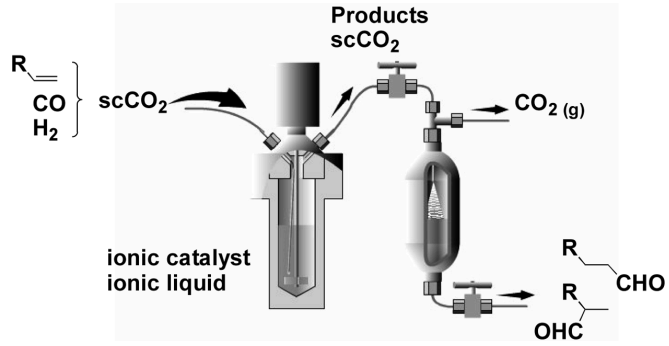


Figure 7: Continuous flow system used by Webb et al. [49]

1.5 Supported ionic liquid phases (SILP) in catalysis

1.5.1 Motivation for the development of SILP catalysis

The concept of using IL-organic biphasic system for homogeneous catalysis proofed to be a convenient strategy for catalyst immobilization. However this approach has also some limitations.[50]

First of all considerable amounts of ILs are needed, which can be problematic from the economical perspective. In recent years many of the commonly used ILs became commercially available, but major cost savings through economies of scale have not been achieved yet. Moreover the usage of bulk IL phases bears the risk of mass transport restrictions, because the reagents have to diffuse into the IL phase to reach the catalyst, leaving the inner portion of the catalytic system ineffective. Usually this issue can be avoided by creating a bigger exchange surface of the IL and organic phase trough emulsions, but this requires extensive stirring. Many ILs feature high viscosity, which makes mass transfer restrictions a issue.

In order to improve the applications of IL based biphasic systems and to overcome the limitations stated above, a new method to immobilize ionic liquids has been proposed by several authors. The groups of Wasserscheid, Fehrmann and others describe the usage of ionic liquids on solid support materials, known as supported ionic liquid phase (SILP) for diverse applications (Figure 8).[51]

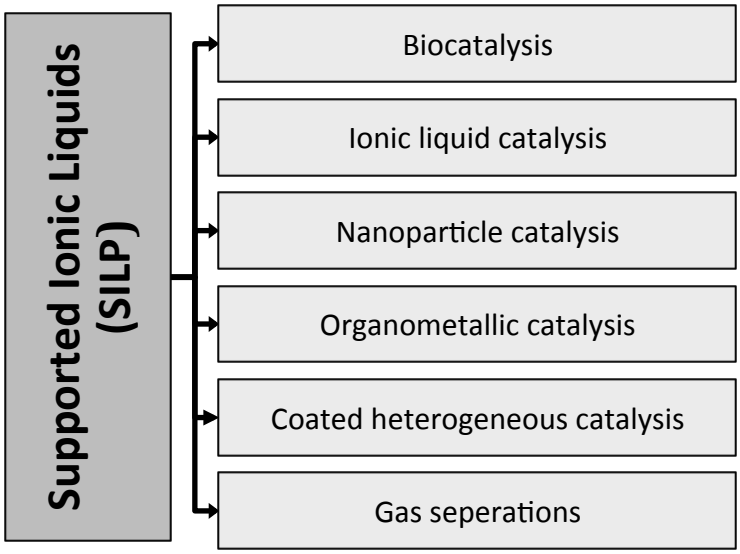


Figure 8: Application opportunities of the SILP technology

1.5.2 Structure of the SILP catalyst

In general, a SILP catalyst consists of a thin layer of ionic liquid, which is immobilized on a solid support material (e.g. silica) with high surface area. The immobilization of the IL is done either through covalent bonding or physisorption via van der Waals and dipole forces. The highly dispersed ionic liquid layer typically contains a well-defined or dissolved transition metal catalyst, although examples with metallic nanocatalysts or biocatalysts are also known. Alternatively, the ionic liquid itself can be catalytically active. Due to the thin layer on a large surface the amount of ionic liquid and sometimes also catalyst can be drastically reduced. Furthermore the mass transfer problems, associated with the analogous biphasic bulk systems, can be avoided.

The resulting SILP catalyst behaves like a typical heterogeneous catalyst and appears as dry free-flowing powder, thereby offering the advantages of handling a solid material. As a consequence, such SILP catalysts can be used in batch operations in the slurry phase, but more interesting on an industrial scale, in fixed-bed reactors operating under continuous flow conditions. Figure 9 illustrates a SILP particle with its porous network, where the ionic liquid is attached. Substrates can easily diffuse into the thin IL layer and products can be removed after the reaction.

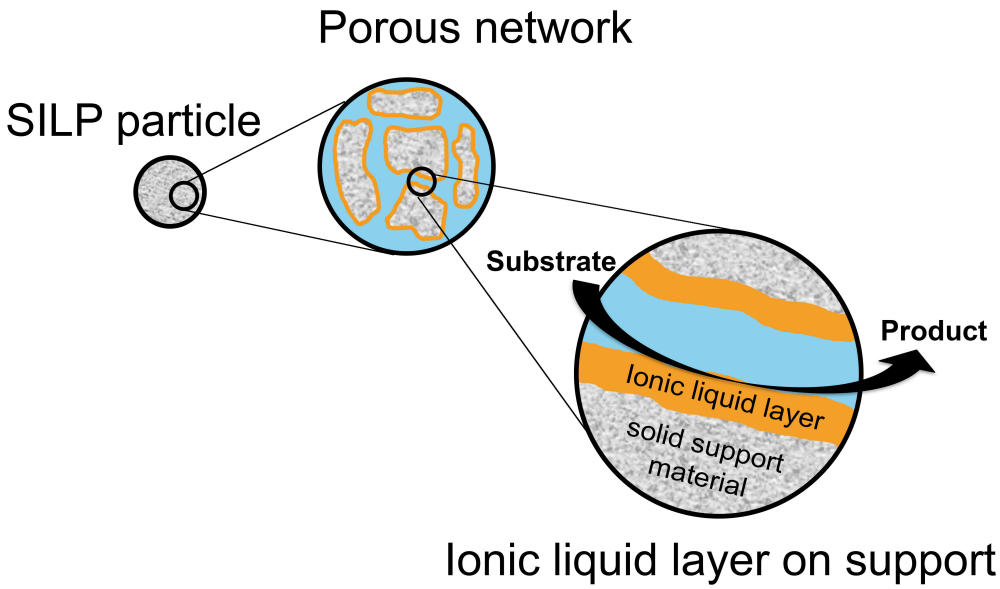


Figure 9: Schematic representation of the SILP catalyst concept

Since the beginning of SILP catalysis different support materials and their characteristics were investigated.[51] The crucial factors for successful SILP catalysts are structural aspects of the porous system and related surface chemistry of the support. The different porosity types (microporous/mesoporous/macroporous) of materials are directly affecting the diffusion process and therefore fundamental in the support selection. Most frequently mesoporous silica materials with a pore size range of 10-100 nm and a high surface area of 100-500 m^2/g are used as SILP support in fixed-bed reactors. Depending on the application, silica requires a thermal pre-treatment ("calcination"; Figure 10, left) to reduce the acidic silanol groups on its surface, which could potentially lead to reactions with the IL, ligands or catalyst. Another option is to chemically modify the surface groups of the support (e.g. by anchoring a molecular layer of ILs) for stronger interactions of the support with the ionic liquid (Figure 10, right).

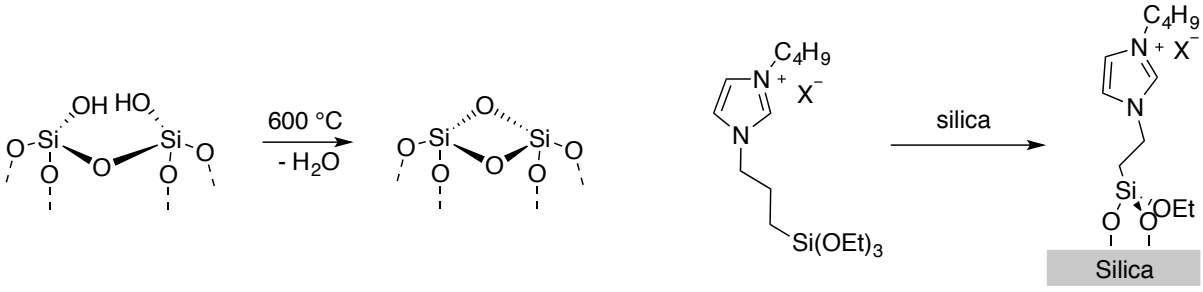


Figure 10: Thermal dehydroxylation (left) and chemical anchoring (right) of surface silanol groups on silica

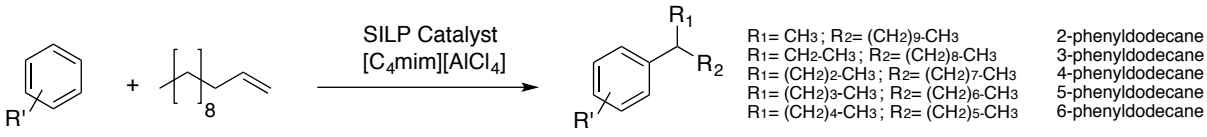
Moreover different metal oxides like Al_2O_3, TiO_2, ZrO_2 or mesoporous carbon have been used as support with diverse surface areas and pore volumes; also polymer based support materials have been reported.[52]

1.5.3 Examples for the development of SILP catalysis

While the history of supported liquid phase catalysts with organic solvents as well as supported aqueous liquid phase systems dates back to 1966 as recently reviewed by Francio et al.[53] the SILP concept emerged only in the late 1990s when ionic liquids gained significant interest in research. Different reaction types are currently under research, and some selected examples are described below.

Friedel-Crafts type alkylations and acylations

One of the first examples of using SILP catalysts in literature was reported by DeCastro et al.[54] using supported Lewis acidic ionic liquids for Friedel-Crafts type alkylations (Scheme 6).



Scheme 6: Alkylation of arenes with dodecene

Different support materials were treated with 1-butyl-3-methylimidazolium chloroaluminate (1.5:1 $AlCl_3$/[C_4mim]Cl) and reactions of benzene, toluene, naphthalene and phenol with dodecene were studied in a batch process as well as continuous liquid-phase and gas-phase conditions. High conversion and selectivity was found for the batch experiments, while catalyst deactivation for the continuous experiments was reported. In the traditional process polyalkylation occurs, because the alkylated derivatives are more reactive than the starting material. Under biphasic conditions polyalkylation is disfavored, as the polyalkylated products are less soluble in the ionic liquid phase. The authors also investigated possible leaching via ICP-AES measurements and did not find leached ionic liquid under flow conditions. In the same year they also reported[55] a new immobilization strategy by anchoring either the cation or the anion on the silica support material via the silica OH groups.

In 2001 the group expanded their investigations towards Friedel-Crafts acylations[56] of aromatic compounds by using 1-butyl-3-methylimidazolium chloroferrate, chloroaluminate and chlorostannate as catalyst. As support material amorphous silica or activated charcoal was used. They showed that the supported ionic liquid on silica was more selective than the unsupported IL experiments, but conversion was lower with the SILP system under batch and flow conditions. The authors also report on catalyst deactivation possibly due to the formation of polyaromatic products accumulating in the ionic liquid phase.

Hydroformylations

One of the most studied reactions in homogeneous catalysis with large impact in chemical industry is the conversion of alkenes to aldehydes through hydroformylation. Although reliable aqueous-organic biphasic processes (Ruhrchemie/Rhone-Poulenc process) exist, catalyst separation from the reaction mixture remains still challenging and requires the modification of the ligands with ionic groups to improve its solubility in water. Moreover, the hydroformylation of higher olefins with n ≥ 6 causes problems in aqueous systems due to limited solubility of the starting materials. Consequently, different examples from slurry phase to gas-phase systems using SILP catalysts were examined.

In 2002 Mehnert and co-workers[57] reported the first slurry phase SILP system for hydroformylation. They immobilized a rhodium precursor ($Rh(acac)(CO)_2$) together with the monodentate phosphane ligands trisodium tris(3-sulfophenyl)phosphine (TPPTS) or tri-1-butyl-2,3-dimethylimidazolium tris(3-sulfophenyl)phosphine (TPPTIM) and additional ionic liquid ($[C_4mim][PF_6]$ and $[C_4mim][BF_4]$) on chemically modified silica (Figure 11).

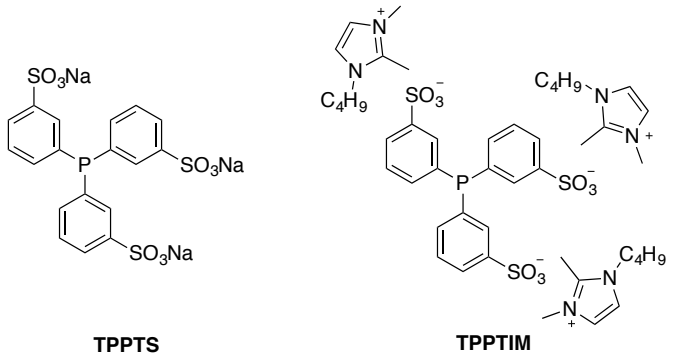
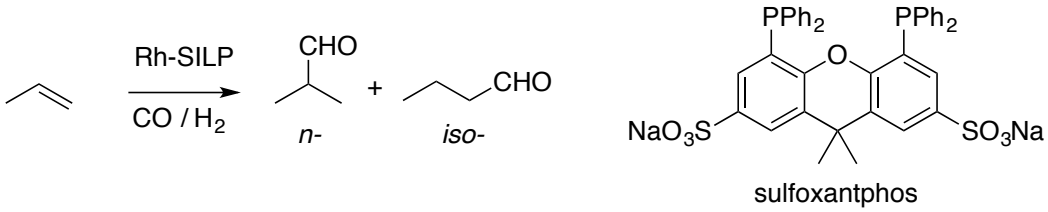


Figure 11: Ligands used in hydroformylation by Mehnert et al.[57]

The authors investigated the reaction of 1-hexene to produce *n*- or *iso*-heptanal and obtained slightly enhanced activity with similar selectivity (*n*/*iso* ratio) for comparable biphasic systems without support. However, the formed product increased the solubility of the ionic liquid layer and therefore significantly shortened catalyst lifetime and leaching was reported. Later in 2005 Yang and co-workers[58] demonstrated improved results in the hydroformylation of 1-hexen by using mesostructured silica (MCM-41) as support together with a rhodium catalysts (Rh/TPPTS) and [C_4mim][BF_4], [C_4mim][PF_6], or 1,1,3,3-tetramethyl-guanidinium lactate (TMGL) as ionic liquid layer.

In order to circumvent problems with leaching under liquid phase conditions, a series of publication starting with Riisager et al.[59] in 2003 described continuous gas-phase hydroformylations using SILP catalysts in fixed-bed reactors. This time propene was used as reagent and two different ionic liquids ([C_4mim][PF_6], [C_4mim][*n*-$C_8H_{17}OSO_3$]) together with a rhodium catalyst and the biphosphine ligand sulfoxantphos were applied on silica (Scheme 7). They obtained high selectivity (*n*/*iso* ratio = 20) and activity (TOF = 37 h^{-1}) for a reaction period over 4 - 5 hours, but after that described decreasing catalyst lifetime.



Scheme 7: Hydroformylation of propene with Rh-SILP and sulfoxantphos ligand

After extensive investigation on the catalyst deactivation, Riisager et al.[60] reported a more stable and fine-tuned SILP system with higher activity and selectivity (95% *n*-butanal). Key findings include the use of excess ligand to compensate the loss induced by acidic OH groups of the partly dehydroxylated silica. Additionally, the authors found that side products with high boiling point accumulated in the IL layer and therefore reduced the effective rhodium concentration. The authors decided to stop the continuous reaction after 180 hours and evacuated the system for 10 minutes to remove the side products from the SILP catalyst, which regenerated the initial activity and selectivity. The group continued their work[61] in the field of hydroformylation with 1-buten, which gave even better results with their developed

SILP system. The use of a technical C_4-feed was recently investigated[62] with butene conversions up to 68% and a selectivity of 93.2% towards *n*-pentenal. Newest trends[63] cover the replacement of silica with base-doped carbon support, allowing to completely suppress the formation of undesired by-products with high boiling point and eliminating the catalyst deactivation over time.

The hydroformylation is, with regard to its importance in industry, probably the most studied reaction for the SILP technology. As a consequence patents[64] were filed and the company Evonik developed a pilot plant (Figure 12) for the conversion of a technical C_4 feedstock to aldehydes. Their developed flow process features an imidazolium-based ionic liquid with optimized ligands and demonstrates long-term stability up to 2000 h.

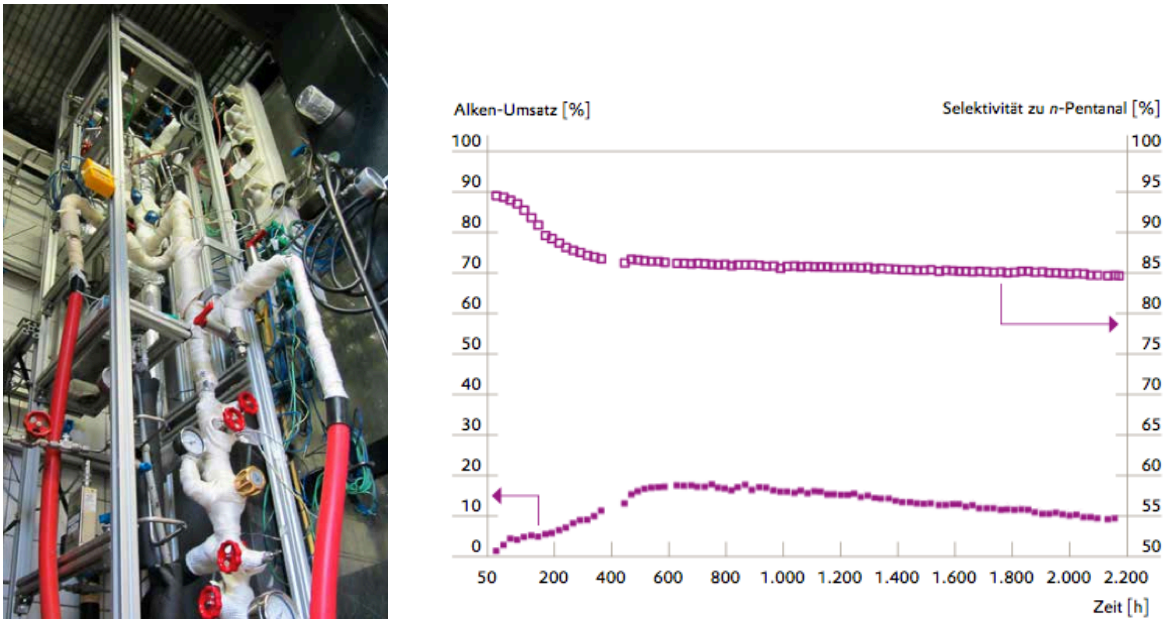


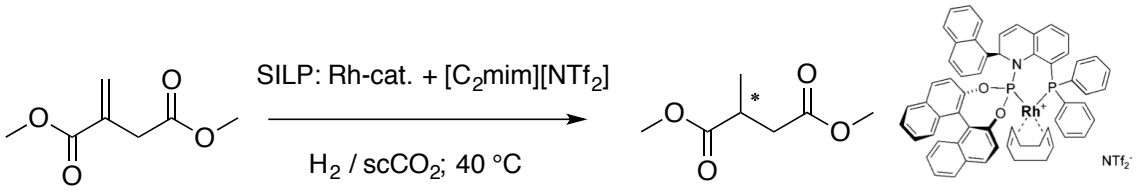
Figure 12: Pilot plant operated by Evonik for hydroformylation (left) and typical diagram obtained for conversion/selectivity over time[65] (right)

1.5.4 SILP catalysts with supercritical carbon dioxide under continuous flow conditions

Based on the examples given in 1.5.3 the potential and utility of SILP catalysts for a wide range of reactions is readily apparent. However, the stability of a SILP system hugely depends on the choice of the mobile phase. SILP systems may be applied in liquid or gas phase, but each methodology has some limitations. Gas phase systems are used for volatile

substrates under conditions where condensation of liquids (substrate, product or side-product) can be avoided. This narrows the substrate range to compounds with high vapour pressure and thermal stability. On the other hand liquid phase systems allow a broader reagent scope, but leaching of the ionic liquid (dissolution or mechanically) from the support material is a frequently faced problem. Especially under continuous flow conditions with polar compounds the dissolution of the ionic liquid leads to a significant loss of ionic liquid and catalyst, and consequently a decrease of the catalytic activity. As a consequence gas-phase reactions are more prominent in literature, whereas liquid-phase SILP catalysis in continuous flow remains less explored. In order to overcome these issues, the use of $scCO_2$ in combination with SILP catalysts was suggested (see also 1.4.1). Supercritical carbon dioxide can be used as a transport vector to introduce substrates into the ionic liquid layer and remove formed products. Moreover the substrate scope is expanded to compounds with low vapor pressure. Also gaseous reagents can be added easily, as they are miscible with $scCO_2$.

One of the first examples of the application of SILP catalysts in combination with $scCO_2$ under continuous flow conditions was reported by Hintermair and co-workers.[66] The authors studied the enantioselective hydrogenation of dimethyl itaconate with a SILP catalyst consisting of $[C_2mim][NTf_2]$ and a commercially available rhodium catalyst based on the chiral ligand QUINAPHOS (Scheme 8). Full conversion was reported after short time on stream with an enantiomeric excess of > 99% for 10 h. Afterwards the enantioselectivity decreased to lower levels of 70 - 75 %ee.



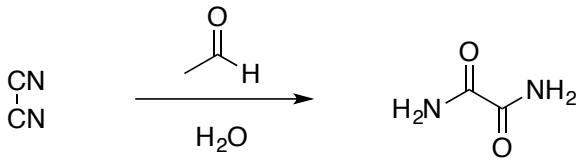
Scheme 8: Asymmetric hydrogenation of dimethyl itaconate (left) and chiral ionic rhodium catalyst (right)

In 2010 Hintermair et al.[67] also investigated the hydroformylation of the higher alkene 1-octene using a continuous flow process with a SILP catalyst in the presence of $scCO_2$. Their SILP system featured $[C_3mim][Ph_2P(3\text{-}C_6H_4SO_3)]$ and $[C_8mim][NTf_2]$ as ionic liquid layer on microporous silica and $Rh(CO)_2(acac)$ as catalyst precursor. The authors studied the influence of the ionic liquid film thickness, syngas/substrate ratio and pressure dependency. At lower

CO_2 pressure the reaction rates were low and leaching of the ionic liquid was reported. When they used higher CO_2 pressures they observed better activity and lower leaching. Under optimized conditions the SILP catalyst system was stable for 40 h with a selectivity similar to the results obtained with the very same catalyst in conventional organic solvents. A steady state turnover frequency (TOF) of 500 h^{-1} and low rhodium leaching of 0.2 ppm was observed.

1.6 General aspects of organocatalysis

In contrast to well-established field of transition metal catalysis with defined catalysts or with mixtures, organocatalysis started to attract interest more recently. Organocatalysis uses substoichiometric amounts of small organic molecules without metal atoms to accelerate a chemical reaction. Although the discovery dates back as early as 1860 when Justus von Liebig[68] synthesized oxamide from dicyan and water catalyzed by acetaldehyde (Scheme 9), the field of modern organocatalysis emerged only in the late 1990s.



Scheme 9: Oxamid synthesis catalyzed by acetaldehyde

While rare previous findings in literature (e.g. Hajos-Parrish reaction[69]) were considered as unique exceptional reactions, systematic research starting later on gave a broader perspective. As a result it was possible to identify the reactive species in the catalytic step and investigate their mechanism of action. Thereafter, a massive number of publications on many versatile reactions appeared to utilize this novel knowledge.

A wide range of advantages are associated with organocatalysis, which makes them also attractive for industrial applications. First of all, a variety of organocatalysts are inexpensive and readily available even in larger quantities. Many of them are derived from biological materials such as amino acids or hydroxy acids and both enantiomers can often be obtained. Furthermore they feature lower toxicity compared to metal analogues. Additionally, these organic compounds are robust towards moisture and air, which is a commonly faced issue in

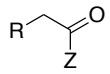
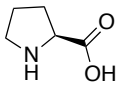
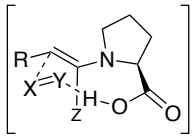
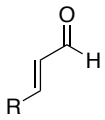
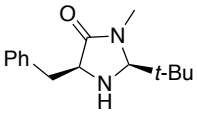
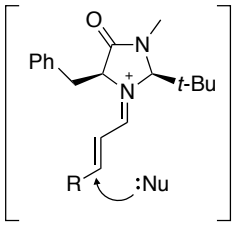
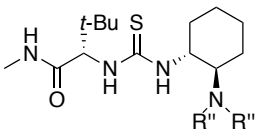
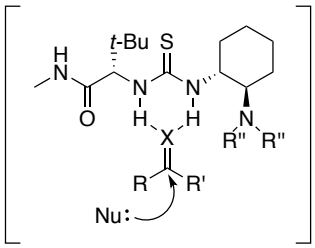
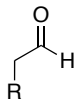
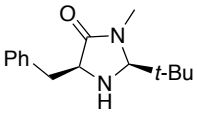
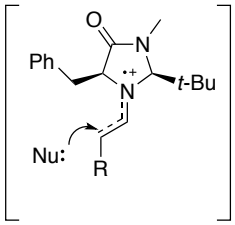
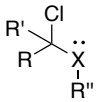
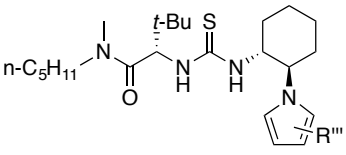
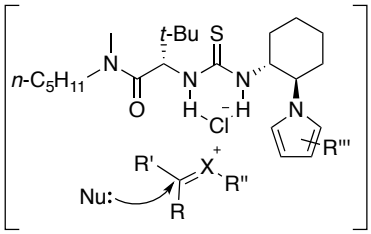
the process design with organometallic compounds. No special equipment, anhydrous solvents or inert gas atmosphere is needed, which lowers also the cost and ensures convenient handling. Especially in the pharmaceutical industry the use of organic molecules is appealing, because metal residues from organometallic catalysts in the product leads to huge costs for purification measures. At the present time, the biggest potential[70] lies probably in the field of enantioselective transformations with chiral organocatalysts, which gained significant interest in academia starting around the year 2000 and is now seen as important synthesis strategy beside traditional organometallic or enzymatic catalysis.

Despite these advantages, the concept of organocatalysis is also associates with some drawbacks that need to be overcome to widen its applicability towards a broad implementation, even in industrial scale. Most organocatalysts feature low turnover frequencies. In order to compensate the lower catalytic activity considerable higher catalyst loadings (even up to 50 mol%) are required. Although the research activity is rising, organocatalysis is still a relatively premature field and not yet well established as synthesis strategy. Another issue associated with organocatalysts is their usually poor solubility in many organic solvents. For example with (*L*)-proline the usage of highly polar solvents (e.g. DMSO, DMF or NMP) is mandatory, because it is hardly soluble in less polar organic solvents and therefore renders work-up and catalyst recycling problematic.

1.6.1 Types of organocatalysts

Reflecting on the large variety of different available organocatalysts it is beneficial to classify them, in order to get an overview of their application possibilities. In literature different approaches have been suggested, but it seems rational to sort them by their mechanism of action as recommended by MacMillan.[70] In general organocatalysts can operate either by activating an electrophile and/or nucleophile, or by creating an asymmetric environment to induce chirality in the target molecule. The first type creates a reactive intermediate through covalent bonding between substrate and organocatalyst (e.g. aminocatalysts, carbenes). The second type is catalytically active via non-covalent bonds like hydrogen bonds or ionic interactions (e.g. thioureas, cinchona alkaloids). Table 5 illustrates the classification of organocatalysts after activation type with typical examples of catalysts and schematic substrates.

Table 5: Overview of typical organocatalysts/substrates as well as their activation type[70]

Type	Substrate	Catalyst	Activation type
Enamine catalysis	 X=Y X = C, N, O, S Y = generic organic atom Z = alkyl, H R = organic chain, ring		
Iminium catalysis	 R = alkyl, aryl		
Hydrogen-bonding catalysis	 X = O, NR R, R', R'' = alkyl, aryl		
SOMO Catalysis	 R = alkyl, aryl		
Counterion Catalysis	 X = O, NR R, R',.. = alkyl, aryl		

1.6.2 Proline as organocatalyst

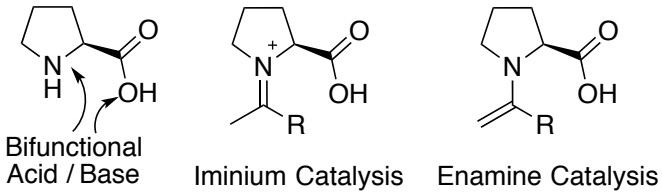


Figure 13: (*L*)-Proline functionalities as organocatalyst

Proline belongs to one of the best-examined organocatalysts: The molecule itself is bifunctional and features a carboxylic acid and secondary amine functional group (Figure 12). While this is true for other amino acids, the cyclic pyrrolidine motif increases the pK_A value of the amine. As a consequence of its Lewis-basic character, it forms iminium or enamine intermediates with carbonyl compounds easily. Additional co-catalytic function was described via the Brønsted acidity of the carboxylate.[71] A huge variety of different asymmetric reactions[72] have been performed with (*L*)-proline as organocatalyst, a short overview is illustrated in Figure 14.

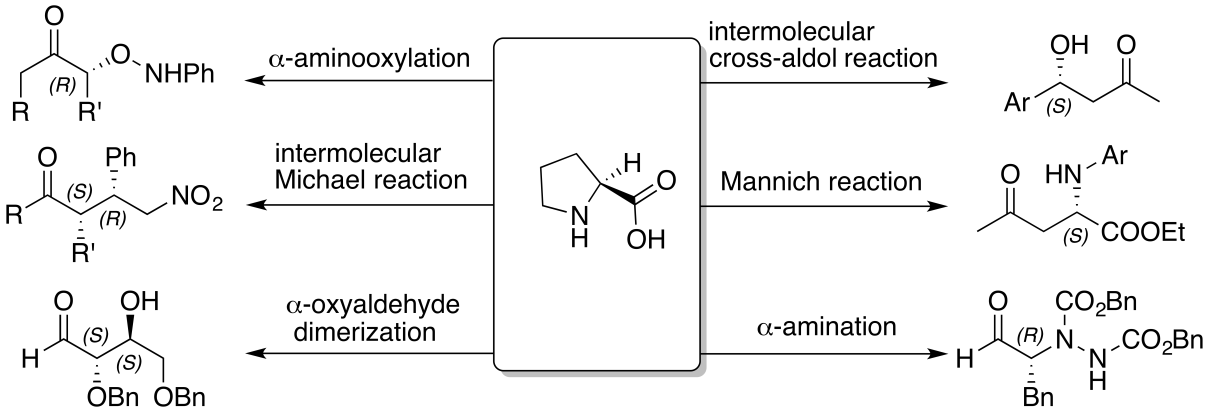


Figure 14: Diverse reaction types catalyzed by proline

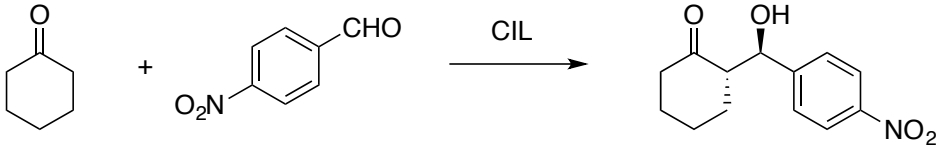
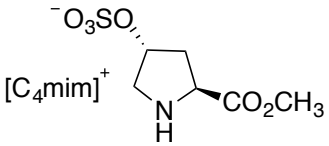
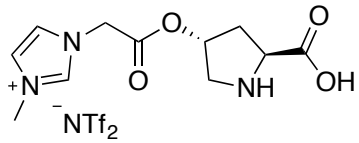
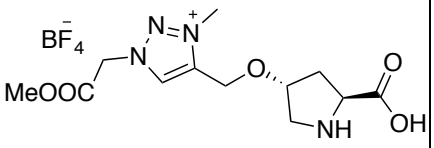
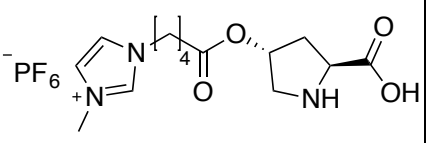
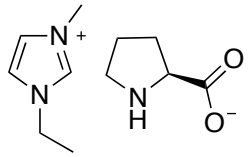
1.6.3 Chiral ionic liquids as organocatalysts

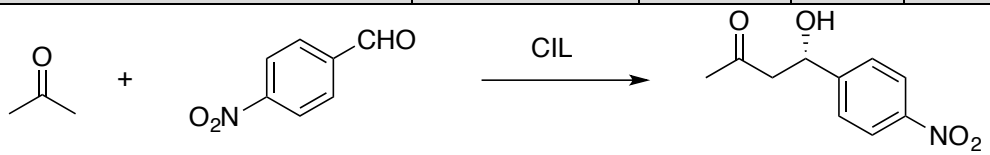
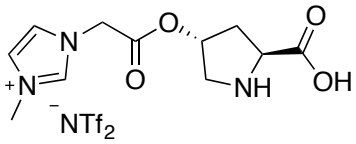
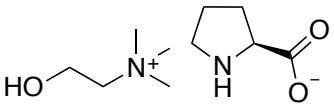
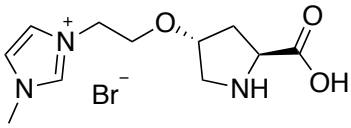
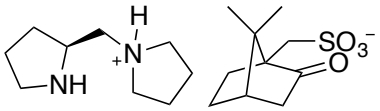
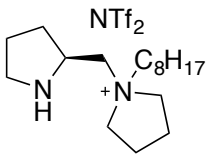
Based on the importance of the Aldol reaction in organic chemistry, it is not surprising that considerable effort has been spent on the development of chiral ionic liquids that can catalyze the asymmetric Aldol reaction and overcome the problems associated with proline as organocatalysts. These chiral ionic liquids are typically based on proline as structural motif, although examples based of on other natural products or even synthetic chiral building blocks were also reported. In case of the Aldol reaction, these chiral ionic liquids can

be either used as a solvent or in sub-stoichiometric amounts. The main benefits lie in the potential recyclability of the chiral ionic liquid-based organocatalysts, which offers an attractive solution to compensate the comparingly high catalyst amounts that are typically required for organocatalyzed Aldol reactions. Additionally, the tuneable solubility of chiral ionic liquids can overcome solubility issues that exist with pure proline, allowing for a broader solvent range, but also opting for the facilitated isolation of the product in terms of a liquid-liquid biphasic catalysis approach.

A brief overview of proline-derived chiral ionic liquids and their application in organocatalytic Aldol reactions is given in Table 6 below.

Table 6: Examples for proline-based chiral ionic liquids for asymmetric Aldol reactions

Entry	Reaction					Ref
	CIL	Conditions	Yield [%]	ee [%]	dr	
						
1		CIL 30 mol% $[C_4mim][NTf_2]$ AcOH	72	52	75:25	[73]
2		CIL 5 mol% H_2O	97	99	96:4	[74]
3		CIL 20 mol%	92	54	90:10	[75]
4		CIL 30 mol% H_2O	95	99	97:3	[76]
5		CIL 30 mol% $[C_4mim][BF_4]$	95	97	78:22	[77]

Entry	Reaction					Ref
	CIL	Conditions	Yield [%]	ee [%]	dr	
						
6		CIL 5 mol% H_2O	87	70	-	[78]
7		CIL 5 mol% H_2O	90	11	-	[79]
8		CIL 10 mol% $[C_4mim][BF_4]$	94	82	-	[80]
9		CIL 20 mol%	41	81	-	[81]
10		CIL 10 mol%	94	72	-	[82]

2 Aim of thesis

Homogenous catalysis provides access to useful catalytic transformations and features high activity and selectivity under mild conditions; however catalyst separation from the product is problematic. The concept of supported ionic liquid-phases allows immobilizing a catalytically active ionic liquid phase as a thin layer on a porous solid support material, aiming to combine advantages of homogenous and heterogeneous catalysis.

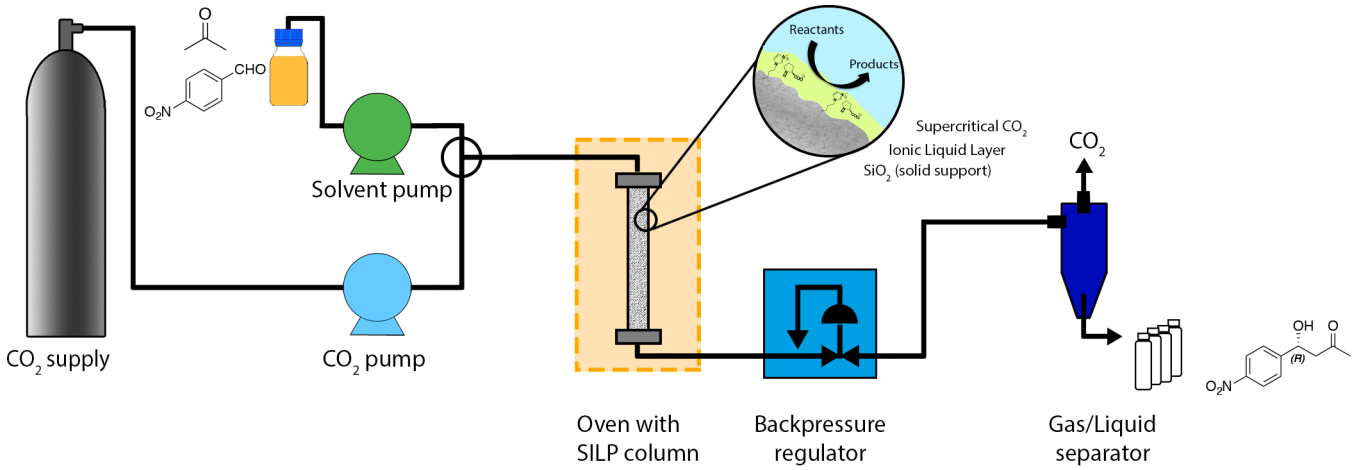


Figure 15: Schematic representation of the continuous flow process used in this work

The aim of this thesis was to develop a continuous flow process using a supported ionic liquid phase (SILP) catalyst in combination with supercritical carbon dioxide as transport media for asymmetric organocatalysis (Figure 15). Three different chiral ionic liquids, based on the (*L*)-proline motif, were synthesized and immobilized on a mesoporous silica. The immobilized chiral ionic liquids were used as organocatalyst for asymmetric Aldol and Mannich reaction in continuous flow.

3 Results and Discussion

3.1 Overview

The control over the formation of asymmetric C-C bonds is one of the most challenging tasks in enantioselective synthesis. Organocatalysts derived from (*L*)-proline can be used for these types of transformations. As described in chapter 1.5.4, the SILP technology in combination with $scCO_2$ provides an efficient strategy for continuous-flow processes with access to a wide substrate range, where even non-volatile compounds can be used under continuous flow conditions. Therefore two different proline-catalyzed asymmetric reactions were chosen and investigated further for their applicability in the supported ionic liquid phase technology.

3.2 Selection of chiral ionic liquids

For the asymmetric Aldol and Mannich reaction (*L*)-proline and its derivatives are commonly used organocatalysts. The three chiral ionic liquids (**CIL 1, 2, 3**), which were used in this thesis, are literature known compounds for asymmetric synthesis (Figure 16). In order to synthesize these different chiral ionic liquids, it is convenient to use starting materials from the chiral pool that are modified to obtain the chiral ionic liquid, while keeping the natural chirality of (*L*)-proline.

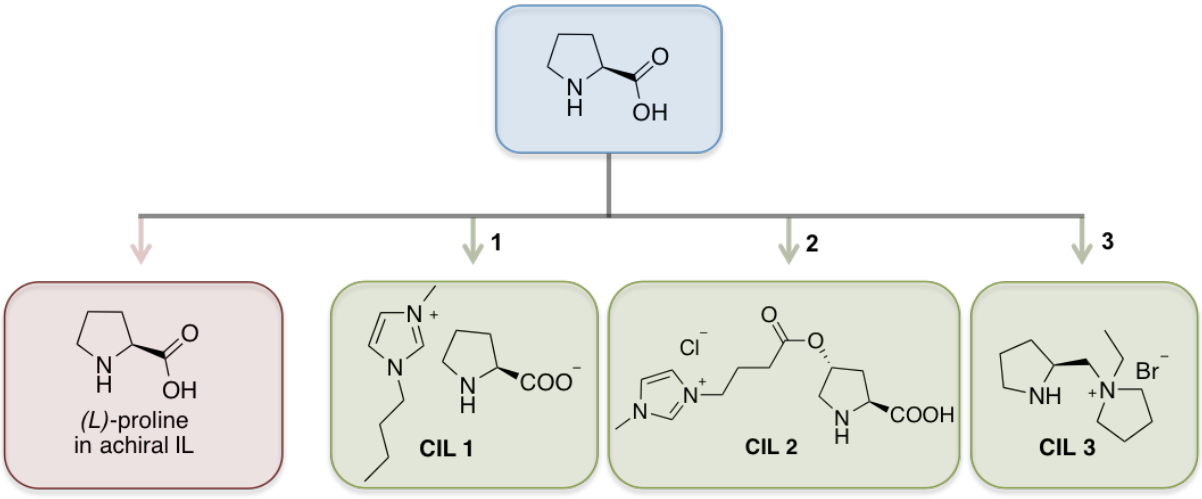


Figure 16: Selection of chiral ionic liquids

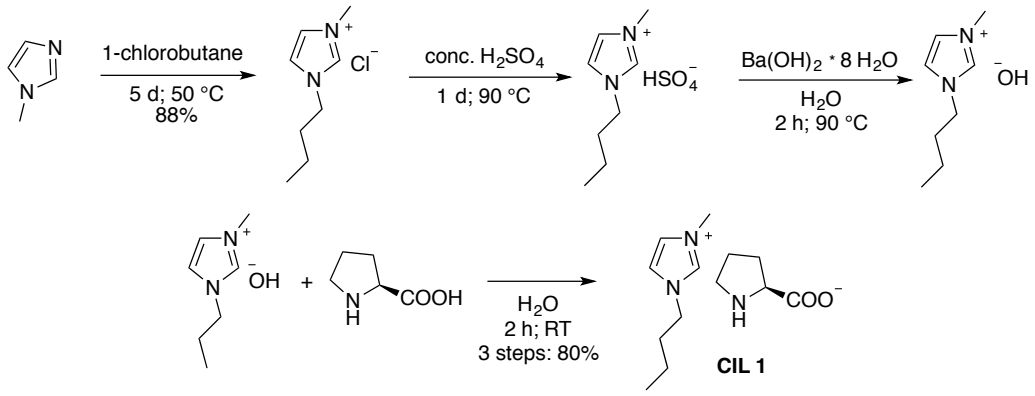
Different types of modifications are possible to give proline based chiral ionic liquids: The most straightforward strategy involves the usage of proline either as cation (prolinium) or

anion (prolinate) together with an according organic or inorganic counterion. This approach was used for the synthesis of **CIL 1** by neutralizing a Brønsted basic ionic liquid with (*L)*-proline. Another option involves the creation of an "ionic liquid-tag" by modifying an existing functional group in order to add an ionic moiety. This strategy was pursued for **CIL 2**, where a side chain with an imidazolium group was attached to 4-hydroxyproline. For **CIL 3** a similar method was used, this time by modification of the carboxylic group with a pyrrolidinium cation moiety. In addition to the chiral ionic liquid strategy, an achiral ionic liquid can simply function as a solvent for unmodified (*L*)-proline.

3.3 Synthesis of chiral ionic liquids

3.3.1 Synthesis of 1-butyl-3-methylimidazolium (*L*)-prolinate (CIL 1)

The general synthesis route towards **CIL 1** involves the halide-free preparation of [C_4mim][OH] and a successive neutralization step with (*L*)-proline.



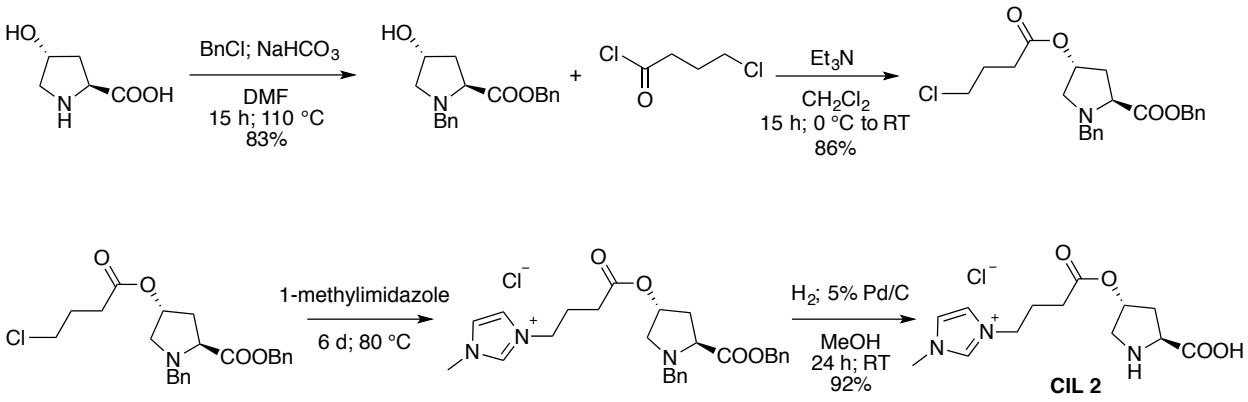
Scheme 10: Synthesis of chiral ionic liquid 1 (CIL 1)

At first [C_4mim][Cl] was prepared by nucleophilic substitution of 1-chlorobutane with 1-methylimidazole in good yields. In all preparations of ionic liquids it is advised to purify the starting materials in order to avoid coloration of the product, which was done here by distillation of both reagents. In order to get a pure product with reliable catalytic activity it is essential to avoid chloride contamination. Different techniques for the halide-free synthesis of ionic liquids are present in literature.[83] While the first attempt for the anion exchange from $[Cl]^-$ to $[OH]^-$ was done with an Amberlite ion-exchange resins, the resulting product still had high levels of chloride present according to the silver(I) nitrate test. As a valid

alternative, an adapted version of the 2-step protocol from Ferguson et al.[84] was used instead. In the first step anion metathesis from $[Cl]^-$ to $[HSO_4]^-$ was performed with concentrated sulfuric acid. After the initial release of gaseous hydrogen chloride, a high-vacuum pump was attached to remove residual HCl dissolved in the ionic liquid. In the next step a second anion exchange was done with $Ba(OH)_2 \cdot 8\ H_2O$ to obtain $[C_4mim][OH]$. The filtration of the fine-grained precipitate ($BaSO_4$) was done over a small pad of silica with minimal loss of substance. In the final step $[C_4mim][OH]$ was neutralized with an equivalent amount of (*L*)-proline. Therefore the exact concentration of the aqueous $[C_4mim][OH]$ solution was determined before, via titration with hydrochloric acid. Finally **CIL 1** could be obtained in 3 steps with a good overall yield of 80%.

3.3.2 Synthesis of 3-(4-(((3*R*,5*S*)-5-carboxypyrrolidin-3-yl)oxy)-4-oxobutyl)-1-methyl-imidazolium chloride (CIL 2)

For the synthesis of **CIL 2** a protecting group strategy was necessary, in order to attach an ester side chain via the hydroxy group of 4-hydroxyproline and create an imidazolium-tag.



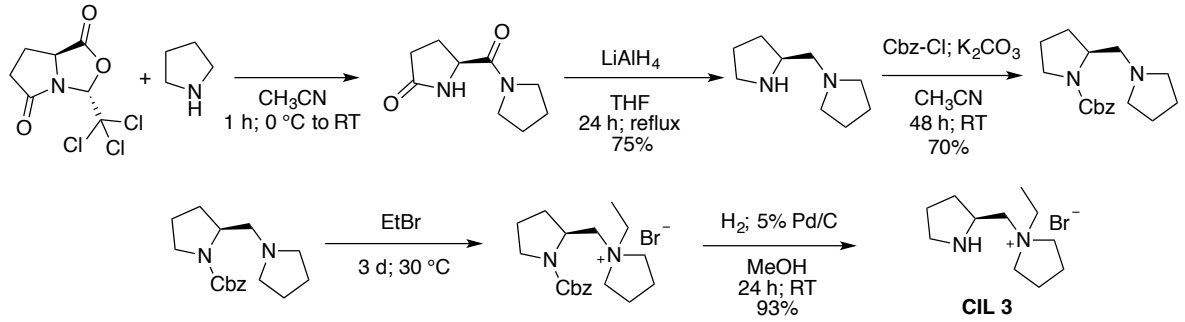
Scheme 11: Synthesis of chiral ionic liquid 2 (CIL 2)

A huge variety of protecting groups have been intensively investigated for amino acids in literature[85], with regard to their importance in the field of peptide chemistry. While it is possible to pursue an orthogonal protecting group methodology, where amine-, hydroxyl- and carboxyl moiety can be modified independently from each other, in this case a simple protection of the amine and carboxyl group is sufficient. In the first synthesis step benzyl chloride provided a fast and convenient way for the benzylation and also satisfied economical considerations. Initially for a smaller scale experiment 2.0 equivalents of benzyl

chloride were chosen, but TLC indicated no complete conversion, therefore 2.3 equivalents were used in a large-scale experiment. In the second synthesis step esterification with an acyl chloride (4-chlorobutyryl chloride) was done with additional triethylamine as base. The nucleophilic substitution of the chloride substituent on the ester side chain was done with 1-methylimidazole to create the desired ionic imidazolium group. Such quarternisation reactions with substrates having longer alkyl chains proceed slowly and therefore long reaction times have been observed (6 days; 80 °C). In order to monitor the reaction progress samples from the reaction mixture were taken and analyzed via ^{1}H NMR. In this case the integrals of the aromatic signals from the imidazolium group were used to determine the conversion. As a consequence of the long reaction time it is advised to carry them out water and oxygen free (inert gas) to avoid by-product formation. In the last step deprotection of the benzyl groups was done via hydrogenation with palladium on charcoal as catalyst. Initially this step was performed in a round bottom flask with a 1 bar hydrogen atmosphere, but after 24 h ^{1}H NMR samples showed still aromatic signals. The usage of a Parr hydrogenation apparatus with a higher hydrogen pressure (5 bar) provided the complete deprotection and as a beneficial side effect it reduced product coloration.

3.3.3 Synthesis of 1-ethyl-1-[(2*S*)-2-pyrrolidinylmethyl]-pyrrolidinium bromide (CIL 3)

The synthesis of **CIL 3** relies on preliminary work by Vasiloiu et al.[82] and provides access to chiral diamines, which are well-established organocatalysts in asymmetric synthesis. The general strategy is the synthesis of the chiral diamine and protection of the secondary amine function in order to perform a quarternisation reaction by alkylating the tertiary amine.



Scheme 12: Synthesis of chiral ionic liquid 3 (CIL 3)

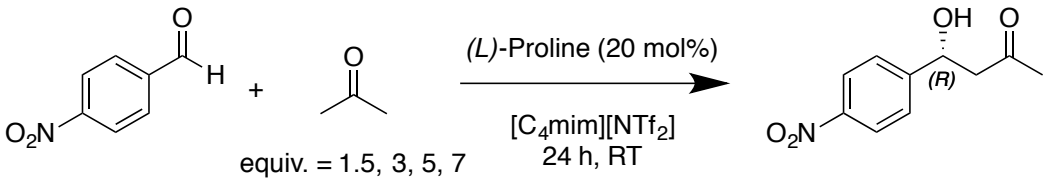
In the first synthesis step, the bicyclic precursor, the adduct of 5-oxo-(*L*)-proline with chloral, was used to form the amide of 5-oxo-(*L*)-proline with pyrrolidine. After that the amide was used without further purification and directly reduced with an excess of $LiAlH_4$ to give the desired chiral diamine. Purification of the diamine was done via distillation with a Kugelrohr apparatus. In the next step benzyl chloroformate was used to introduce a carboxybenzyl protecting group for the secondary amine with a moderate yield of 70%. In the third step, the alkylation of the tertiary amine was done with an excess of 1-bromoethane. Such alkylating agents, with high vapour pressure, can be conveniently removed by applying high vacuum afterwards. The final step comprised the complete deprotection of the Cbz group with hydrogen and palladium on charcoal in a Parr hydrogenation apparatus.

3.4 Reactions under batch conditions

After the synthesis of the three chiral ionic liquids, they were tested under standard batch conditions in order to confirm their catalytic activity for the asymmetric Aldol and Mannich reaction and to compare them with the conventional (*L*)-proline.

3.4.1 Initial studies of the Aldol reaction in $[C_4mim][NTf_2]$:

As a starting point for the investigations of the asymmetric Aldol reaction between acetone and 4-nitrobenzaldehyde (Scheme 13) some initial pre-experiments were conducted using (*L*)-proline as conventional organocatalyst in $[C_4mim][NTf_2]$, which was selected as neutral and unreactive ionic liquid phase for the SILP materials. This reaction is frequently utilized as benchmark Aldol reaction catalyzed by proline and its derivatives. 4-Nitrobenzaldehyde is especially favourable for this reaction, as it contains no hydrogen atom in position α, which avoids self-condensation and limits its role to the electrophilic carbonyl component. Additionally the nitro moiety in *para* position enhances the electrophilicity of the aldehyde group. In order to determine the amount of acetone needed for this reaction with an ionic liquid as solvent, a variation of the equivalents of acetone was studied for (*L*)-proline.



Scheme 13: Asymmetric Aldol reaction in $[C_4mim][NTf_2]$

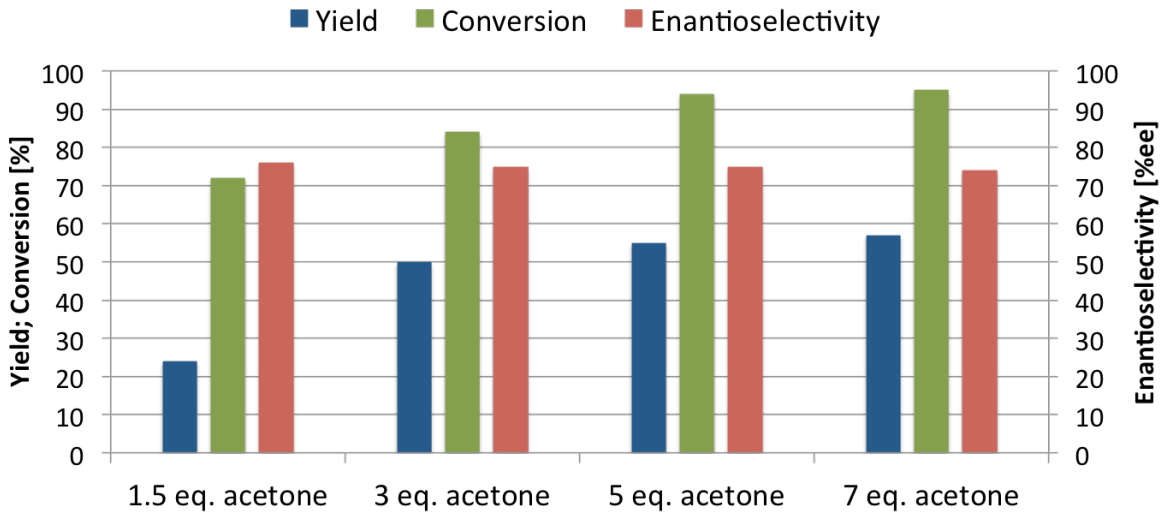


Figure 17: Results from initial test reactions

The reaction was performed with 0.66 mmol aldehyde and 0.13 mmol (*L*)-proline in 1 mL of $[C_4mim][NTf_2]$ at room temperature for 24 h with variable amounts of acetone. Yield and and conversion was determined by HPLC analysis and enantiomeric excess via HPLC using a Daicel CHIRALPAK AS-H. As illustrated in Figure 17, at least 5 equivalents of acetone are required for high conversions and yields around 55% in $[C_4mim][NTf_2]$.

3.4.2 Aldol reaction with chiral ionic liquids under batch conditions

After initially establishing the catalytic activity of (*L*)-proline in $[C_4mim][NTf_2]$, also the catalytic activity of the selected chiral ionic liquids was examined. These experiments were conducted in DMSO, which is the standard solvent for Aldol reactions in organocatalysis.[86]

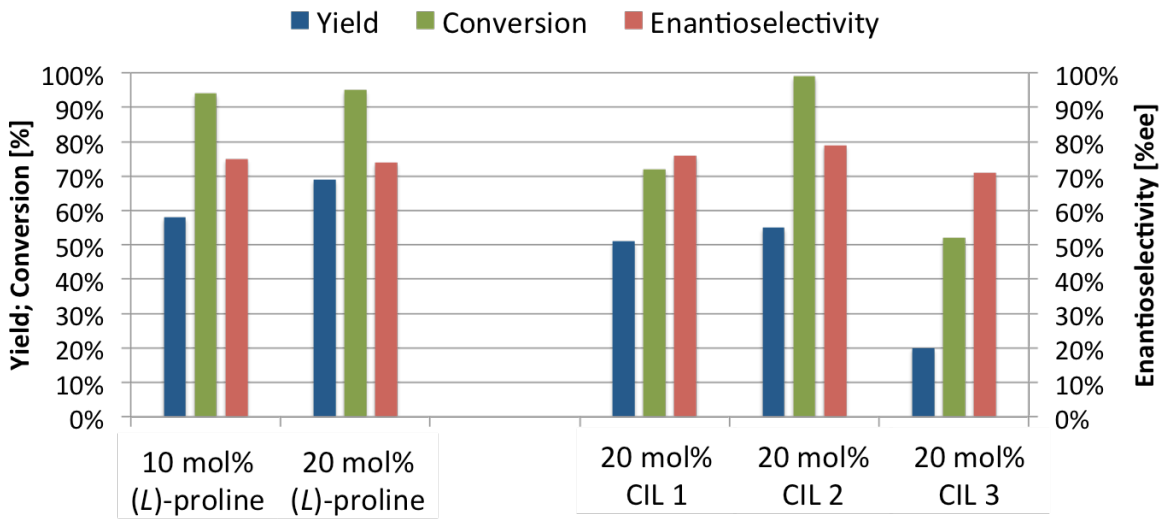


Figure 18: Results from asymmetric Aldol reaction in DMSO

The reaction was performed in 2 mL anhydrous DMSO with 20 mol% of the chiral ionic liquid and 0.2 mL acetone for 24 hours at room temperature. For comparison reasons the reaction was also examined with 10 and 20 mol% of (*L*)-proline under the specified conditions. After the extraction step the yield and conversion was determined via HPLC analysis and enantiomeric excess with a chiral HPLC column. As illustrated in Figure 18 all the tested chiral ionic liquids show good enantioselectivity comparable or even higher than (*L*)-proline. However the yields of all the tested chiral ionic liquids are lower compared to the conventional (*L*)-proline. In literature[82,76] higher yields could be obtained for imidazolium-tagged hydroxyproline and diamine structures, after anion metathesis to hydrophobic anions ($[NTf_2]$, $[PF_6]$, $[BF_4]$). Hydrophilic anions usually lead to moderate yields, but feature

reliably good enantioselectivity. In 2010 Qian et al.[77] examined the Aldol reaction with 30 mol% of $[C_2mim][Pro]$ as organocatalyst in $[C_4mim][BF_4]$ and they were able to gain 91% yield and a good selectivity of 74 %ee. They also proposed a transition state for cyclohexanone as starting material (Figure 19).

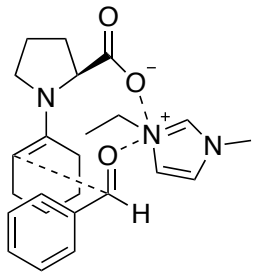


Figure 19: Proposed transition state with cyclohexanone and aromatic aldehyde by Qian et al.[77]

The gap between conversion and yield suggests the formation of by-products, which was investigated in detail for the continuous flow systems. Only by using **CIL 1** (51%) and **CIL 2** (55%) as organocatalyst comparable amounts of the product are formed, which makes them appealing for the desired SILP application.

For the asymmetric Aldol reaction, a catalysis mechanism (Figure 20) for (*L*)-proline was proposed by List et al.[86] in the year 2000, which was based on the observed enzyme catalysis in class-I aldolases. At first a nucleophilic attack of the secondary amine group of (*L*)-proline on the ketone occurs to give a carbinol amine intermediate, which dehydrates directly to give an iminium species (**1**). After an imine-enamine tautomerization a nucleophilic enamine species (**2**) is formed, which attacks the electrophilic acceptor (carbonyl component) for the C-C bond formation. The formed iminium-Aldol intermediate (**3**) undergoes hydrolyzation to the final Aldol product and the initial catalyst.

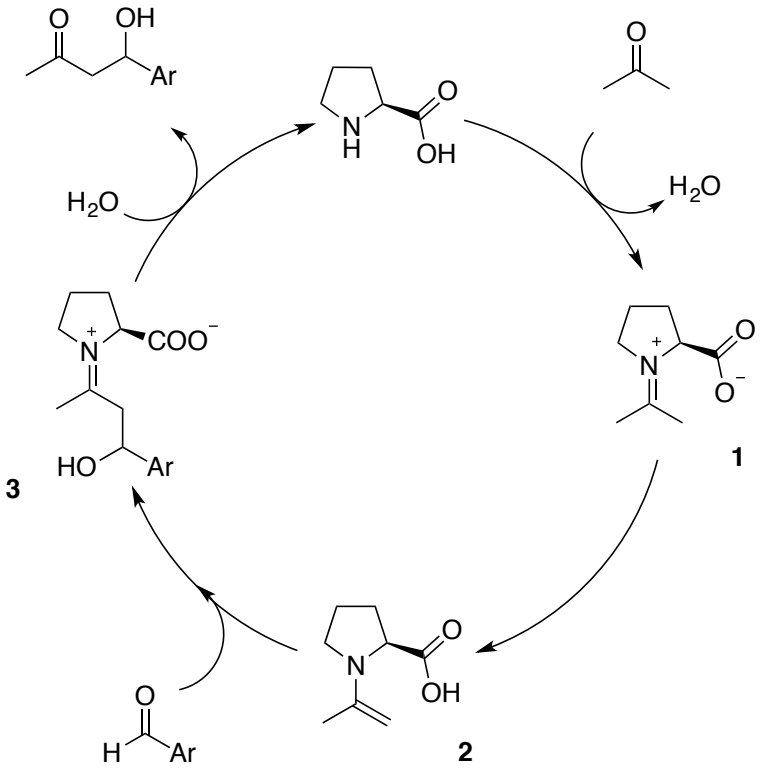


Figure 20: Proposed catalytic cycle of (*L*)-proline

The enantioselectivity of this reaction was explained by List and co-workers[71] with a metal-free version of the Zimmermann-Traxler model to describe the transition state (see Figure 19). However, after energy calculations were performed, the model was modified as computational data suggested that coordinating of the N-H group is not involved in the transition state.

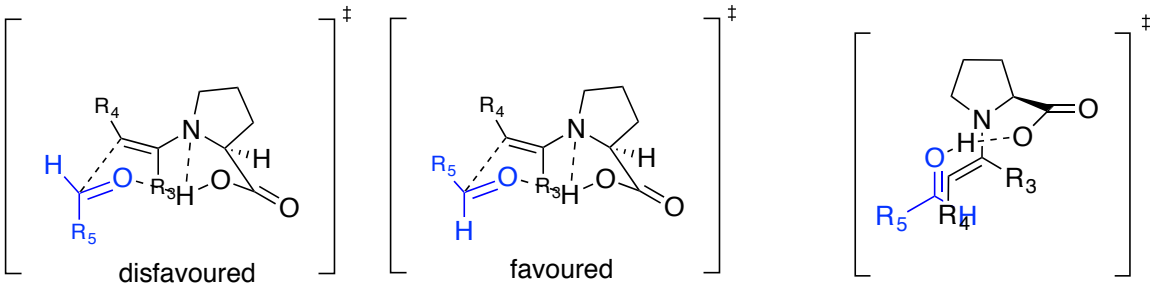


Figure 21: Zimmermann-Traxler model explaining the favoured re-facial attack (left) and new proposed model of the transition state (right)

CIL 1 and **2** feature the carboxyl group from (*L*)-proline, which was recognized to have a co-catalytic function in the catalysis cycle and transition state via hydrogen bonding (Figure 21). In contrary **CIL 3** is derived from the proline structure with an additional pyrrolidine ring to give a chiral diamine. Normally these pyrrolidine-pyrrolidine combined diamine structures

require an additional use of a strong acid, like trifluoroacetic acid to activate the substrate via hydrogen bond formation (Figure 22; left). By incorporating a bulky quaternary ammonium group Vasiloiu et al.[82] could establish a possibility to induce chirality via electrophilic activation without the need for hydrogen bond activation and therefore no additional acid is necessary for these organocatalysts (Figure 22, right).

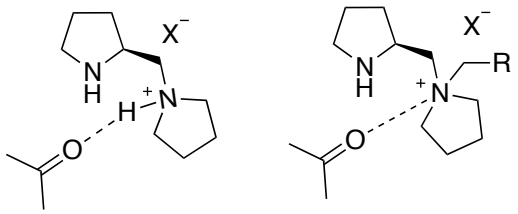
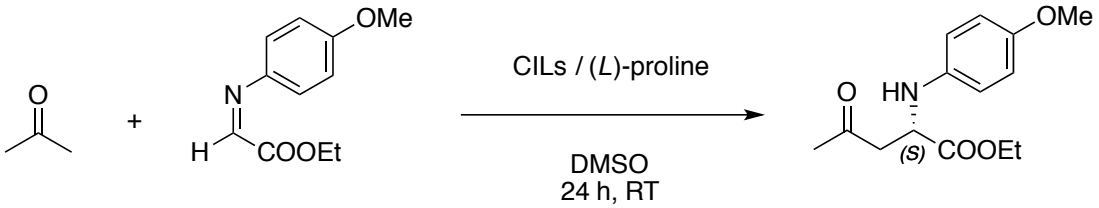


Figure 22: Activation via hydrogen bond formation with chiral diamine (left) and electrophilic activation with pyrrolidinium moiety (right)

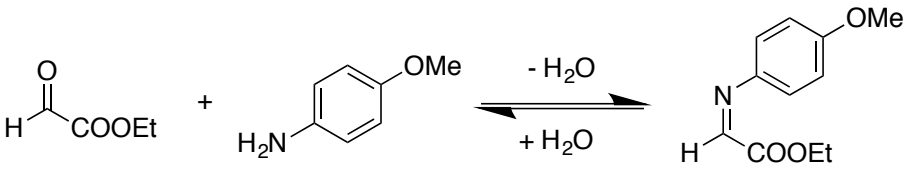
3.4.3 Mannich reactions with chiral ionic liquids under batch conditions

The chiral ionic liquids, and for comparison reasons also (*L*)-proline, were also tested in the asymmetric Mannich reaction with DMSO as solvent (Scheme 14).



Scheme 14: Asymmetric Mannich reaction with CILs and (*L*)-proline in DMSO

For this Mannich reaction a precursor aldimine had to be synthesized from ethyl glyoxalate and 4-methoxyaniline (Scheme 15). Ethyl glyoxalat is commercially available as 50% solution in toluene, which is partly polymerized ("polymer form"; Poly(ethyl glyoxylate); TCI (Tokyo Chemical Industry Co., LTD.)). Available literature[87] on this substance used it mostly without further purification, while some authors suggest depolymerization at elevated temperatures and distillation. In this work, it was found to be most convenient to prepare the aldmine and keep it water-free under inert gas atmosphere and distil it freshly prior use.



Scheme 15: Aldimine synthesis from ethyl glyoxalate and 4-methoxyaniline

The reaction was conducted with 0.38 mmol aldimine and 0.5 mL acetone in 2mL anhydrous DMSO. The catalyst loading of the chiral ionic liquids was 20 mol% and for comparison reasons the reaction was also performed with 10 and 20 mol% of (*L*)-proline. After 24 hours of stirring at room temperature the product was extracted and yield as well as enantiomeric excess was quantified using HPLC analysis with a Daicel CHIRALPAK IB column.

Figure 23 summarizes the obtained results: As reported (*L*)-proline provides good yield (≤ 73%), as well as very good enantiomeric excess (≤ 96 %ee). In comparison the results for the chiral ionic liquids are more diverse. **CIL 1** gave comparable good yield (55%) and enantioselectivity (77 %ee) and therefore seems suitable as ionic liquid-based organo-

catalyst in this reaction. In contrast for **CIL 2** and **3** only traces (~ 5%) of the product could be obtained.

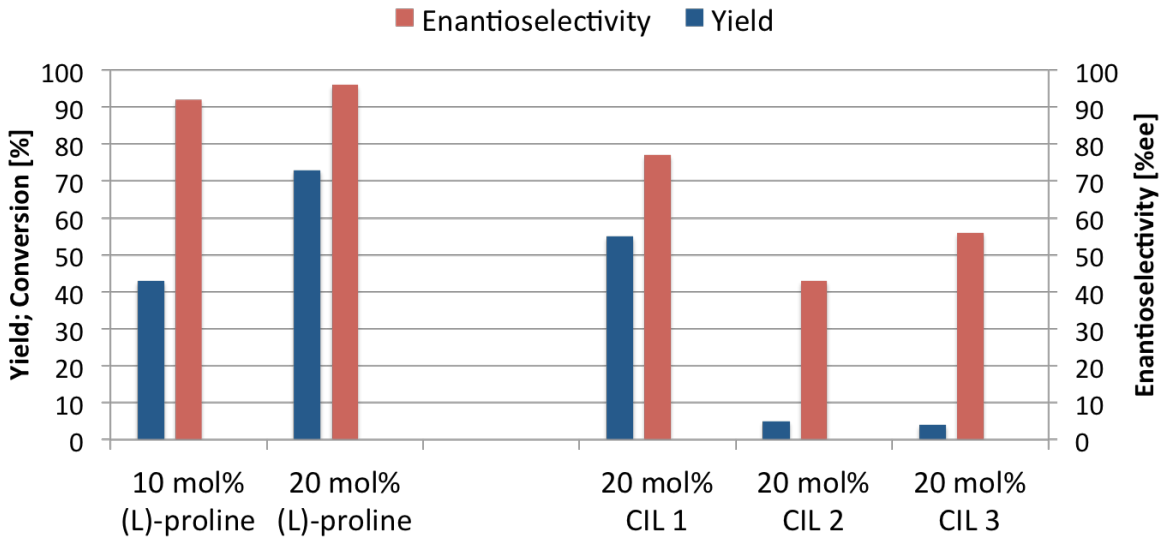


Figure 23: Results from asymmetric Mannich reactions in DMSO

Interestingly in this reaction the enantioselectivities are opposite (*S*) to those observed in intermolecular Aldol reaction (*R*) as noted by List and co-worker.[71] The transition state as well as a proposed catalysis mechanism for *N*-PMP-protected imino ethyl glyoxylates was extensively studied in the Barbas group[88,89] and explained with a nine-membered ring in chair conformation (Figure 24).

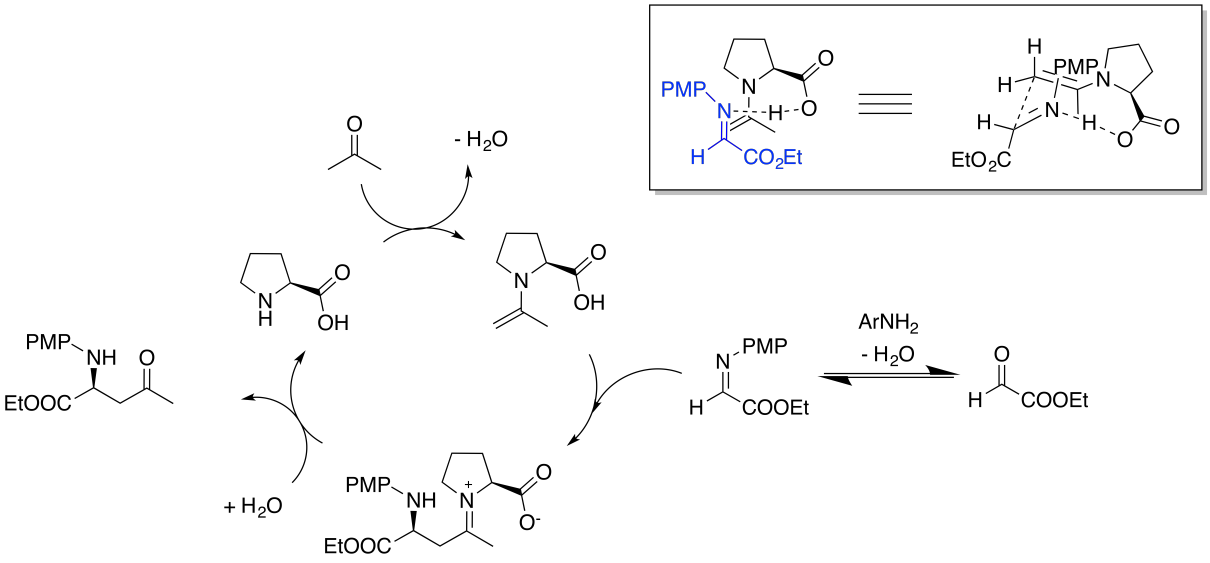


Figure 24: Proposed catalysis cycle and transition state for asymmetric Mannich reaction with (*L*)-proline

3.5 Leaching studies under continuous flow conditions

After successfully establishing the application of chiral ionic liquids for the asymmetric Aldol and Mannich reaction under batch conditions, the development of a continuous flow system was approached. Initially, supported ionic liquid catalysts had to be synthesized, and leaching studies using $scCO_2$ with optional co-solvents had to be performed as described below in detail.

3.5.1 Preparation of supported ionic liquid catalysts

The SILP catalysts were prepared following a literature protocol, which used the wet impregnation technique. In this method a slurry consisting of organic solvent, ionic liquid and support material is prepared and the solvent is slowly removed under reduced pressure. The ionic liquid loading is defined as the amount of ionic liquid relative to the mass of the support and typically ranging between 10 - 25 wt% in literature.[52] All three chiral ionic liquids were prepared by using methanol as solvent and a mesoporous silica (silica 60, Merck) as support. Methanol was used as a solvent because it provided a complete dissolution of the hydrophilic chiral ionic liquids, which is essential for a uniform layer on the support material. Additionally, (*L*)-proline was supported by using the achiral ILs $[C_4mim][NTf_2]$ and $[C_4mim][Br]$. For all prepared systems a dry and free flowing powder was obtained, which has a multilayer of ionic liquid on its surface. An overview of all supported ionic liquid catalysts for asymmetric organocatalysis is given below.

Table 7: Overview of supported chiral ionic liquid and supported proline systems on silica; [a] mol% based on the amount of IL; [b] cellulose

Component	Loading
$[C_4mim][NTf_2]$ with (*L*)-proline (20 mol%[a])	35 wt% 20 wt% 20 wt%[b]
$[C_4mim][Br]$ with (*L*)-proline (20 mol%[a])	20 wt%
CIL 1	5 wt% 10 wt% 20 wt%
CIL 2	10 wt% 20 wt%
CIL 3	10 wt% 20 wt%

3.5.2 Leaching studies

Before the prepared SILP catalysts could be tested for the reactions under continuous flow conditions a method was developed in order to investigate the loss of the ionic liquid layer from the support material. In general, leaching of the ionic liquids can be caused by dissolution into the mobile phase and/or by mechanically forces resulting from the flowing fluid. For the studied reactions acetone is needed as a reagent and solvent, therefore the stability was tested for an acetone/$scCO_2$ mixture (1:9) as well as pure $scCO_2$.

The general setup of the SCF system, used for the flow reactions is shown in Figure 25 and a more detailed description of its components and the experiment is available in chapter 5.6.2.

1 CO_2 pump
2 Co-solvent or reagent pump
3 Oven with packed SILP column
4 Backpressure regulator
5 Gas/Liquid separator

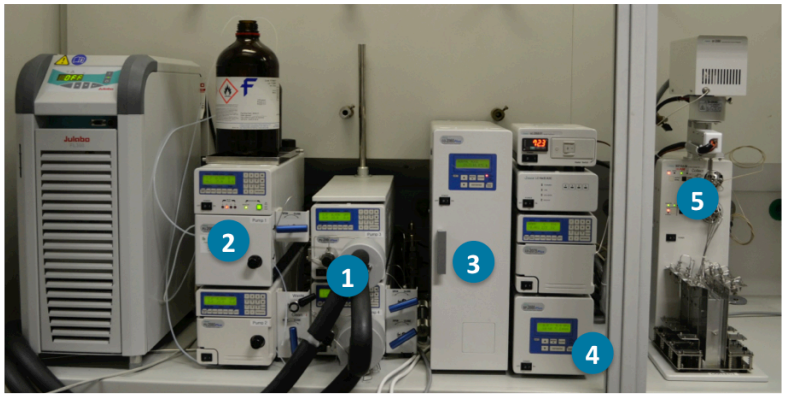


Figure 25: SCF system used for flow experiments

For the leaching studies the process parameters are presented in Table 8. The amount of leached ionic liquid was determined gravimetrically, and analysis via ^1H NMR was run to confirm its identity.

Table 8: Process parameter for leaching studies

Parameter	Value
Oven temperature	40 °C
Temperature at the BPR	60 °C
Pressure	15 MPa
Column dimensions	150 mm × 4.6 mm (2.5 cm^3)
Flow rate and composition	0.9 mL/min $scCO_2$ 0.1 mL/min acetone
	1 mL/min $scCO_2$
Duration	120 min

The obtained data (Table 9) suggests that ionic liquids are in fact not soluble in a stream of pure $scCO_2$. Basically no leaching (max. 0.2%) of the ionic liquids could be detected. In contrast, the addition of the polar co-solvent acetone leads to significant leaching for the hydrophobic $[C_4mim][NTf_2]$ layer (for a 35 wt% IL loading up to 38%). The available literature on SILP systems with $scCO_2$ (see 1.5.4) frequently uses imidazolium-based ionic liquids with the $[NTf_2]$ anion, but acetone as additional reagent limits their application. In general it is known in literature that fluorination makes compounds more soluble in $scCO_2$, however ionic liquids feature very low vapour pressure, which prohibits this behaviour. Only in the cases where acetone is added as co-solvent the solubility rises, because $[C_4mim][NTf_2]$ is soluble in acetone. For $[C_4mim][PF_6]$ Wu et al.[47] described an increased solubility when 10 mol% of acetone are added to $scCO_2$. It became evident that $[C_4mim][NTf_2]$ could not be used as ionic liquid layer for the immobilization of (*L*)-proline. The obtained residue from the leaching tests with acetone/$scCO_2$ and $[C_4mim][NTf_2]$ was analysed via ^1H NMR and showed clearly the signals of the $[C_4mim]$ cation. The hydrophilic $[C_4mim][Br]$ is hardly miscible with acetone and as a consequence $[C_4mim][Br]$ was used to support (*L*)-proline in order to circumvent the leaching problem. No signals from the ionic liquid or (*L*)-proline could be observed in the ^1H NMR from the leaching experiments. For all the prepared hydrophilic chiral ionic liquids no detectable leaching could be observed, suggesting that they can be used in a continuous flow system with acetone and $scCO_2$ without complications.

Table 9: Results from leaching studies

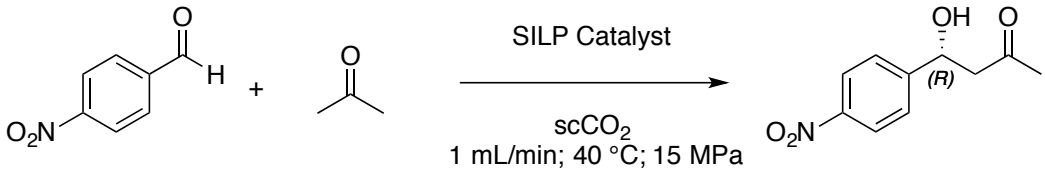
SILP Catalyst	Solvent system (v/v)	Leaching [wt%]
35 wt% $[C_4mim][NTf_2]$ with (*L*)-proline (20 mol%) on silica	$scCO_2$/acetone (9:1)	38.0
20 wt% $[C_4mim][NTf_2]$ with (*L*)-proline (20 mol%) on silica	$scCO_2$	0.2
	$scCO_2$/acetone (9:1)	15.4
20 wt% $[C_4mim][NTf_2]$ with (*L*)-proline (20 mol%) on cellulose	$scCO_2$/acetone (9:1)	8.5
20 wt% $[C_4mim][Br]$ with (*L*)-proline (20 mol%) on silica	$scCO_2$/acetone (9:1)	0.2
20 wt% CIL 1 on silica	$scCO_2$	< 0.1
	$scCO_2$/acetone (9:1)	0.2
20 wt% CIL 2 on silica	$scCO_2$/acetone (9:1)	< 0.1
20 wt% CIL 3 on silica	$scCO_2$/acetone (9:1)	0.2

3.6 Asymmetric organocatalysis under continuous flow conditions

3.6.1 General setup for continuous flow reactions

After the investigation of the chiral ionic liquids under standard batch conditions, the research was expanded towards a continuous flow process. The three different chiral ionic liquids and (*L*)-proline (in [C_4mim][Br]) were prepared as SILP catalyst on mesoporous silica with different ionic liquid loadings. Each of these obtained materials was packed into a column (150 × 4.6 mm) and placed into the pre-heated oven of the SCF system (for details see 5.6.3). After pressurizing this system with pure $scCO_2$, the co-solvent pumps were used to introduce the starting materials dissolved in acetone into the $scCO_2$ flow. The reagents were carried through the catalytic reaction zone and after that the pressure was released with a backpressure regulator. The obtained crude product was collected in fractions every hour for a total duration of 6 hours and their composition was determined via HPLC analysis.

3.6.2 Asymmetric Aldol reaction



Scheme 16: Asymmetric Aldol reaction with SILP catalyst

In order to establish a continuous flow process different process parameters have to be considered. The regular parameters, which also apply for batch reactions, are temperature and pressure. For this type of asymmetric Aldol reaction it is known in literature[90] that higher temperatures provide better yield but lower enantioselectivity. As a consequence the temperature was set to 40°C, to ensure supercritical conditions at the lowest temperature possible. The effect of pressure is mostly related to the solvation power of $scCO_2$ and pre-studies showed that pressures around 8 MPa gave solubility problems with 4-nitrobenzaldehyde. One article by Liu et al.[91] on this reaction in $scCO_2$ showed that higher pressure is beneficial for the yield, without affecting the selectivity. To avoid these solubility problems the pressure was therefore adjusted to 15 MPa. In contrary to batch reactions in the field of flow chemistry there are additional parameters, which have to be considered. Flow rates, resistance time and reagent concentration were adapted from comparable

literature sources[92] without $scCO_2$ to fit the system dimensions and to obtain high conversion of the starting materials. Table 10 presents the process parameters used for the continuous flow experiments of the asymmetric Aldol reaction. The starting material 4-nitrobenzaldehyde is introduced as a pumpable solution in acetone (20 mg/mL), which acts as solvent and reagent.

Table 10: Process parameters for the Aldol reaction in continuous flow mode

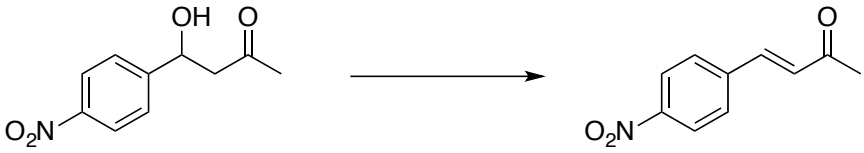
Parameter	Value
Oven temperature	40 °C
Temperature at the BPR	60 °C
Pressure	15 MPa
Column dimensions	150 mm × 4.6 mm (2.5 cm^3)
CO_2 flow rate	0.9 mL/min
Substrate flow rate	0.1 mL/min (20 mg/mL 4-nitrobenzaldehyde in acetone)
Residence time	59 s

The experiments with the chiral ionic liquids supported on silica revealed that only **CIL 1** shows good conversion for the flow reactions, while **CIL 2**, **3** and (*L*)-proline in [C_4mim][Br] failed to do so. Up to 50% yield could be observed with **CIL 1** after 120 min, whereas only 6% were found for **CIL 2** and 4% for **CIL 3**. Similarly, for the system (*L*)-proline in [C_4mim][Br] only traces of the product could be detected. An often-faced difficulty for continuous flow systems is the crystallization of either product or substrate in the capillaries, which can lead to clogging and unsteady flow. The starting material for this Aldol reaction (4-nitrobenzaldehyde) is a solid and therefore low conversion leads to an accumulation in the supercritical fluid system. After 2 hours the crystallized starting material clogged the capillary, which lead to increased pressure and shutdown of the pumps due to over-pressure.

Table 11: Comparison of different SILP systems for asymmetric Aldol reaction after 120 min; [a] yields obtained from fraction 2 (60-120 min) [b] due to low yield, enantioselectivity is not reported

SILP Catalyst	Yield [%][a]	Enantioselectivity [%ee]
CIL 1 (20 wt%)	50	14
CIL 2 (20 wt%)	6	4
CIL 3 (20 wt%)	4	-[b]
(*L*)-proline with 20 wt% [C_4mim][Br]	traces	-[b]

The reason for these divergent findings could be a result of the lower catalytic activity of **CIL 2** and **3** compared to **CIL 1**, which becomes more evident for short contact times of the substrate with the catalyst in a continuous flow system. Another possible explanation for this behaviour could also be linked to the viscosity difference between **CIL 1** and the others. While **CIL 1** has moderate viscosity allowing better diffusion of the reagents into the ionic liquid layer, the other two chiral ionic liquids are highly viscose and **CIL 2** is in a nearly glass-like state. This trend can be confirmed also for (*L*)-proline in [C_4mim][Br], which is a solid at 40 °C. It seems that without swelling through the mobile phase the catalyst is not readily accessible for the substrates. On the one hand a moderate viscosity is needed to stabilize the ionic liquid layer on the support material, but on the other hand to high viscosity leads to significant mass transport limitations, which makes the application difficult for a continuous flow system. Analysis after the continuous flow reaction showed that the colour of the SILP materials changed from white to red/yellow, indicating that a by-product is also formed that accumulates in the SILP material. For the Aldol reaction it is possible that the hydroxyl group eliminates from the product, resulting in the formation of the highly coloured α,β-unsaturated ketone (Scheme 17). Especially sterically not-demanding ketones, like acetone are prone to this type of side reaction. For this reason, the by-product was synthesized as a reference material for quantification following a standard Wittig protocol. Figure 26 shows the SILP catalyst with **CIL 1** at different ionic liquid loadings before and after the reaction.



Scheme 17: Formation of the elimination product

Figure 26: Comparison of initial (left) and three spend SILP catalysts with 20, 10 and 5 wt% CIL 1 loading

In contrast **CIL 1** with an ionic liquid loading of 10 wt% showed significant catalytic activity as illustrated in Figure 27. An overall high conversion of 4-nitrobenzaldehyde is obtained and after 3 hours the system stabilizes and yield is quite constant around 45%. However under these conditions it was not possible to gain any enantioselectivity and a moderate amount of the elimination product is formed at the same time.

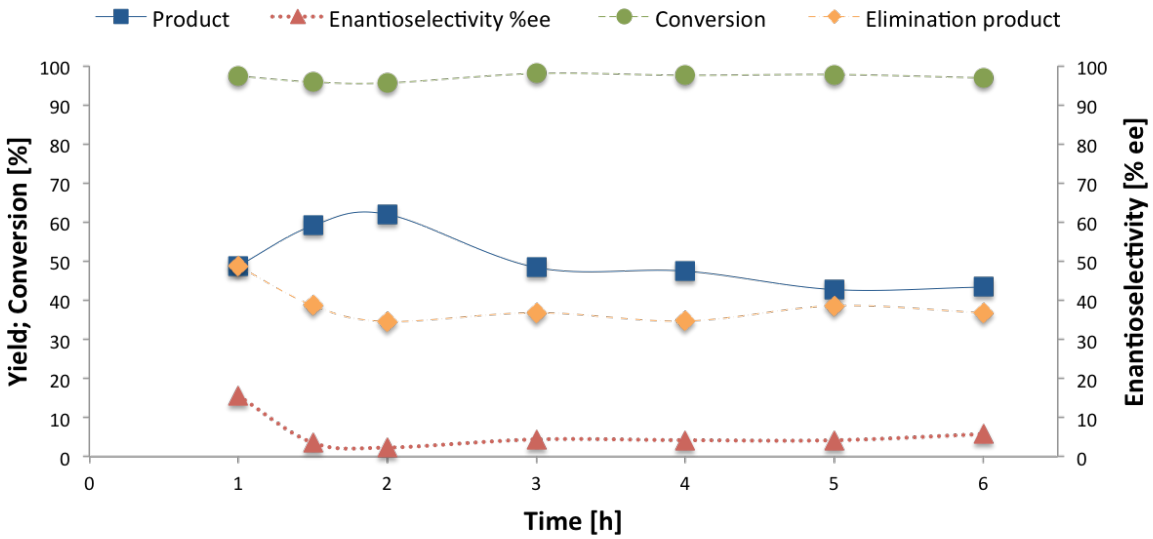


Figure 27: Results from Aldol continuous flow reaction with CIL 1 (10 wt%)

Based on these findings the loading of **CIL 1** was increased to 20 wt% and it became apparent, that a higher ionic liquid loading is very beneficial for the yield and selectivity. As illustrated in Figure 28, after 3 hours the system stabilizes with good yields around 55%. This time also selectivity could be obtained with an enantiomeric excess of up to 21%. The amount of elimination product is lower compared to the 10 wt% ionic liquid loading and conversion for the starting material is at 80% over a time period of 6 hours.

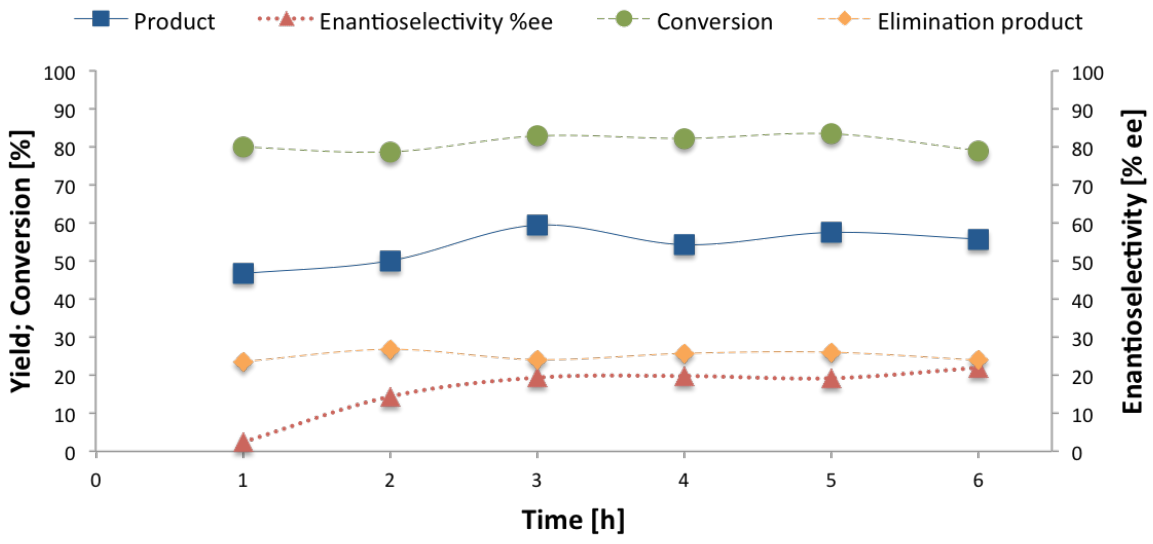
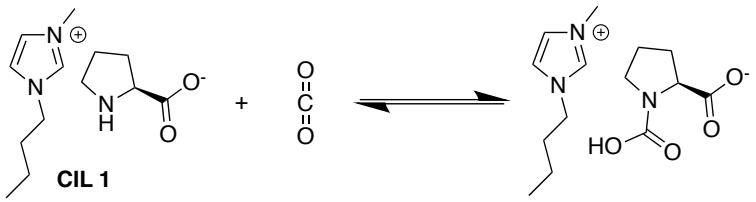


Figure 28: Results from Aldol continuous flow reaction with CIL 1 (20 wt%)

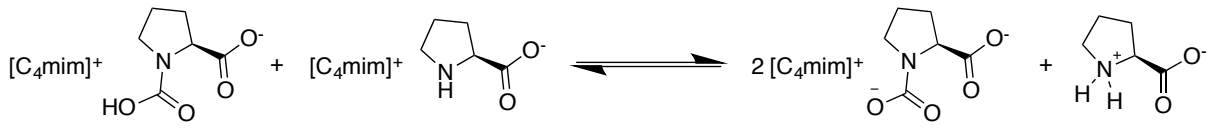
A further reduction of the chiral ionic liquid to 5 wt% was not possible, as low conversion and yield (9% after 120 min) resulted in the accumulation of the staring material in the SCF system, which lead to clogging of the capillaries.

The complete different performance of **CIL 1** compared to the other ionic liquids could be caused by a high CO_2 solubility, resulting in an overall changed structure of the catalytic species. In 2010 Gurkan and co-workers[93] described, that prolinate-based ionic liquids based on the trihexyl(tetradecyl)phosphonium cation can absorb significant high amounts of CO_2 with a nearly 1:1 stoichiometry. The authors report the reaction of the amine group with CO_2, which leads to the formation of a carbamic acid. This equilibrium reaction is favoured under high pressure and illustrated for **CIL 1** in Scheme 18.



Scheme 18: Formation of carbamic acid in CIL 1 (1:1 mechanism)

It seems that this carbamic acid derivative does also catalyze the Aldol reaction, as even higher conversion compared to batch mode was obtained. However, the formation of the enamine intermediate is clearly hindered, which results in the reduced selectivity compared to the conventional batch process. Later in 2016 Yang et al.[94] investigated the possibility of a subsequent reaction of the carbamic acid derivate to form a ammonium carbamate species (Scheme 19). The authors could show that this is a minor pathway for prolinate-based ionic liquids and CO_2 is mostly absorbed through physical absorption and chemically via the carbamic acid formation mechanism.



Scheme 19: Subsequent reaction of carbamic acid towards ammonium carbamate (1:2 mechanism)

Initial studies executed by Liu et al.[91] indicate, that exactly this Aldol reaction can be carried out with (*L*)-proline under batch conditions in pure $scCO_2$. The authors report that, they could gain 35% yield and 72 %ee at 15 MPa and 40 °C. Cassaro et al.[95] repeated the very

same experiment under the same conditions and they reported similar yield (36%), but a lower enantioselectivity of 56 %ee. These findings clearly suggest that $scCO_2$ has not commonly an inhibiting effect on aminocatalysis. Additionally noteworthy is also the usage of **CIL 1** in combination with CO_2 as highly active catalyst for the formation of cyclic carbonates. Girard and co-workers[96] studied different task-specific ionic liquids for the chemical fixation of CO_2 to form cyclic carbonates from styrene oxide and they could show that **CIL 1** provides complete conversion (99%) for the starting materials.

3.6.3 Asymmetric Mannich reaction

For the asymmetric Mannich reaction under continuous flow conditions SILP catalysts based on **CIL 1** and (*L*)-proline (with [C_4mim][Br]) were chosen, because **CIL 2** and **3** showed low activity under the batch conditions. The system parameters (Table 12) were similar to the Aldol reaction, but the reaction was also investigated at an elevated temperature of 60 °C to accelerate the product formation.

Table 12: Parameters for asymmetric Mannich reaction

Parameter	Value
Oven temperature	40 °C and 60 °C
Temperature at the BPR	60 °C
Pressure	15 MPa
Column dimensions	150 mm × 4.6 mm (2.5 cm^3)
CO_2 flow rate	0.9 mL/min
Substrate flow rate	0.1 mL/min (20 mg/mL aldimine in acetone)
Residence time	59 s

In contrary to the Aldol reaction, with the prepared SILP catalysts only traces of the Mannich product could be detected at 40 °C (Figure 29). A similar result was found for the conventional organocatalyst (*L*)-proline in [C_4mim][Br].

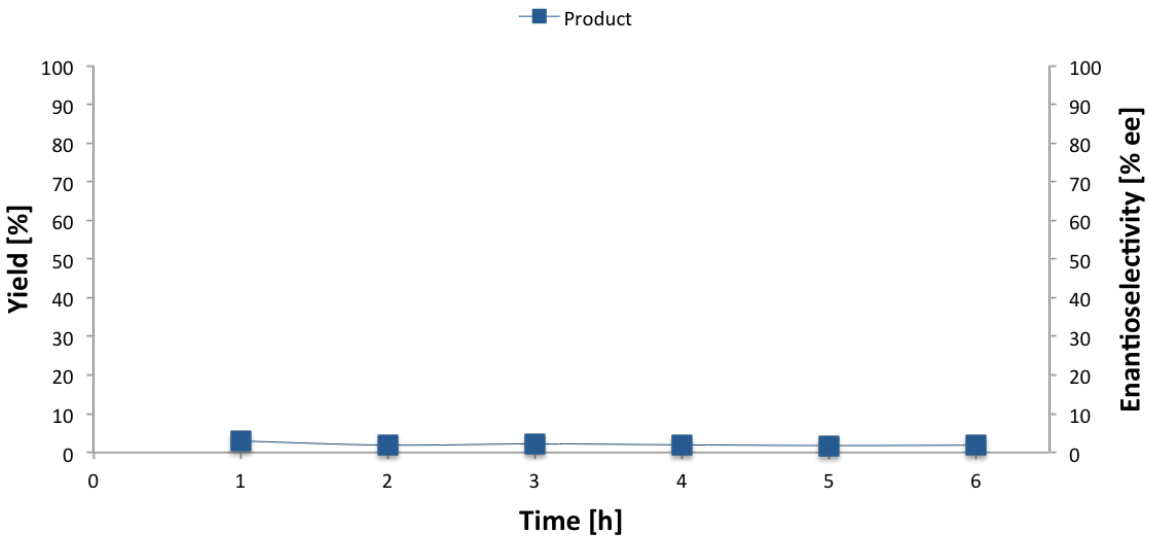


Figure 29: Results with 20 wt% of CIL 1 at 40 °C; due to low yield, ee-values are not reported

An increase of the reaction temperatures to 60 °C resulted in improved performance, and product formation could be detected. However, yields remained low with a maximum of 10% and a moderate selectivity around 20 %ee (Figure 30).

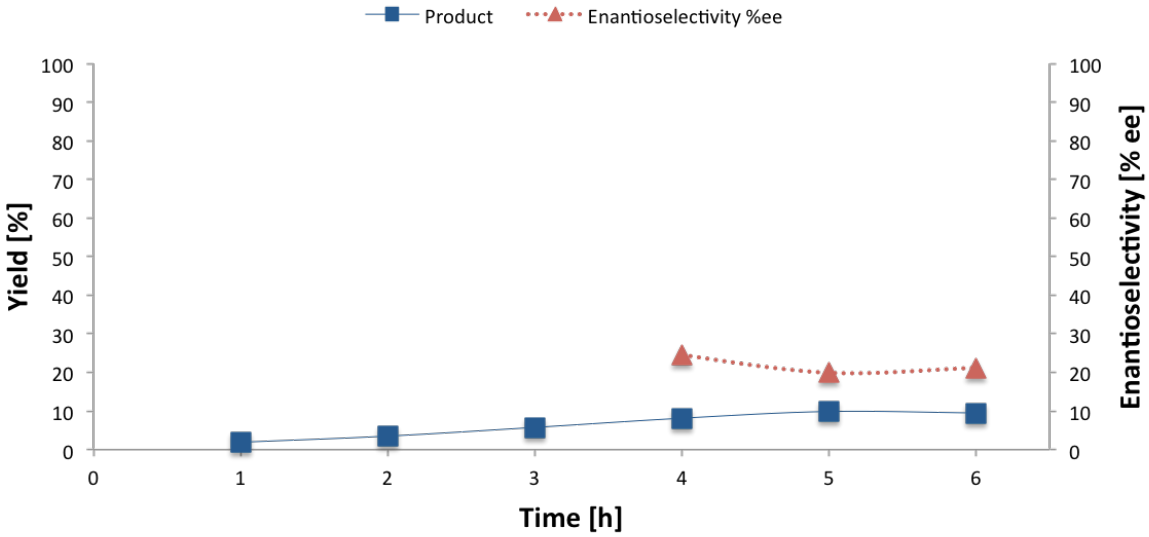


Figure 30: Results with 20 wt% of CIL 1 at 60 °C; due to low yield, ee-values are not reported (1-3 h)

As observed for the Aldol reaction, a decrease of chiral ionic liquid loading resulted in improved yields, and up to 22% could be isolated (Figure 31). However, after a maximum at 3 hours yields decreased again, and selectivity remained extremely low.

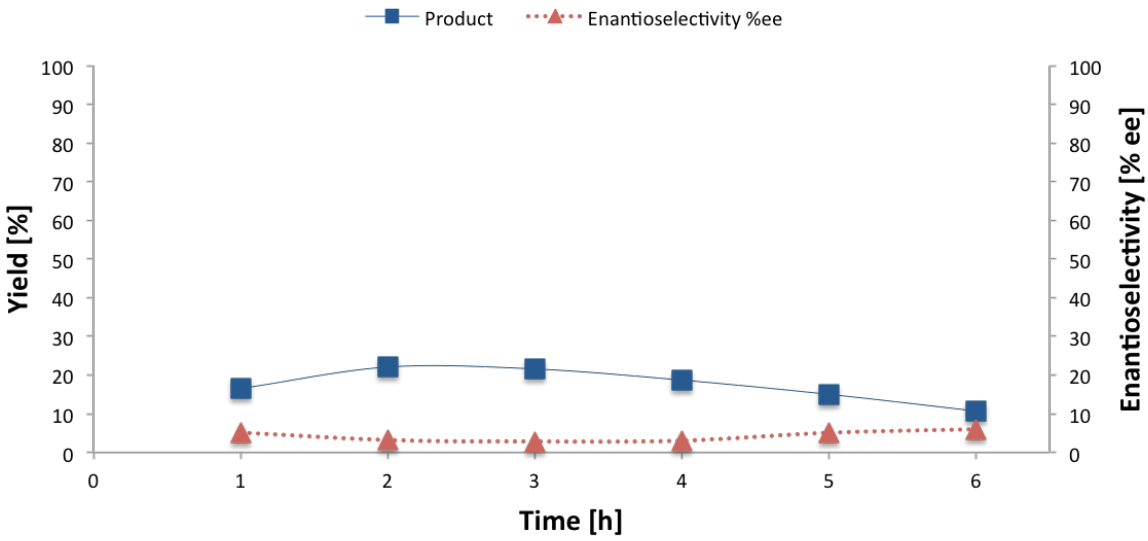


Figure 31: Results with 10 wt% of CIL 1 at 60 °C

One reason for the low yields might be the partial deprotection of the aldimine that was observed, perhaps a side effect of the acidic surface groups of silica or the carbamic acid. Due to the poor performance of supported chiral ionic liquids in this reaction compared to the batch process, the work on continuous asymmetric Mannich reactions was not further continued.

4 Conclusions

In the present work, three different chiral ionic liquids, based on the (*L*)-proline motif, were successfully synthesized. Their catalytic activity was evaluated for asymmetric Aldol and Mannich reactions in batch process mode and compared to (*L*)-proline as conventional organocatalyst. The obtained chiral ionic liquids could be immobilized on mesoporous silica for the preparation of supported ionic liquid phase catalysts. Studies on ionic liquid leaching were performed and it could be demonstrated that amino-acid derived chiral ionic liquids can be immobilized as a thin layer on a silica support with minimal losses in a continuous flow system relying on $scCO_2$ and acetone as solvent.

Furthermore a reaction set-up for a continuous flow system was developed, allowing to use solid reagents in a SILP system with supercritical carbon dioxide as transport medium. For the asymmetric Aldol reaction of 4-nitrobenzaldehyde and acetone it was possible to achieve a stable yield of up to 60% over a time period of 6 hours. Although the enantioselectivity (20 %ee) of this reaction was clearly below the expectation it is nevertheless an early example for a continuous flow reaction applying the SILP technology for an organocatalysed asymmetric transformation.

5 Experimental

5.1 General remarks and analytical methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Solvents for preparative chromatographic separations were distilled before usage. The solvents toluene, methanol, dichloromethane, diethylether and tetrahydrofuran were dried using a *PureSolve*-drying system from the company „Innovative Technologies“. Dimethyl sulfoxide (Acros) and dimethylformamide were dried and stored over molecular sieve (3 Å).

^{1}H and ^{13}C NMR spectra were recorded from $CDCl_3$, d_2-D_2O, d_4-MeOD or d_6-DMSO solutions on a Bruker AC 200 (200 MHz) or Bruker Advance UltraShield 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm using tetramethylsilane as internal standard and coupling constants (J) are given in hertz (Hz). The following conventional abbreviations for the description of multiplicities were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintett, sext = sextet, m = multiplet, brs = broad singlet.

TLC analysis was done with precoated aluminium-backed plates (silica gel 60 F_{254}; Merck) and visualized either at 254 nm for UV active compounds or by submerging in an acidic phosphormolybdic acid / cerium sulfate solution and heating.

Preparative column chromatography was performed on standard glass columns or on a Büchi Sepacore MPLC system, using silica gel from Merck (40-63 µm) with the solvents stated in the procedure.

For the quantification of the product, elimination product and starting material of the Aldol reaction (see 5.4.1) an analytical HPLC system produced by JASCO with a Reprosil 100 C18, column (5 µm; 250 × 4.6 mm) was used with ethyl benzoate as internal standard. The method parameter for the separation were the following:

(A) ACN/H_2O 50:50, flow rate 0.8 mL/min, 30 °C, column Reprosil 100 C18

The enantiomeric composition was determined via HPLC on a DAIONEX UPLC system, equipped with a PDA plus detector (190-360 nm). As stationary phase either a DAICEL CHIRALPAK IB or AS-H column (250 × 4.6 mm, 5 µm) was used. The following methods were used for the separation of the enantiomers:

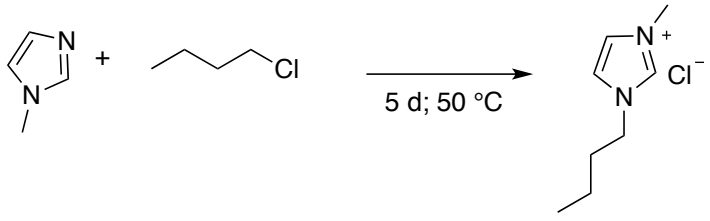
(B) *n*-heptane/*i*-PrOH 85:15, flow rate 1 mL/min, 25 °C, column DAICEL CHIRALPAK AS-H
(C) *n*-heptane/*i*-PrOH 90:10, flow rate 1 mL/min, 25 °C, column DAICEL CHIRALPAK IB

Titration measurements for 1-butyl-3-methylimidazolium hydroxide solution (5.3.2) were performed on a Mettler Toledo Seven Excellence system, equipped with an InLab Power Pro-ISM pH-electrode, which was calibrated with commercial standard solutions.

5.2 Synthesis of chiral ionic liquids

5.2.1 Synthesis towards 1-butyl-3-methylimidazolium (*L*)-prolinate (CIL 1)

5.2.1.1 Synthesis of 1-butyl-3-methylimidazolium chloride ([C_4mim][Cl]) (1)



$C_8H_{15}N_2Cl$
174.67

1

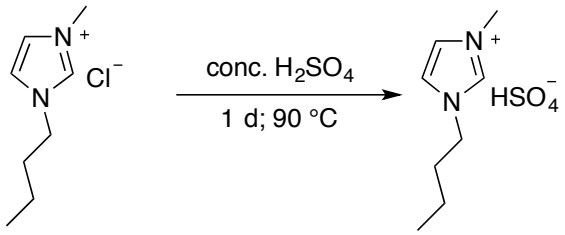
Freshly distilled 1-methylimidazole (1.0 equiv., 1.145 mol, 94 g) was placed in a 1 L round-bottom flask equipped with a reflux condenser. Under vigorously stirring freshly distilled 1-chlorobutane (1.2 equiv., 1.374 mol, 127.2 g) was added dropwise to the reaction mixture. The temperature was adjusted to 50 °C and the progress of the reaction was monitored via ^{1}H NMR samples. After 5 days, the sample showed full conversion for 1-methylimidazole and the reaction mixture was cooled to room temperature. The orange viscous product was transferred into a 5 L round-bottom flask, where it was crystallized three times from a pre-dried acetonitrile/ethyl acetate mixture (3:2).

After drying at high vacuum (0.09 mbar) for two days, 177 g (88%) of the colorless crystalline product **1** was obtained.

Analytical data was in accordance to literature.[97]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.55 (s, 1H, imidazole $C_2\underline{H}$), 7.73 and 7.56 (m, 2H, imidazole $C_{4,5}\underline{H}$), 4.27 (t, 2H, J = 7.36 Hz, N-$C\underline{H}_2CH_2$-), 4.08 (s, 3H, N-$C\underline{H}_3$), 1.84 (q, 2H, $NCH_2C\underline{H}_2$-), 1.32 (m, 2H, $NCH_2C\underline{H}_2CH_2$-), 0.89 (t, 3H, J = 7.38 Hz, -$CH_2C\underline{H}_3$)

5.2.1.2 Synthesis of 1-butyl-3-methylimidazolium hydrogensulfate (2)

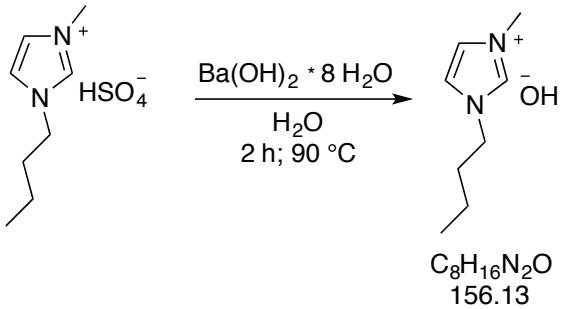


$C_8H_{16}N_2O_4S$
236.29

1 **2**

1-Butyl-3-methylimidazolium chloride **1** (1.0 equiv., 61.71 mmol, 10.78 g) was placed in a round-bottomed flask equipped with a magnetic stirring bar and a stopcock. An equivalent amount of concentrated sulfuric acid (1.0 equiv., 61.71 mmol, 6.30 g, 96%) was added slowly under stirring and the stopcock was connected to a tube packed with NaOH pellets and a vacuum pump. After the visible generation of HCl stopped, the reaction mixture was warmed in an oil bath to 70 °C and the vacuum pump was set to minimal pressure (9 mbar). After 15 h the reaction mixture was connected to a high vacuum pump (0.09 mbar) for 2 h to remove any residual HCl dissolved in the ionic liquid. After that, the chloride content was quickly checked using a sample of the product and one drop of acidic aqueous silver(I) nitrate (0.30 M $AgNO_3$ in 1.0 M HNO_3).[84] No white precipitate was observed, which indicates low chloride levels. Product **2** was then directly used for the next step without further purification (see 5.2.3).

5.2.1.3 Synthesis of 1-butyl-3-methylimidazolium hydroxide (3)

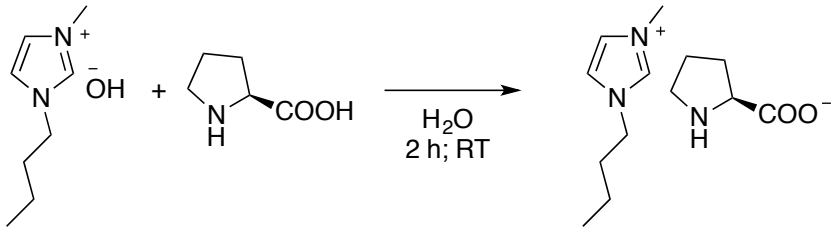


2 **3**

1-Butyl-3-methylimidazolium hydrogen sulfate (1.0 equiv., 61.71 mmol, 14.58 g) was directly used as obtained from 5.2.1.2 in a one-pot reaction methodology. The starting material **2** was dissolved in 100 mL hot deionized water ("Milli-Q" purified water, 90 °C) under vigorous stirring. Meanwhile a solution of barium hydroxide octahydrate (1.2 equiv., 74.05 mmol, 23,36 g) was prepared in 200 mL hot water. The barium hydroxide solution was then added to the hydrogen sulfate solution and residual barium hydroxide was rinsed two times with a small amount of water (5 mL) and added to the reaction mixture. This cloudy suspension was heated up to 90 °C for two hours to complete the anion exchange from hydrogen sulfate to hydroxide. After that, the reaction mixture was cooled and stored in the fridge over night to precipitate the fine-grained barium sulfate. The white precipitate was removed from the product via vacuum filtration with a glass sintered funnel and a small layer of silica.

After the filtration, the air-sensitive solution was transferred into a 500 mL volumetric flask and two 10 mL aliquots were taken for a titration with an HCl solution. The titration curves were in agreement with the expected yield with minor losses caused by the filtration step. The 1-butyl-3-methylimidazolium hydroxide solution (c = 0.098 M) was directly used for the last anion exchange from hydroxide to (*L*)-prolinate (see 5.2.4).

5.2.1.4 Synthesis of 1-butyl-3-methylimidazolium (*L*)-prolinate (CIL 1)



$C_{13}H_{23}N_3O_2$
253.34

3 **CIL 1**

The aqueous solution of 1-butyl-3-methylimidazolium hydroxide (**3**) (c = 0.098 M) from the previous reaction step (see 5.2.1.3) was transferred into a 500 mL round bottom flask with a magnetic stirring bar. Consequently (*L*)-proline (1.0 equiv., 49.36 mmol, 5.68 g) was added and the reaction mixture was stirred under room temperature for 2 hours to complete the acid-base reaction. Finally the water was removed under reduced pressure, which gave the product **CIL 1** as clear viscous oil (12.50 g, 3 steps: 80%).

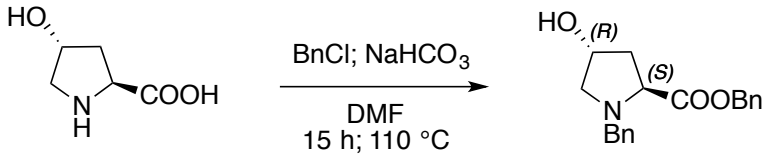
Analytical data was in accordance with literature.[98]

^{1}H NMR (400 MHz, D_2O): δ = 7.33 and 7.29 (m, 2H, imidazole), 4.05 (t, J = 7.14 Hz, 2H, N-$C\underline{H}_2$-), 3.74 (s, 3H, N-$C\underline{H}_3$), 3.39 - 3.48 (m, 1H, pro C(2)$\underline{H}$), 2.92 - 3.01 (m, 1H, pro C(5)$\underline{H}$), 2.66 - 2.75 (m, 1H, pro C(5)$\underline{H}$), 1.95 - 2.06 (m, 1H, NH), 1.66 - 1.75 (m, 2H, Im-$CH_2C\underline{H}_2CH_2$-), 1.54 - 1.64 (m, 4H, pro-C(2,3)$\underline{H}_2$), 1.11 - 1.22 (m, 2H, Im-$CH_2CH_2C\underline{H}_2$-), 0.77 (t, J = 7.4 Hz, 3H, butyl -$C\underline{H}_3$)

^{13}C NMR (100 MHz, D_2O): δ = 179.2 (s, pro C=O), 145.1 (d, Im C(2)), 143.0 and 141.8 (d, Im C(4,5)), 61.3 (d, pro C(2)), 49.2 (t, butyl C(1)), 45.9 (t, pro C(5)), 32.4 (q, N-$\underline{C}H_3$), 30.0 (t, butyl C(2)), 24.6 (t, pro C(3)), 18.6 (t, pro C(4)), 17.5 (t, butyl C(3)), 12.6 (q, butyl C(4))

5.2.2 Synthesis towards 3-(4-(((3*R*,5*S*)-5-carboxypyrrolidin-3-yl)oxy)-4-oxobutyl)-1-methylimidazolium chloride (CIL 2)

5.2.2.1 Synthesis of benzyl (2*S*,4*R*)-1-benzyl-4-hydroxyprolinate (4)



$C_{19}H_{21}NO_3$
311.38

4

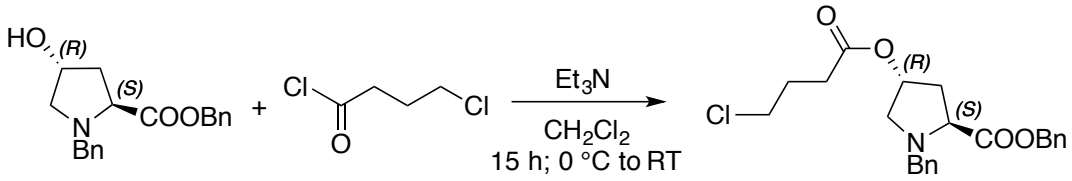
(2*S*,4*R*)-4-Hydroxyproline (1.0 equiv., 38.15 mmol, 5 g) was dissolved in 60 mL anhydrous DMF and $NaHCO_3$ (2.3 equiv., 87.74 mmol, 7.37 g) was added to the solution. Benzyl chloride (2.3 equiv., 87.74 mmol, 11.10 g) was added dropwise and the reaction mixture was heated at 110 °C with a reflux condenser for 15 hours. After TLC indicated complete conversion, the reaction was cooled to room temperature and hydrolyzed with 30 mL water. The mixture was transferred into a separation funnel and EtOAc was added. The organic layer was washed successively with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via column chromatography (180 g silica, DCM/MeOH 40:1) to yield **4** as colorless oil (9.85 g, 83%).

Analytical data was in accordance with literature.[99]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11-7.32 (m, 10H, aromat), 4.97 - 5.04 (m, 2H, O-C$\underline{H}_2$Ph), 4.28 - 4.35 (m, 1H, pro C(4)H), 3.78 - 3.84 (m, 1H, pro C(2)H), 3.51 - 3.58 (m, 2H, N-C$\underline{H}_2$Ph), 3.17 - 3.23 (m, 1H, pro C(5)H), 2.75 - 2.84 (m, 1H, pro C(5)H), 2.36 - 2.46 (brs, 1H, OH), 2.11 - 2.19 (m, 1H, pro C(3)H), 1.93 - 2.02 (m, 1H, pro C(3)H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (s, COO), 138.0 (s, N-CH_2-$\underline{C}$-aromat), 135.7 (s, COO-CH_2-$\underline{C}$-aromat), 129.0/128.6/128.3 (m, 10C, aromat), 70.1 (d, pro C(4)), 66.4 (t, COO$\underline{C}H_2$Ph), 63.6 (t, N$\underline{C}H_2$Ph), 61.0 (d, pro C(2)), 58.0 (t, pro C(5)), 39.4 (t, pro C(3))

5.2.2.2 Synthesis of benzyl (2*S*,4*R*)-1-benzyl-4-((4-chlorobutanoyl)oxy)pyrrolidine-2-carboxylate (5)



$C_{23}H_{26}ClNO_4$
415.91

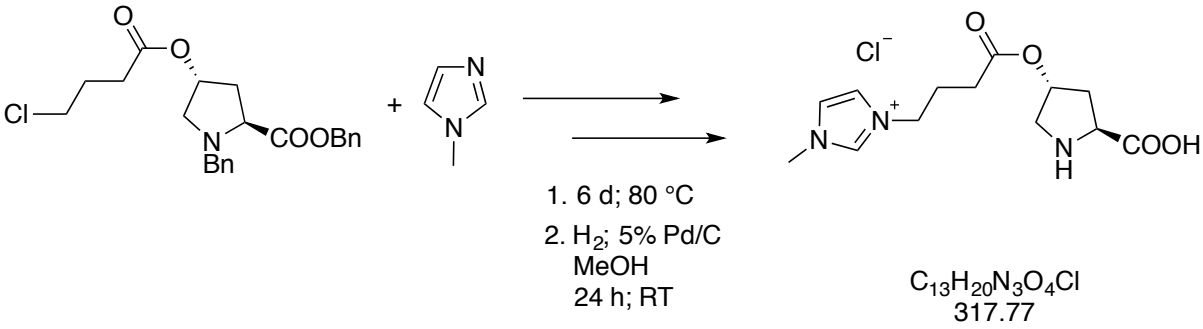
4 **5**

The benzyl protected 4-hydroxyproline **4** (1.0 equiv., 28.90 mmol, 9 g) was dissolved in 50 mL anhydrous CH_2Cl_2 and cooled to 0 °C under an argon atmosphere. Then triethylamine (1.0 equiv., 28.90 mmol, 2.92 g) was added to the solution. Freshly distilled 4-chlorobutyryl chloride (1.05 equiv., 30.34 mmol, 4.27 g) was added dropwise to the reaction mixture. After 15 hours of stirring at room temperature, TLC showed complete conversion for the starting material. The organic phase was washed two times with a 1 N HCl solution and then with a saturated $NaHCO_3$ solution. The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified via column chromatography (180 g silica, DCM/MeOH 30:1) to give product **5** as yellowish oil (10.3 g, 86%).

Analytical data was in accordance with literature.[76]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.33 (m, 10H, aromat), 5.12 - 5.18 (m, 1H, C(4)H), 5.01 - 5.10 (m, 2H, OCH_2Ph), 3.81 - 3.87 (m, 1H, C(2)H), 3.47 - 3.58 (m, 4H, NCH_2Ph and $-CH_2Cl$), 3.32 - 3.38 (m, 1H, C(5)H), 2.43 - 2.50 (m, 1H, C(5)H), 2.35 - 2.41 (m, 2H, $OOC-CH_2-$), 2.26 - 2.34 (m, 1H, C(3)H), 2.06 - 2.14 (m, 1H, C(3)H), 1.94 - 2.02 (m, 2H, $OOC-CH_2CH_2CH_2Cl$)

5.2.2.3 Synthesis of 3-(4-(((3*R*,5*S*)-5-carboxypyrrolidin-3-yl)oxy)-4-oxobutyl)-1-methyl-imidazolium chloride (CIL 2)



5 **CIL 2**

Compound **5** (1.0 equiv., 24 mmol, 10 g) was placed in a round-bottom flask, flushed with argon and mixed with 1-methylimidazole (1.0 equiv., 24 mmol, 1.97 g). The reaction mixture was then sealed with a septum and heated to 80 °C. After 6 days, ^{1}H NMR indicated complete conversion of compound **5** and the viscous ionic liquid was directly used for the following deprotection step.

Analytical data was in accordance with literature.[76,78]

^{1}H NMR (400 MHz, DMSO): δ = 9.19 (s, 1H, imidazole), 7.71 and 7.77 (m, 2H, imidazole), 7.20 - 7.46 (m, 10H, aromat), 5.05 - 5.16 (m, 3H, COO-C$\underline{H}_2$Ph and pro C(4)H), 4.14 - 4.23 (m, 2H, Im-C$\underline{H}_2$-), 3.81 - 3.89 (m, 4H, Im-C$\underline{H}_3$ and pro C(2)H), 3.54 - 3.61 (m, 2H, N-C$\underline{H}_2$Ph), 2.47 - 2.53 (m, 2H, pro C(5)H_2), 2.30 - 2.37 (m, 2H, pro-OCO-C$\underline{H}_2$), 2.22 - 2.29 (m, 1H, pro C(3)H), 2.08 - 2.16 (m, 1H, pro C(3)H), 1.96 - 2.06 (m, 2H, Im-CH_2C$\underline{H}_2$$CH_2$)

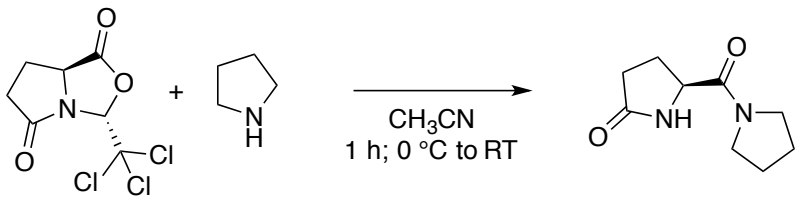
The intermediate was used without further purification. The ionic liquid was dissolved in 80 mL anhydrous MeOH and after degassing, palladium on charcoal (0.1 equiv., 1.352 mmol Pd, 2.8 g, 5 % Pd/C) was added to the solution. The mixture was then hydrogenated in a Parr apparatus at 5 bar of hydrogen pressure for 24 hours. The product was filtrated over a pad of Celite to remove the catalyst and the solvent was removed under reduced pressure. Product **CIL 2** could be obtained as brownish viscous oil (7.0 g, 92%).

^{1}H NMR (400 MHz, MeOD): δ = 8.94 - 9.12 (brs, 1H, imidazole), 7.69 and 7.62 (m, 2H, imidazole), 5.35 - 5.49 (m, 1H, pro C(4)H), 4.23 - 4.43 (m, 3H, Im-CH_2-, C(2)H), 3.91 - 4.05 (m, 3H, N-$C\underline{H}_3$), 3.58 - 3.69 (m, 1H, pro C(5)H), 3.42 - 3.55 (m, 1H, pro C(5)H), 2.45 - 2.59 (m, 2H, -CH_2-OCO-), 2.15 - 2.32 (m, 4H, Im-CH2$C\underline{H}_2CH_2$ and C(3)H_2)

^{13}C NMR (100 MHz, MeOD): δ = 174.6 (s, pro -COOH), 173.1 (s, ester -COO-), 136.0 (d, imidazole), 123.6 and 122.1 (d, imidazole), 74.0 (d, pro C(4)), 60.2 (d, pro C(2)), 50.6 (t, Im-CH_2-), 48.4 (t, pro C(5)), 35.6 (q, Im-CH_3), 34.9 (t, pro C(3)), 30.1 (t, Im-$CH_2CH_2\underline{C}H_2$-), 24.4 (t, Im-$CH_2\underline{C}H_2CH_2$)

5.2.3 Synthesis towards 1-ethyl-1-[(2*S*)-2-pyrrolidinylmethyl]-pyrrolidinium bromide (CIL 3)

5.2.3.1 Synthesis of (5*S*)-(pyrrolidine-1-carbonyl)-pyrrolidin-2-one (7)



$C_9H_{14}N_2O_2$
182.22

7

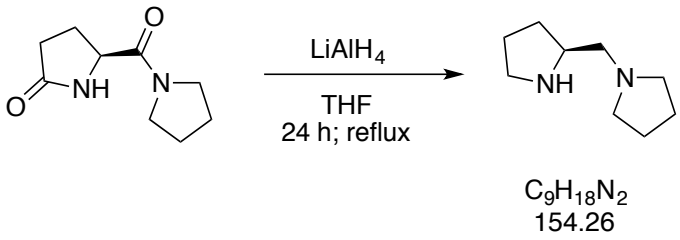
The starting material[a] (1.0 equiv., 30.95 mmol, 8 g) was dissolved in 150 mL anhydrous acetonitrile and cooled to 0 °C under an argon atmosphere. Then pyrrolidine (1.0 equiv., 30.95 mmol, 2.20 g, ρ = 0.866 g/cm^3) was added dropwise with a syringe to the reaction mixture. After complete addition, the mixture was stirred at room temperature for 1 hour. The solvent and chloral was completely removed under reduced pressure and after checking ^{1}H NMR, the product **7** could be collected as brown oil, which was used without further purification in synthesis step 5.5.2.

[a] Available on the lab from previous experiments

Analytical data was in accordance with literature.[100, 101]

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.21 (brs, 1H, NH), 4.28 - 4.35 (m, 1H, pro C(2)H), 3.40 - 3.55 (m, 4H, pyrrolidine C(2,5)H_2), 2.38 - 2.49 (m, 2H, pro C(4)H_2), 2.13 - 2.30 (m, 2H, pro C(3)), 1.87 - 2.02 (m, 4H, pyrr. C(3/4)H_2)

5.2.3.2 Synthesis of 1-[(2*S*)-2-pyrrolidinylmethyl]-pyrrolidine (8)



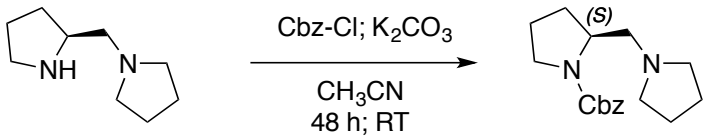
7 **8**

Lithium aluminium hydride (4.0 equiv., 123.6 mmol, 4.69 g) was suspended in 100 mL anhydrous THF and cooled to 0 °C with an ice bath under an argon atmosphere. Compound **7** (1.0 equiv., 30.95 mmol, 5.63 g) was dissolved in 60 mL anhydrous THF, transferred into an dropping funnel and added to the $LiAlH_4$ suspension in small portions to avoid extensive gas development. After complete addition of compound **7** the reaction mixture was heated to reflux for 24 hours. When TLC indicated complete conversion, the workup was done according to the literature protocol.[102] At first 5 mL of water were added slowly to the reaction mixture and then 5 mL of a 15% aqueous sodium hydroxide solution followed. After that, again 15 mL of water were added to completely hydrolyze any residual $LiAlH_4$. The precipitate and the organic phase where filtrated over a pad of Celite and washed with a small portion of EtOAc. The combined organic layers where dried using Na_2SO_4 and the solvent was removed under reduced pressure. Finally the crude product was purified via distillation using a Kugelrohr apparatus (75 °C; 0.9 mbar) to give product **8** (3.58 g, 75%) as colorless oil.

Analytical data was in accordance with literature.[101,103]

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.08 - 3.17 (m, 1H, pro C(2)H), 2.82 - 3.01 (m, 2H, pro C(5)H_2), 2.30 - 2.63 (m, 6H, methylen, pyrr. C(2,5)H_2), 2.30 - 2.36 (m, 1H, pro C(4)H), 1.84 - 1.95 (m, 1H, pro C(4)H), 1.67 - 1.82 (m, 6H, pro C(3)H_2, pyrr. C(3,4)H_2)

5.2.3.3 Synthesis of benzyl (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxylate (9)



$C_{17}H_{24}N_2O_2$
288.39

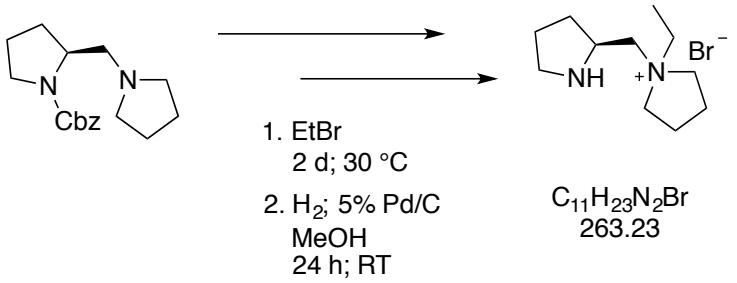
8 **9**

Potassium carbonate (2.0 equiv., 38.88 mmol, 5.37 g) was suspended in 30 mL anhydrous acetonitrile under an argon atmosphere. Then compound **8** (1.0 equiv., 19.44 mmol, 3 g) was dissolved in 20 mL acetonitrile and added to the suspension. The reaction mixture was cooled with an ice bath to 0 °C and benzyl chloroformate (1.4 equiv., 27.21 mmol, 4.64 g) was added dropwise with a syringe over a period of 10 minutes. After that, the ice bath was removed and the reaction mixture was stirred at room temperature for 48 hours until TLC suggested complete conversion of the diamine. The reaction was quenched using 10 mL of water and then extracted by three portions 30 mL Et_2O. The combined organic layers were washed once with a brine solution and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and purification was done using MPLC (DCM:MeOH 40:1 to 5:1). The product **9** could be obtained as yellow oil (3.9 g, 70%).

Analytical data was in accordance with literature.[82]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 - 7.37 (m, 5H, aromat), 4.99 - 5.13 (m, 2H, Cbz-CH_2), 3.81 - 3.98 (brs, 1H, pro C(2)H), 3.26 - 3.39 (m, 2H, pro C(5)H_2), 2.26 - 2.61 (m, 6H, methylen, pyrr. C(2,5)H_2), 1.88 - 1.96 (m, 1H pro C(3)H), 1.73 - 1.88 (m, 3H, pro C(3)H, pro C(4)H_2), 1.59 - 1.70 (m, 4H, pyrr. C(3,4)H_2,)

5.2.4 Synthesis of 1-ethyl-1-[(2*S*)-2-pyrrolidinylmethyl]-pyrrolidinium bromide (CIL 3)



9 **CIL 3**

Compound **9** (1.0 equiv., 13.52 mmol, 3.9 g) was placed into a 50 mL round-bottom flask, closed with a septum and flushed with argon. Then freshly distilled ethyl bromide (1.5 equiv., 20.28 mmol, 2.21 g) was added with a syringe and the reaction mixture was warmed to 30 °C. After 2 days of stirring ^{1}H NMR showed complete conversion of compound **9** and the viscous ionic liquid was washed three times with Et_2O, before solvent and residual bromoethane was removed under high vacuum (0.09 mbar).

Analytical data was in accordance with literature.[104]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 - 7.39 (m, 5H, aromat), 4.99 - 5.10 (m, 2H, Cbz-C$\underline{H}_2$), 4.18 - 4.31 (m, 1H, pyrr. C(2)H), 3.92 - 4.07 (m, 2H, methylene), 3.65 - 3.86 (brm, 3H, pyr. C(5)H, pyrrolidinium C(2,5)H), 3.36 - 3.58 (brm, 5H, pyr. C(5)H, pyrrolidinium C(2,5)H, N^+-C$\underline{H}_2$CH$_3$), 1.80 - 2.33 (brm, 8H, pyrr. C(3,4)H_2, pyrrolidinium C(3,4)H_2), 1.26 - 1.43 (t, 3H, N^+-CH$_2$C$\underline{H}_3$)

The intermediate was then used without further purification for the final deprotection step. The ionic liquid precursor was dissolved in 50 mL anhydrous MeOH and after degassing, palladium on charcol (0.1 equiv., 1.352 mmol Pd, 2.8g 5 % Pd/C) was added to the solution. The mixture was then hydrogenated in a Parr apparatus at 5 bar of hydrogen pressure for 24 hours. The reaction mixture was filtrated over a pad of celite to remove the catalyst and the solvent was removed under reduced pressure. The product **CIL 3** could be obtained as yellow viscous oil (3.3 g, 93%).

Analytical data was in accordance with literature.[104]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 - 4.18 (m, 1H, pyrrolidine C(2)H), 3.57 - 3.96 (brm, 7H, pyrrolidinium C(2,5)H_2, NH, methylene CH_2) 3.38 - 3.54 (m, 2H, N^+-CH_2-), 2.96 - 3.07 (m, 1H, pyrr. C(5)H) 2.77 - 2.94 (m, 1H, pyrr. C(5)H), 1.98 - 2.32 (brm, 5H, pyrr. C(4)H, pyrrolidinium C(3,4)H_2), 1.70 - 1.84 (m, 1H, pyrr. C(4)H), 1.55 - 1.69 (m, 1H, pyrr. C(3)H), 1.25 - 1.49 (m, 3H, pyrr. C(3)H, N^+-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz, $CDCl_3$): 62.9 (t, 2C, pyrrolidinium C(2,5)), 62.5 (t, methylene), 55.3 (t, N^+-CH_2-), 53.8 (t, pyrr. C(2)), 47.1 (d, pyrr. C(5)), 31.3 (t, pyrr. C(3)), 25.4 (t, pyrr. C(4)), 21.7 (t, 2C, pyrrolidinium C(3,4)), 9.3 (q, N^+-$CH_2\underline{C}H_3$)

5.3 Preparation procedure for supported ionic liquid catalysts

Different preparation procedures for supported ionic liquid catalysts exist in literature[49,77], in this work SILP catalysts were prepared following the wet impregnation technique.[50] An exemplary procedure for the SILP-catalyst preparation with 10 w% loading of **CIL 1** follows these steps:

In a 250 mL round-bottom flask 4.5 g of silica (silica 60, Merck) and 0.5 g **CIL 1** were suspended with 60 mL anhydrous MeOH. After that, the suspension was stirred at room temperature until the ionic liquid was completely dissolved. Then the solvent was removed under reduced pressure with a rotary evaporator to give a dry free-flowing powder. For complete removal of any solvent traces, additional drying under high vacuum over night was performed.

5.4 Asymmetric Aldol reaction under batch conditions

5.4.1 General procedure for the asymmetric Aldol reaction using chiral ionic liquids

The following procedure, adapted from literature[95], was chosen for the enantioselective aldol reaction between 4-nitrobenzaldehyde and acetone:

A solution of the chiral ionic liquid **2** (0.2 equiv., 0.1 mmol, 31.77 mg) in anhydrous DMSO (2 mL) with acetone (13.6 equiv., 6.8 mmol, 0.5 mL) was prepared and stirred for 5 minutes to dissolve the catalyst. After that, 4-nitrobenzaldehyde (1.0 equiv., 0.5 mmol, 75.56 mg) was added to the solution and stirred for additional 24 hours at room temperature. The reaction mixture was then treated with saturated aqueous ammonium chloride solution (1 mL) and extracted several times with EtOAc (3 × 5 mL). Aliquots were taken and together with the internal standard diluted with MeOH to a defined volume (1 mL). The yield, conversion, enantioselectivity and amount of the elimination product were determined using HPLC measurements (see 5.1 Method A).

NMR data was in accordance with literature.[105] Absolute configuration was determined by comparison of HPLC data from literature[106] using a CHIRALPAK AS-H column.

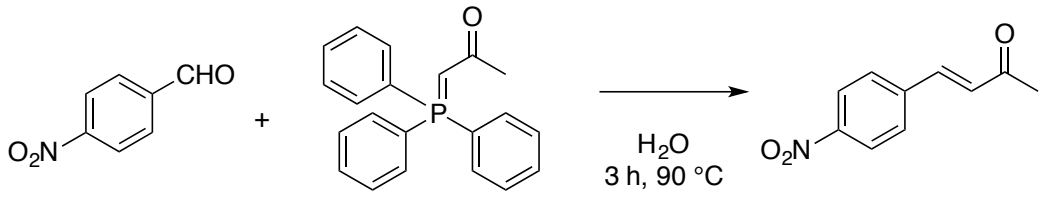
^{1}H NMR (400 MHz, $CDCl_3$):	δ = 8.13 (d, J=8.7 Hz, 2H, aromat), 7.46 (d, J=8.6 Hz, 2H, aromat), 5.14 - 5.23 (m, 1H, -C<u>H</u>OH), 3.27 - 3.35 (brs, 1H, -O<u>H</u>), 2.75 - 2.82 (m, 2H, C<u>H</u>$_2$-CO), 2.16 (s, 3H, CO-C<u>H</u>$_3$)	
^{13}C NMR (100 MHz, $CDCl_3$):	δ = 208.6 (s, C=O), 150.1 (s, aromat), 147.2 (s, C-NO_2), 126.4 (d, 2C, aromat), 123.8 (d, 2C, aromat), 68.9 (d, C-OH), 51.5 (t, COH-C<u>H</u>$_2$), 30.7 (q, CO-C<u>H</u>$_3$)	
Chromatographic Data:	Method (A):	tr(product) = 6.0 min
		tr(4-nitrobenzaldehyde) = 7.5 min
		tr(elimination product) = 9.1 min
		tr(IS: ethyl benzoate) = 16.1 min
	Method (B):	tr(R; major) = 22.9 min and tr(S) = 30.6 min
Enantiomeric excess:		ee = 79% (*R*)
Yield:		55%

5.4.2 General procedure for the asymmetric Aldol reaction using proline

The reaction using (*L*)-proline (0.2 equiv., 0.1 mmol, 11.51 mg) as catalyst were done according to procedure 5.4.1.

Yield:	69%
Enantiomeric excess:	ee = 74% (*R*)

5.4.2.1 Synthesis of 4-(4-nitrophenyl)-but-3-en-2-one as reference material



$C_{10}H_9NO_3$
191.19

11

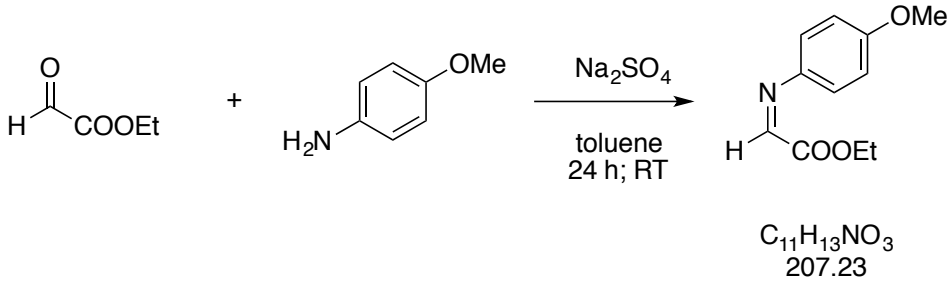
A solution of 4-nitrobenzaldehyde (1.0 equiv., 5.29 mmol, 0.8 g) and commercially available 1-(triphenyl-phosphoranyli-dene)-2-propane (1.5 equiv., 7.9 mmol, 2.52 g) in water was heated to 90 °C and stirred for 3 hours. Then the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtrated and solvent was removed under reduced pressure. The crude product was purified via column chromatography (60 g silica, EtOAc/PE 1:5) to give compound **11** as a bright yellow powder (616 mg, 61%).

Analytical data was in accordance with literature.[107]

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.26 (d, 2H, aromat), 7.70 (d, 2H, aromat), 7.53 (d, 1H, ArCH=), 6.82 (d, 1H, ArCH=C<u>H</u>-) 2.43 (s, 3H, CO-C<u>H</u>$_3$)

5.5 Asymmetric Mannich reaction under batch conditions

5.5.1 Synthesis of ethyl (2*E*)-[(4-methoxyphenyl)imino]acetate



$C_{11}H_{13}NO_3$
207.23

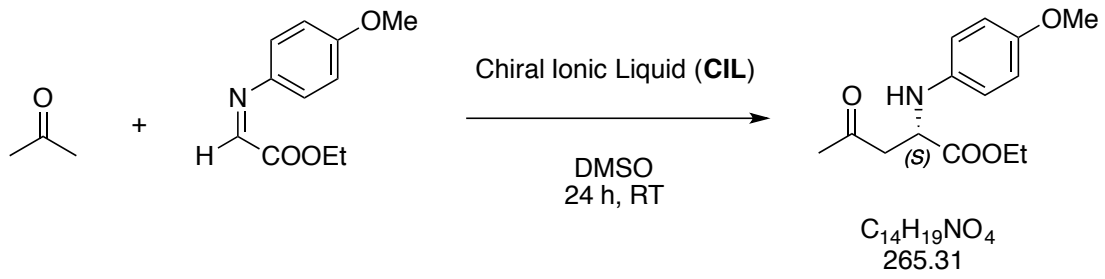
12

A solution of freshly sublimated 4-methoxyaniline (1.0 equiv., 60 mmol, 7.38 g) in anhydrous toluene (60 mL) was prepared and sodium sulphate (2.5 equiv., 120 mmol, 17.04 g) was added. Then ethyl glyoxalate (1.0 equiv., 60 mmol, 12.26 g, 50% in toluene) was added and stirred at room temperature for 24 hours. After complete conversion, Na_2SO_4 was removed via filtration and toluene was removed under reduced pressure. The crude red product was purified via destillation using a Kugelrohr apparatus (83 °C; 0.2 mbar) to obtain the product **12** as yellow oil (9.07 g, 73%).

Analytical data was in accordance with literature.[108]

^{1}H NMR (400 MHz, CDCl3): δ = 7.84 (s, 1H, HC(COOEt)), 7.27 (d, J = 8.8 Hz, 2H, aromat), 6.83 (d, J = 8.9 Hz, 2H, aromat), 4.31 (q, J = 7.14 Hz, 2H, ethyl), 3.73 (s, 3H, OMe), 1.30 (t, J = 7.10 Hz, 3H, ethyl)

5.5.2 General procedure for asymmetric Mannich reaction using chiral ionic liquids



12 **13**

The following procedure was adapted from literature[109] for the enantioselective Mannich reaction of (*E*)-ethyl 2-((4-methoxyphenyl)imino)acetate **12** and acetone:

A solution of the chiral ionic liquid 1 (0.2 equiv., 0.076 mmol, 19.25 mg) and aldimine **12** (1.0 equiv., 0.38 mmol, 80 mg) in anhydrous DMSO (2 mL) was prepared. This mixture was stirred until the catalyst was completely dissolved. Acetone (13.6 equiv., 6.8 mmol, 0.5 mL) was added with a syringe to the reaction mixture and stirred for additional 24 hours at room temperature. The reaction was hydrolyzed with saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 × 5mL) several times. Aliquots were taken and together with the internal standard diluted with MeOH to a defined volume (1 mL). The yield and enantioselectivity were determined using HPLC measurements (see 5.1 for details).

NMR data was in accordance with literature.[109] Absolute configuration was determined by comparison of HPLC data from literature[109,110] using a CHIRALPAK IB column.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 - 6.70 (m, 2H, aromat), 6.54 - 6.61 (m, 2H, aromat), 4.26 (t, J = 5.6 Hz, 1H, CH-N), 4.09 (q, J = 7.12 Hz, 2H, COO-CH_2-), 3.66 (s, 3H, OCH_3), 2.88 (d, J = 5.56, 2H, CO-CH_2-), 2.10 (s, 3H, CH_3-CO-), 1.19 (t, J = 7.12 Hz, 3H, COO-$CH_2C\underline{H}_3$)

Chromatographic Data: Method (C): tr(R) = 11.8 min and tr(S; major) = 13.0 min

Enantiomeric excess: ee = 77% (*S*)

Yield: 55%

5.5.3 General procedure for the asymmetric Mannich reaction using (*L*)-proline

The reaction using (*L*)-proline (0.2 equiv., 0.076 mmol, 8.75 mg) as catalyst were done according to procedure 5.5.1.

Yield:	73%
Enantiomeric excess:	ee = 96% (*S*)

5.6 Experiments under continuous flow conditions

5.6.1 Setup of the continuous flow system

All continuous flow experiments were performed on a modified supercritical fluid extraction system produced by the company JASCO (Jasco Corporation, Tokyo, Japan). The liquid carbon dioxide was purchased from Messer Austria GmbH with a purity of > 99,995%.

The system consists of a liquid CO_2 supply cylinder with an ascension pipe, which is connected to a recirculating cooler (FL300, JULABO GmbH) which prevents phase transition to the gas state. The cooled liquid carbon dioxide is then transported to two CO_2 pumps (PU-2086+), which pressurize the whole system in order to reach the supercritical state. An HPLC solvent pump (PU-2082+) is used to deliver reactants and solvents into the $scCO_2$ flow. After mixing the reagents with $scCO_2$, the solution is carried to a thermostated oven (CO-2060+), where the SILP catalyst is located in conventional HPLC columns (150 mm × 4.6 mm). The exiting stream of the continuous-flow system is then decompressed by the backpressure regulator (BP-2080+) and passed through a gas/liquid separator (HC-2086-01). The CO_2 is released and the product is collected in fractions by an automatic collection unit (SCF-Vch-Bp).

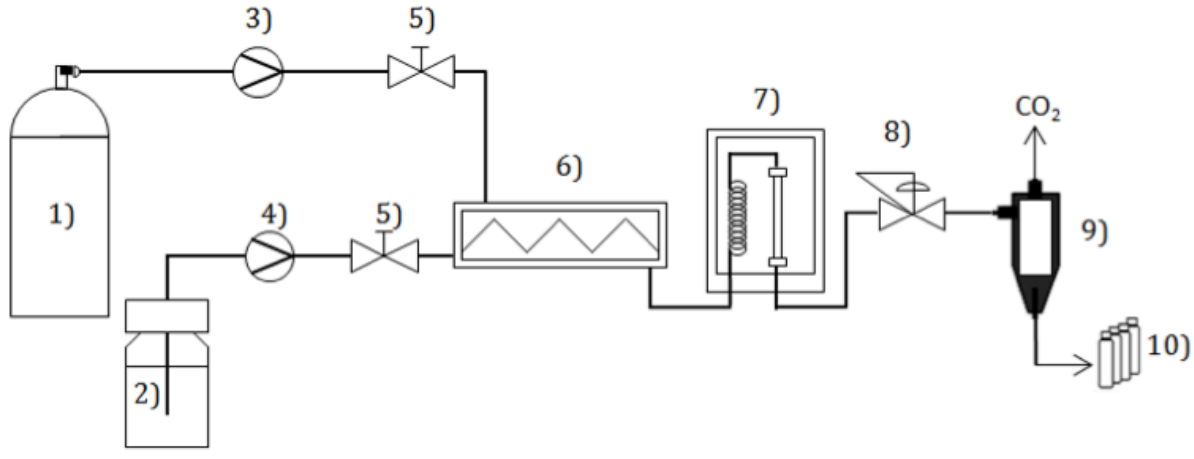


Figure 32: Schematic of the $scCO_2$ system (adapted from C. Hauzenberger[111])

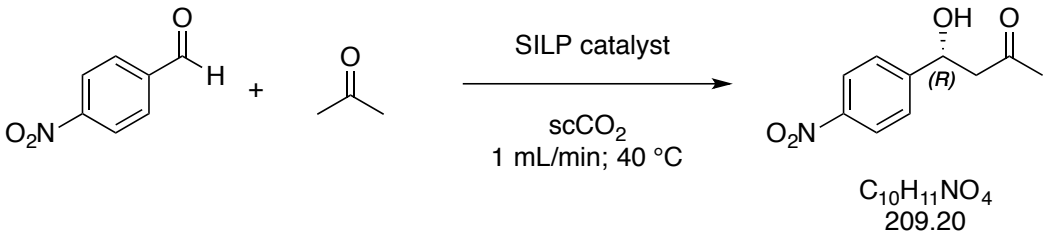
(1) CO_2 supply cylinder; (2) substrate supply; (3) CO_2 pump, (4) solvent pump; (5) hand operated valves; (6) mixing unit; (7) oven with catalyst column; (8) back pressure regulator; (9) gas-liquid separator; (10) collection unit

5.6.2 General procedure for the leaching studies

In order to investigate the loss of the ionic liquid layer from the solid support material, leaching studies have been conducted.

First a defined amount of SILP catalyst material was packed into an HPLC column (150 mm × 4.6 mm; volume = 2.50 cm^3) and the column was inserted into the pre-heated oven at 40 °C. After thermal equilibration the flow rate was set to 1 mL/min and the CO_2 pumps were started. When the pressure reached 15 MPa the solvent pump was started to add acetone to the $scCO_2$ ($scCO_2$/acetone 9:1; total flow rate: 1 mL/min). The product was collected after the backpressure regulator in a 30 mL vial for 120 minutes. After this time period, the flow was stopped and the vial removed. The remaining volatiles in the vial were removed under reduced pressure and weight of the leached ionic liquid was determined gravimetrically.

5.6.3 General procedure for continuous flow reactions



An exemplary general procedure for the flow experiments follows these steps:

At first the SILP catalyst with 20 wt% of chiral ionic liquid **1** on silica was prepared as described in chapter 5.3. After that the SILP material was packed into an HPLC column (1.61 g; 150 × 4.6 mm) and connected to the system in the oven at 40 °C. After thermal equilibration, the CO_2 pumps were started at a flow rate of 1 mL/min until the pressure reached 15 MPa. Consequently the solvent pumps were turned on, pumping a solution of 4-nitrobenzaldehyde in acetone (20 mg/mL) into the $scCO_2$ flow. The total flow rate was adjusted to 1 mL/min consisting of 0.9 mL/min $scCO_2$ and 0.1 mL/min of the aldehyde solution. The collection unit, after the backpressure regulator, was programmed to collect fractions (30 mL vials) in 60 minutes intervals for a total duration of 360 minutes.

The remaining volatiles (acetone residues) in the vials were removed under reduced pressure and weight of the resulting product was determined gravimetrically. The product in the vials was diluted with MeOH to a defined volume and the amount of product, starting material and elimination product was determined using HPLC measurements (see 5.1 Method A). Enantioselectivity of the product was determined via HPLC using a DAICEL CHIRALPAK AS-H column (see 5.1 Method B).

6 Appendix

6.1 List of abbreviations

AcOH	acetic acid	MeCyh	methylcyclohexane
Bn	benzyl	MPLC	medium pressure liquid chromatography
BPR	backpressure regulator	NaOH	sodium hydroxide
[$C_n$mim]	1-alkyl-3-methylimidazolium	Na_2SO_4	sodium sulfate
Cbz	carboxybenzyl	NMP	*N*-methyl-2-pyrrolidone
CH_2Cl_2	dichloromethane	Et_3N	triethylamine
CIL	chiral ionic liquid	PE	petrol ether
DMF	dimethylformamide	Ph	phenyl
DMSO	dimethyl sulfoxide	PMP	*para*-methoxyphenyl
ee	enantiomeric excess	Pro	proline
EtBr	ethylbromide	Pyrr.	pyrrolidine
EtOAc	ethyl acetate	o.n.	over night
Et_2O	diethyl ether	RT	room temperature (25 °C)
EtOH	ethanol	$scCO_2$	supercritical carbon dioxide
equiv.	molar equivalent	SCF	supercritical fluid
HCl	hydrochloric acid	SILP	supported ionic liquid phase
HPLC	high pressure liquid chromatography	TLC	thin layer chromatography
Im	imidazole	TOF	turnover frequency
IL	ionic liquid	tr	retention time
i-PrOH	*iso*-propanol		
MeOH	methanol		

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