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Innovative Approaches for Catalyst Removal and Recycling in Organocatalysis

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Table of Contents

List of Symbols and Abbreviations

AAILs	Amino acid ionic liquids
AdCPN	Adamantoyl cupreine
API	Active pharmaceutical ingriedient
APS	Ammonium peroxydisulphate
BC	1,2-butylene carbonate
Bis	*N-N'*-methylenebisacrylamide
BzCPN	Benzoyl cupreine
CD	Cinchonidine
CN	Cinchonine
CO_2	Carbon dioxide
CPN	Cupreine
DCM	Dichloromethane
$(DHQ)_2AQN$	Hydroquinine anthraquinone-1,4-diyl diether
$(DHQ)_2Pyr$	Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DM	DuraMem
DVB	Divinylbenzene
ee	Enantiomeric excess
EtOAc	Ethyl acetate
FBS	Fluorous biphasic systems
FFMR	Falling-film microreactor
HBzCPN	Hydro benzoyl cupreine
HCPN	Hydro cupreine
HPLC	High performance liquid chromatography
IL	Ionic liquid
iPrOH	Isopropanol
LauCPN	Lauroyl cupreine
Leu	Leucine
MLS	Microemulsions with nonionic surfactants
MMM	Mixed matrix membranes
MWCO	Molecular weight cut-off
OATS	CO_2-based organic-aqueous tunable systems
OSN	Organic solvent nanofiltration
PI	Polyimide
PILs	Poly(ionic liquid)s
PivCPN	Pivaloyl cupreine
PS	Polystyrene
QD	Quinidine
QN	Quinine
SEM	Scanning electron microscope
SHOP	Shell Higher Olefin Process
SHS	Switchable-hydrophilicity solvents
SSS	Switchable solvent systems
SWOT	Strengths-Weaknesses-Opportunities-Threats
TEMED	*N,N,N',N'*-Tetramethylene-1,2-diamine
THF	Tetrahydrofuran
TMS	Thermomorphic solvent systems
TON	Turnover number
VBImBr	1-Vinyl-3-butylimidazolium bromide
VEImBr	1-Vinyl-3-ethylimidazolium bromide
VEImCl	1-Vinyl-3-ethylimidazolium chloride

Index of Figures, Schemes & Tables

Abstract

Due to the growing demand for enantiomerically pure compounds in fine- and pharmaceutical industry there is a strong increase of interest in asymmetric catalysis. In addition to bio- and organometallic-catalyzed processes organocatalysis gained a considerable impact in the past decades for a sustainable chemistry. Organocatalysts demonstrate herein benefits like low costs, low toxicity, high selectivity and simple handling. However, a significant disadvantage of organocatalysis so far is the use of high catalyst loadings between 1 and 30 mol% to obtain high selectivities and productivities.

To overcome this drawback this project aimed at the development of efficient catalyst recycling concepts. For this purpose, three innovative strategies for catalyst recycling were designed, investigated and evaluated. Within the first stage, organic solvent nanofiltration was used for recovery and reuse of an organocatalyst. This method is particularly attractive for subsequent industrial processes since no immobilization, no additives or additional energy consumption are required. The embedding of organocatalysts in IL-based hydrogels as a second possibility for catalyst and product separation is interesting both as a novel immobilization method as well as an unconventional reaction medium. Switchable solvent systems, which are already established for transition metal catalysts, were investigated as the third separation method to optimize the organocatalytic reaction. Adapted to the respective separation process modification to the catalyst framework for improving enantioselectivity is carried out. As a final step, all three methods in terms of catalyst recycling, stability and productivity are compared and evaluated.

Zusammenfassung

Das Interesse an asymmetrische Katalyse wächst stetig an aufgrund der erhöhten Nachfrage an enantiomerenreinen Produkten in der Fein- und pharmazeutischen Industrie. Neben der Enzymkatalyse und Organometallkatalyse werden verstärkt Organokatalysatoren für diesen Zweck eingesetzt.

Ein wesentlicher Nachteil der Organokatalyse ist bislang der Einsatz hoher Katalysatorbeladungen (1-30 mol%), um hohe Selektivitäten und Produktivitäten zu erreichen. Im Rahmen dieser Arbeit soll dieser Nachteil durch Rückgewinnung des Katalysators minimiert werden. Hierfür werden drei neuartige Strategien zur Katalysatorrezyklierung entwickelt, getestet und bewertet. Als erstes Verfahren zur Rückgewinnung und Wiederverwendbarkeit des Katalysators wird die organophile Nanofiltration eingesetzt. Dieses Verfahren ist speziell für einen späteren industriellen Prozess sehr attraktiv, da keine Immobilisierung, keine zusätzlichen Additive und kein zusätzlicher Energieaufwand nötig sind. Die Einbettung von Organokatalysatoren in ionische Flüssigkeiten basierte Hydrogele als zweite Methode ist sowohl als neuartige Immobilisierungsmethode als auch als unkonventionelles Reaktionsmedium interessant. Schaltbare Lösungsmittelsysteme als dritte Methode, die sich bereits in der Übergangsmetallkatalyse als Trennverfahren etabliert haben, werden in dieser Arbeit für die Organokatalyse gewinnbringend eingesetzt. Angepasst an das jeweilige Abtrennungsverfahren werden Modifikationen am Katalysatorgerüst vorgenommen. Den finalen Schritt bildet ein Vergleich aller drei Methoden in Hinblick auf Katalysatorrezyklierung, Stabilität und Produktivität.

1. Introduction

Catalytic processes are of outstanding importance in chemistry. More than 90% of all chemical products undergo at least one stage of a catalytic process during their synthesis.[1] The majority of industrial processes operate with heterogeneous catalysts, where the catalyst is easily removed from the process stream. However, in recent decades, homogeneous catalyzed processes have strongly established themselves that about 10% of all catalytic reactions are catalyzed homogeneous.[2] For "sustainable" and "green" chemistry a separation and an almost complete removal of the catalyst is a necessity.[3] Therefore, research interest in sustainable, efficient, and reliable catalyst recycling concepts is steadily increasing. In this study, key trends, research directions, industrial applications, and future scope will be outlined and compared with the presented work in the field of organocatalyst removal.

1.1. Why Homogeneous Catalysis?

"Catalysis" includes a variety of heterogeneous, homogeneous, and enzymatic catalysis. Heterogeneous catalysis, which takes place between different phases, is mostly applied on an industrial scale.[4] However, the field of homogeneous catalysis has grown enormously in recent years. Homogeneous catalysts such as (organo)metallic complexes, enzymes, and organocatalysts offer a lot of advantages over their heterogeneous counterparts (Table 1), especially in terms of high selectivity (chemoselectivity, regioselectivity, and enantioselectivity).[5] These catalysts are typically well investigated, their catalytic centers can be easily defined, and the mechanism is well understood. Organometallic catalysts are widely used in industry for fine chemicals as well as bulk chemicals (such as hydroformylation, carbonylation, oxidation, hydrogenation, and metathesis) with millions of tons produced per year.[6] Enzymatic catalysis, which is considered as a separate branch of catalysis, has also gained a significant impact and is widely included in many commercial applications.[7] This is not surprising, due to the advantages of the high stability and activity of enzymes under mild conditions (such as temperature, pressure and pH).[7d, 8] In addition, the reactions can be carried out in aqueous media, which provides a "greener" chemical route.

In fact, there is a growing interest in "greener" and more environmentally acceptable processes in the chemical industry. In this context, Anastas and Warner defined the 12 principles of green chemistry, which include sustainable development, more renewable forms of energy, and reduction of pollution via innovative technologies that reduce or eliminate the use or generation of hazardous substances.[9] More recently, the principles have been extended to the 12 principles of green engineering, which illustrate alternatives in chemical processes, new designs, and technological innovations.[9b] Besides enzyme catalysis, organocatalysis has also become a powerful area of green chemistry.[10] These catalysts present an environmental and economic advantage over

organometallic catalysts, especially for stereoselective asymmetric reactions. The area of organocatalysis has established itself in the last decades and has since then shown a rapid development in research. The still ongoing interest is reflected in the recently awarded prizes for two pioneers in organocatalysis — Prof. Dr. David MacMillan (Ernst-Schering-Price, 2015) and Prof. Dr. Benjamin List (Leibniz-Price, 2016).

Table 1. Homogeneous vs. Heterogeneous Catalysis.

	Advantages	Disadvantages
Homogeneous	• mild reaction conditions • high activity and selectivity • efficient heat transfer • high reaction rates • well understood mechanism	• difficult catalyst separation and recycling • product contamination
Heterogeneous	• simple product and catalyst separation • continuous process • long catalytst life	• heat transfer • low activity and selectivity • catalyst leaching • only in a few cases under-standing of the mechanism • low reaction rates

1.2. Organocatalysis for Obtaining Enantiopure Products

The demand is steadily increasing for sustainable, efficient, and reliable methods to obtain enantiomerically pure compounds as precursors in the pharmaceutical industry. Various approaches are already described in literature for this demanding task (Table 2).[11] High performance liquid chromatography (HPLC) using chiral stationary phases has proven its feasibility for the separation of racemic mixtures at all scales of production. [12] Another classical method which can be used in any scale is the fractional crystallization of diastereomeric salts.[13] However, the disadvantage of these methods is that the respective yield of enantiopure product is limited to only 50%. Afterwards, the non-desired enantiomer has to be used for another application or has to be recycled after racemization. Another possibility is synthesis starting from the “chiral pool” of substances, i.e., enantiopure natural products such as carbohydrates, amino acids, alkaloids and terpenes.[14] Nevertheless, application of this possibility on a larger scale is limited to the commercial availability of the starting materials. Among the described approaches, asymmetric synthesis with chiral auxiliaries (such as enzymes, transition metal catalyst or organocatalysts) is currently the most successful strategy. The

advantage of biocatalysts is their high regio- and enantioselectivity, so that it is often possible to achieve enantiomeric excesses higher than 99%.[15] However, the number of applications is limited by the narrow substrate specificity of many biocatalysts.

Table 2. Comparison of different methods to obtain enantiopure compounds.

Methods	Advantages	Disadvantages
Racemate resolution		
• diasteromeric-salt-resolution	+ inexpensive	- only 50% yield - low atom efficiency
• preparative HPLC - chiral stationary phase required - may require derivatization	++ high stereoselectivity + high range of applications	- expensive - time-consuming
Use of substances from "chiral pool"	+ sustainability + non-toxic	- commercial availability - limited availability - often only one enantiomer formed
Asymmetric synthesis		
• enzyme catalysis	++ high stereoselectivity	- lack of robustness - commercial availability
• transition metal catalysis	+ high range of applications + high stereoselectivity	-- toxicity - reactions typically under inert conditions - product contamination -- expensive
• **organocatalysis**	++ large range of applications + high stability + sustainability + inexpensive	-- high catalyst loading -- product contamination during downstream-processing

Numerous homogeneous transition metal catalysts have been developed in recent years and now present a wide range of reactions with high stereoselectivity, but the high toxicity and the use of inert conditions, as well as product contaminations with metals, are a disadvantage in this field.[16] Compared with this, organocatalysis has established itself as an efficient and widely applicable synthesis method for enantiopure products. [17]

The historical development and important reactions in organocatalysis are described in chapter 1.3. Organocatalysis is herein defined as the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.[18] Organocatalysts consisting of C, H, N, S and P can be achiral and chiral, and they can be Lewis bases, Lewis acids, Brønsted bases and Brønsted acids. Suitable organocatalysts are both natural products as well as novel chiral compounds (Figure 1). For example, the organocatalyst proline, an amino acid, contains both a nucleophilic secondary amino group and a carboxylic acid group and is commercially available in both enantiomeric forms, and therefore shows advantages over enzymatic methods. [19] The proline-catalyzed ROBINSON annulation was one of the earliest examples of an enantioselective reaction using a chiral organic catalyst.[20] Another famous example is the well-known COREY-BAKSHI-SHIBATA (CBS) catalyst, which is an asymmetric catalyst derived from proline.[21] The oxazaborolidine catalyst is used for the COREY-ITSUNO reduction of achiral ketones to produce the corresponding non-racemic alcohol.[22] Moreover, cinchona alkaloids present an important class of organocatalysts which catalyze many useful organic reactions with high enantioselectivities.[23] Due to their great potential in organocatalysis and their use in this thesis, they are described in more detail in chapter 1.4. The MACMILLAN imidazolidinone organocatalyst developed by MACMILLAN *et al.* can be also used for a variety of asymmetric transformations, such as DIELS-ALDER reactions, cycloadditions, pyrrole FRIEDEL-CRAFTS reactions, and α-chlorinations with high levels of enantioselectivity.[24] The application of some thiourea organocatalysts was reported in the asymmetric STRECKER reaction by JACOBSEN *et al*.[25] Highly effective chiral thiourea derivatives and their analogues were developed for many organic transformations.

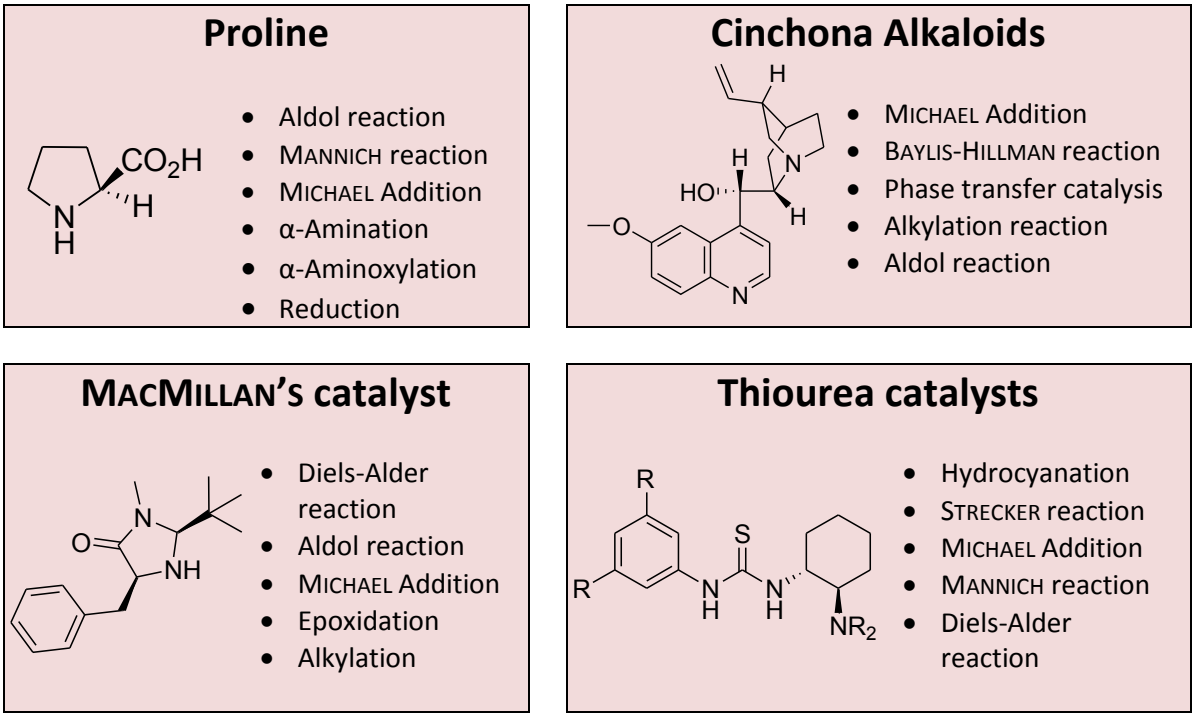


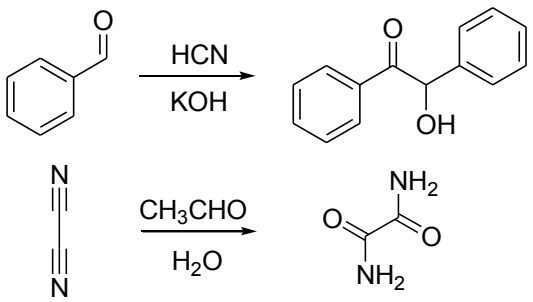
Figure 1. Few famous examples of organocatalysts and the catalyzed reactions (for details refer to text).

The described organocatalysts usually have considerable advantages in comparison to classical organometal catalysts.[26] They are generally stable against air and water, meaning that the use of inert gas atmosphere and dry solvents for reactions is not required. In addition, they are usually less expensive and have a significantly lower toxicity, so that environmental pollution and product contamination with toxic metals can be avoided and waste disposal is unnecessary. Due to the moderate reaction temperatures, significant energy savings can be achieved. All these advantages have contributed in recent years to provoking an increased interest in the development of new and highly selective organocatalytic processes.

1.3. Historical Developments in Organocatalysis

This chapter will present a short background of the development and some examples in the field of organocatalysis. A full overview will not be attempted, within this chapter due to the many reactions involving organocatalysts; only organocatalytic reactions connected to this thesis and historically important reactions will be described.

A closer look into history shows that examples of organocatalysis already existed in the early 19th century. The first example of an organocatalyzed reaction was reported by FRIEDRICH WÖHLER and JUSTUS VON LIEBIG in 1832.[27] In that instance, two equivalent of benzaldehyde reacted in the presence of cyanide to generate α-hydroxyl ketone (Scheme 1, Eqn. 1). Another related reaction was discovered by JUSTUS VON LIEBIG in 1860.[28] Dicyan and water reacted in the presence of acetaldehyde to oxamide (Scheme 1, Eqn. 2).

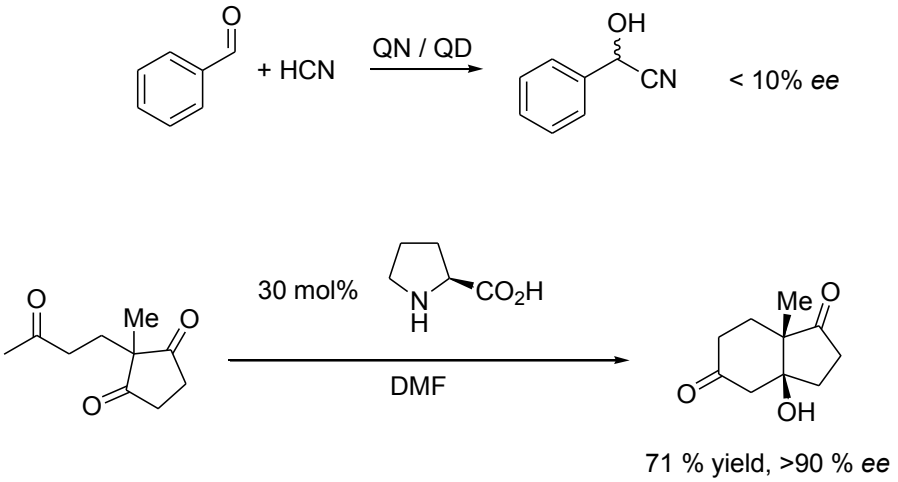


(1) WÖHLER and LIEBIG, 1832.

(2) LIEBIG, 1860.

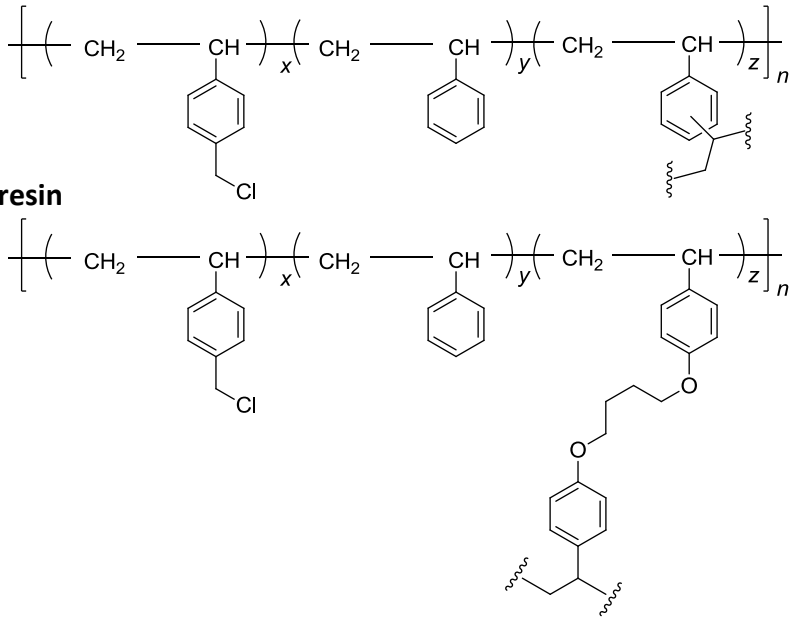
Scheme 1. First examples of organocatalytic reactions.

However, the actual term "organocatalysis" was not initially used to describe these reactions. The first reaction to be denoted "organocatalytic" was reported by BREDIG and FISKE in 1912 (Scheme 2, Eqn. 3), when the asymmetric addition of HCN to benzaldehyde, catalyzed by cinchona alkaloids, leads to a poor enantiomeric excess of 10%.[29] The breakthrough was achieved by HAYOS and PARRISH at Hoffmann La Roche as well as EDER, SAUER and WIECHERT at the laboratories in Schering AG in 1971.[30] The most relevant example is the discovery of the L-proline-promoted asymmetric ROBINSON annulation reaction, which is also called the HAJOS-PARRISH-EDER-SAUER-WIECHERT reaction (Scheme 2, Eqn. 4). In 1981, INOUE *et al.* introduced a cyclic dipeptide organocatalyst.[31] This cyclic dipeptide, which is readily available from L-histidine and L-phenylalanine, catalyzed the addition of HCN to benzaldehyde with up to 90% *ee*.



Scheme 2. Breakthrough organocatalyzed reactions in 20th century.

JULIÁ *et al.* described the asymmetric epoxidation of chalcones by using poly-amino acids such as poly-alanine and poly-leucine in the early 1980s. In this reaction, enantiomeric excesses of >90% are achieved. The discovery of organocatalysts for polymeric immobilization pioneered by MERRIFIELD *et al.* created a new field of polymer-supported organocatalysts which allows for their easy separation. Traditionally, polymer-supported organocatalysts are prepared by anchoring modified catalyst precursors onto polymer supports, which was first developed for solid-phase peptide synthesis in the 1960s.[32] An important example is the MERRIFIELD resin, a chloromethylated and divinylbenzene (DVB) crosslinked polystyrene (PS), which is shown in Figure 2a.[33] Furthermore, JANDA *et al.* introduced a tetrahydrofuran-derived crosslinker to give the commercial available product JandaJel™ (Figure 2b).[34] The recycling of a polymer-enlarged oxazaborolidine for the enantioselective reduction of ketones, which has already been mentioned, was introduced by GIFFELS *et al.* in 1998.[35] Molecular weights up to 13800 g mol^{-1} could be achieved by the coupling of the organocatalyst to polystyrene gels.



a) **MERRIFIELD resin**

b) **JANDA JEL™**

Figure 2. Two examples for polymer-supports in organocatalysis.

In the 21st century, organocatalysis began a rapid development in numerous research groups worldwide, with two independent publications by LIST and coworkers on enamine catalysis[36] and by MACMILLAN and coworkers on iminium catalysis promoted by chiral secondary amines.[24a] Figure 3, as generated from a *Web of Science* search, demonstrates the increasing interest in research after these two works and shows the high potential for future applications.

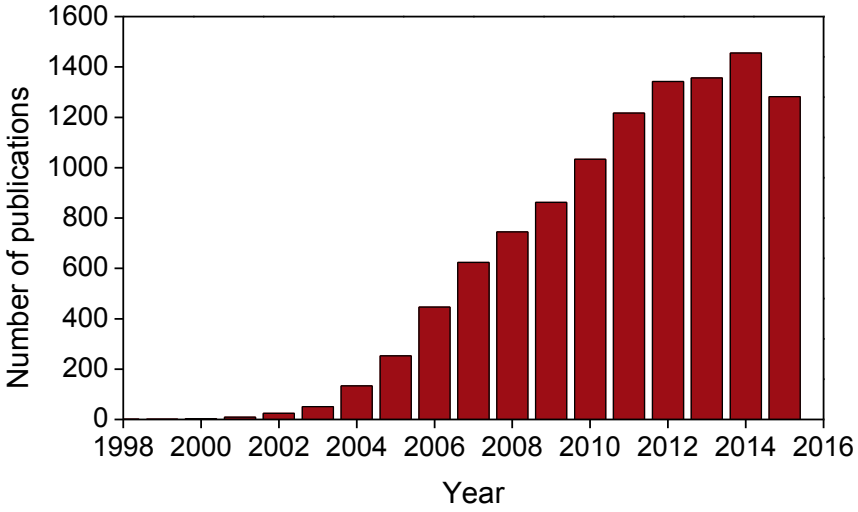
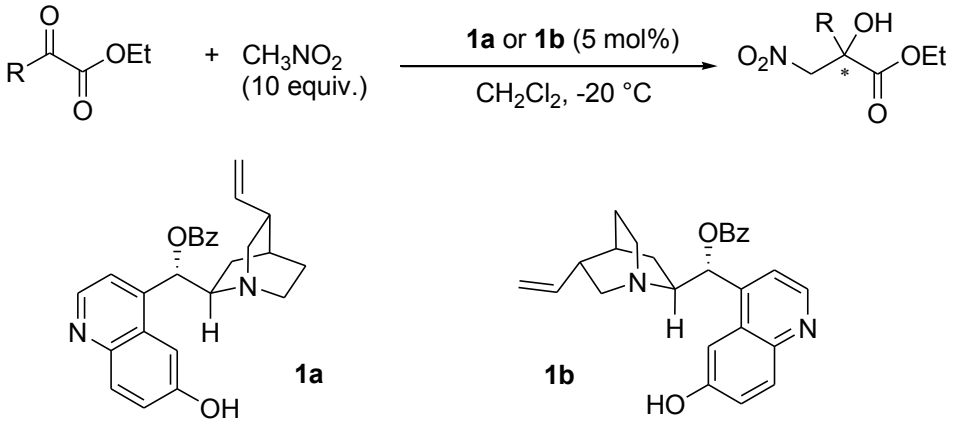


Figure 3. Number of publications with the term "organocatalysis" since 1998. Results from Web of Science (09.01.2016).

A large number of interesting organocatalytic enantioselective reactions, such as epoxidations, reductions, the aza-HENRY reaction, aldol reactions, STRECKER reactions, FRIEDEL-CRAFTS, MICHAEL addition, Diels-Alder, and MANNICH reactions have been explored and published in the last decades.[17-18, 26b, 26c] Among them, the HENRY (nitroaldol) reaction represents a powerful carbon-carbon bond-forming reaction between a carbonyl compound and the nucleophilic nitroalkane for the synthesis of valuable enantioenriched β-nitroalcohols. Cinchona alkaloids, phase transfer catalysts, thioureas, and guanidines are defined as key organocatalysts for the asymmetric HENRY reactions.[37] The first organocatalytic enantioselective reaction was published by NÁJERA *et al.* in 1994, and this reaction with aldehydes promoted by the use of enantiomerically pure guanidines as catalysts gives an enantiomeric excess up to 54%.[38] Due to this report many organocatalysts, such as guanidinium salt or guanidine-thiourea bifunctional organocatalysts, have been designed.[39] In comparison, the use of ketones as substrates for this reaction has been less well explored due to the lower reactivity. Nevertheless, in this thesis the HENRY reaction will be performed with α-ketoesters based on the works by DENG *et al.* in 2006 (Scheme 3).[40] The addition of nitromethane to α-ketoester promoted by C6'-OH catalysts derived from cinchona alkaloid gives high enantiomeric excesses of up to 97%. Further work shows that an exchange of the phenol moiety with a better hydrogen bond donor, such as a thiourea group, could improve these catalysts. Furthermore, the modified catalyst on the C9 substituent with a benzoyl group is even more effective.[41] In general, these catalysts can promote reactions in a wide range of substances with high enantioselectivities and relatively low catalyst loadings (5 mol%).[42]



Scheme 3. Enantioselective addition of nitromethane to α-ketoester catalyzed by cinchona alkaloids **1a** and **1b**, described by DENG *et al.*

1.4. Cinchona Alkaloids as High Enantioselective Organocatalysts

Why are cinchona alkaloids recognized as a privileged class of catalysts in the field of organocatalysis?

The answer is obvious.[42-43] They are:

- commercially available in two enantiomeric forms
- inexpensive
- multifunctional
- stable under mild conditions
- easily tunable
- in possession of diverse functionality

As shown in the previous chapter, the use of cinchona alkaloids is well known and relatively well understood. The structure of the main alkaloids was clarified by RABE in 1908.[44] They are extracted from the bark of the cinchona trees, with a production of about 700 tons/year.[45] All four main cinchona alkaloids — quinine (QN), quinidine (QD), cinchonine (CN) and cinchonidine (CD) (Figure 4) — are commercially available, although quinine is very inexpensive at 3.50 €/g. Quinine represents the most significant alkaloid due to its beneficial properties as an antimalarial agent. In 1977, quinine was officially incorporated as a medicine against malaria in the pharmacopoeia.[46] RABE and KINDLER reported the first partial synthesis of quinine and quinidine starting from quinotoxine in three steps.[47] These compounds feature five stereogenic centers and contain a quinuclidine unit, a quinoline ring, a secondary alcohol, and a vinyl group.[48] The absolute configuration at C3 and C4 is maintained in all four alkaloids, whereas in the

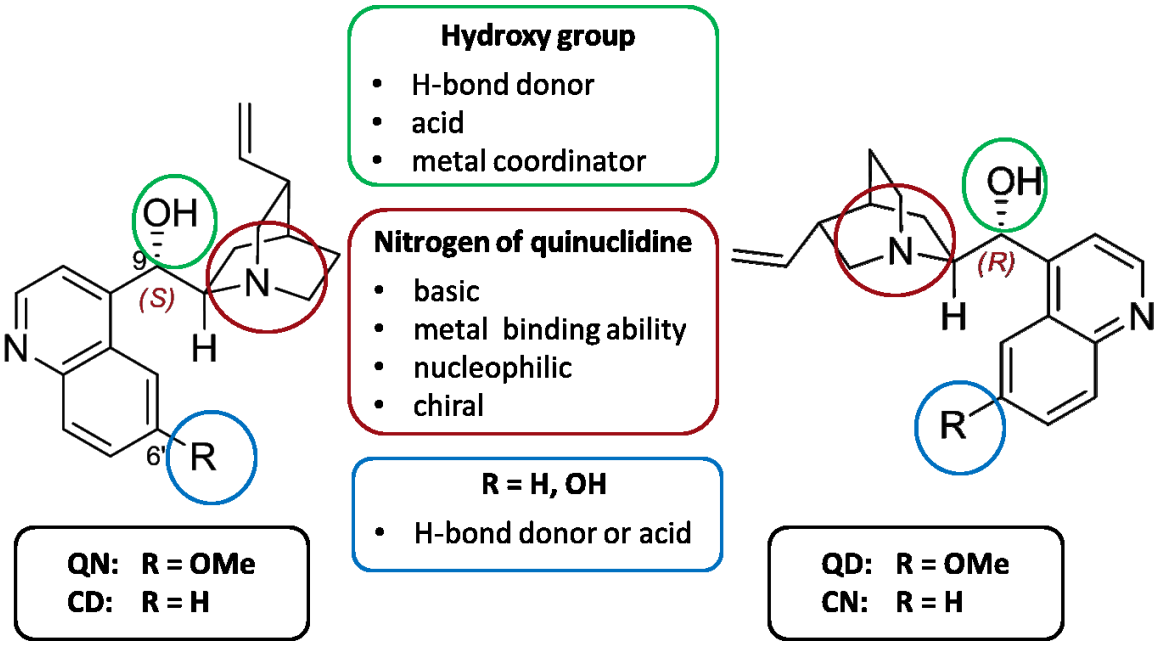


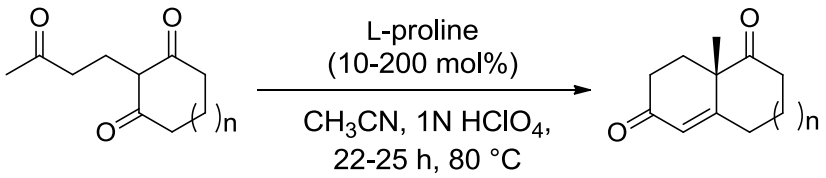
Figure 4. Four main cinchona alkaloids and their active sites.

configuration of quinuclidine, nitrogen N1, C8 and C9 is inverted (QN/QD and CD/CN).[49] The nitrogen atom in the bicyclic system is the most basic one, with a pK_a range from 8 to 9.[50] In contrast, the nitrogen of the quinoline is less basic, with a pK_a range around 5. Therefore, the tertiary amine base of the quinuclidine unit is primarily responsible for its catalytic activity. Fortunately, cinchona alkaloids act as bifunctional organocatalysts, since the nitrogen atom in the quinuclidine ring is able to deprotonate a variety of nucleophiles and the C9 OH-group can activate electrophiles through hydrogen bonding.[51] The high complexity of functionalities allows them to act as surface modifiers for asymmetric heterogeneous reactions, chromatographic selectors, and ligands for transition metal complexes.[50, 52] One of the most famous examples is the osmium-catalyzed asymmetric dihydroxylation of olefins by SHARPLESS *et al.*[53] They coupled two molecules of hydroquinine through a phthalazine unit while achieving excellent enantiomeric excesses of >97%. Furthermore, cinchona alkaloids can be alkylated at the nitrogen center to form quaternary ammonium salts for phase-transfer reactions.[54] Especially in recent years, many applications of cinchona alkaloids as catalysts in asymmetric organocatalysis (such as MICHAEL ADDITION, MANNICH-, ALDOL-, HENRY- or DIELS-ALDER reactions) have been reported.[26d, 55] The first asymmetric reaction with significant levels of enantioselectivity was reported by PRACEJUS; *O*-acetylquinine was used as a catalyst for the addition of methanol to phenylmethylketene, obtaining α-phenyl methylpropiate with an enantiomeric excess of 74%.[56] Nevertheless, for a long time, a detailed understanding of the mechanism and therefore of the activity and selectivity of these compounds was not sought. HIEMSTRA and WYNBERG showed that the enantioselectivity is dependent on both the C9 hydroxy group and the basic quinuclidine.[57] Removing or substituting the C9 hydroxy group resulted in a decrease of enantioselectivity. An ether cleavage of the carbon-oxygen bond at the C6' position to yield cupreine also influences the enantioselectivity.[41] DENG and coworkers proposed

that the phenolic OH could serve as hydrogen bond donor, activating the electrophile.[40] The advantage of these cupreines over quinines is the possibility of further functionalization at the C6' position for improving the catalytic performance.[43a] Outstanding enantiomeric excesses were observed with modified cinchona alkaloids containing a thiourea function at C9-position for a number of conjugate additions. HIEMSTRA and coworkers showed that a derived catalyst bearing a thiourea moiety at the C6'-position also improves the catalyst activity.[41]

1.5. Industrial Applications in Organocatalysis

Industrial applications of enantioselective catalysis have traditionally been dominated by metal-catalyzed and biocatalytic procedures.[55b, 58] With respect to the broad variety of efficient syntheses and the economic aspects, organocatalysis shows a very high potential for use on a larger scale.[59] This application can provide an unique approach to allow access to key synthetic intermediates for pharmaceuticals with high enantioselectivity and purity. Furthermore, the use of organocatalytic reactions can lower the environmental impact of industrial processes by decreasing the number of synthetic steps and minimizing the amounts of byproducts.[60] For example, the HAJOS-PARRISH-EDER-SAUER-WIECHERT reaction mentioned in chapter 1.3 is used industrially for the production of steroids at the Schering AG in multikilogram scale (Scheme 4).[59] In that reaction, the starting materials **2** and **3**, which are readily available from natural substances, reacted with an amount of 10-200 mol% L-proline to the corresponding steroids **4** and **5**, with enantioselectivities up to 84%.

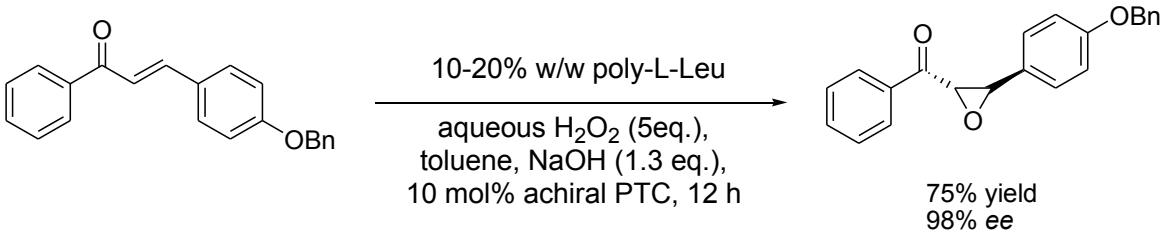


2: n=0
3: n=1

4: n=0, 87% yield, 84% *ee*
5: n=1, 83% yield, 71% *ee*

Scheme 4. Organocatalytic one-pot synthesis of steroid intermediates at multikilogram scale.

The most important and extensively reported industrial application in the field of organocatalysis is the epoxidation of chalcones. In 1980, JULIÁ *et al.* reported a simple asymmetric epoxidation catalyzed by polyamino acid.[61] This reaction was developed by several research groups for the synthesis of chalcone-derived epoxides by utilizing hydrogen peroxide as an oxidant and by performing under triphasic conditions.[62] It offers a large number of advantages, such as use of an environmentally friendly organocatalyst, a cheap oxidant and base (NaOH), and high enantioselectivities of up to 95%. Nevertheless, this process also has some drawbacks, such as the use of high catalyst amounts (up to 200% w/w) and preactivation of the catalyst and long reaction times (up



Scheme 5. JULIÁ-COLONNA epoxidation, developed by Bayer AG.

to five days) within the technical application. Researchers at Bayer AG improved this process towards a technically applicable epoxidation; the catalyst synthesis was improved, cheap reagents were used, and the reaction time was decreased significantly.[63] Furthermore, the catalyst does not require preactivation by increasing the catalyst activity. In comparison, the epoxidation of chalcone is carried out in a triphasic reaction system with the presence of an achiral phase-transfer catalyst as an additive and 10-20% (w/w) of the poly-L-Leu organocatalyst for 12 hours (Scheme 5). The desired product was obtained with 75% yield and an enantioselectivity of 98%. Further process development was achieved by using a continuously operated process in a chemzyme membrane reactor.[59, 64] The polymer-enlarged organocatalyst can be retained and reused without loss of activity. This process represents a good example for an organocatalytic application on a large scale; several other examples which are not described in more detail are summarized in Table 3.

Table 3. Industrial applications of organocatalytic asymmetric reactions.

Organocatalytic reaction	Catalyst	Company	References
Aldol reaction	L-proline	Schering AG	[65]
Epoxidation of chalcone	Poly-/oligo Leu	Bayer AG	[63, 66]
Epoxidation of alkenes	Chiral ketone	DSM	[67]
Strecker reaction	(Thio-)urea	Rhodia ChiRex	[65a, 68]
Alkylation of indanone	Alkaloid	Merck	[69]
Alkylation of glycinates	Phase-transfer cat.	Nagase	[65a, 70]
Reduction of ketones	CBS catalyst	PPG-Sipsy	[71]

The above described applications have shown that organocatalysis can be a valuable tool for industrial-scale solutions, but *why is the number of large-scale organocatalyzed applications limited*?

First, the development of an economic and scalable organocatalytic reaction requires time, ressources, and precious raw materials without any guarantee of success. In addition, not every process developed in academic laboratories can be scaled up successfully. For example, a lot of reactions were rejected at the industrial level because of laws such as no use of hazardous or toxic substances, high enantioselectivities

(typically >99% *ee*), or because specialized equipment must be used.[58a] Other typical problems are the requirement of high catalysts loadings, difficulties in recycling the catalyst, slow reaction rates, and solvent limitations. Some critics suggest that low turnover numbers (TONs) might limit the potential uses of organocatalysis for industrial applications.[72] But the most salient considerations for large-scale applications are cost and safety. In comparison to metal-based catalysts, the lower costs of organocatalysts can generally compensate for the required high catalyst loadings.

1.6. Catalyst Recycling Concepts

This chapter will only show an overview of catalyst recycling concepts; a detailed discussion of results and publications is given in Chapter 3.

For a large-scale application, the investigation of innovative methods for separation and highly efficient recycling of the organocatalyst is indispensable. In comparison to homogeneous catalysis where the catalyst can be separated in solid form by simple unit operations such as filtration, in this situation the homogeneous catalyst is dissolved together with the reactants in the reaction medium. For the separation of such a homogeneous catalyst, different strategies such as heterogenization, membrane filtration, precipitation, and multiphase systems exist. In the simplest case, the volatile products are distilled, and the thermal stability of the catalyst decides whether it can be reused.

Membrane technology is a reliable separation process which is steadily growing in importance for the recovery of the catalyst, especially the organic solvent nanofiltration (OSN). This method offers the advantage that the sensitive catalyst can be separated under mild conditions from the organic solution. The strength of this method, compared with other separation methods, lies in the simplicity of the process.[73] Nevertheless, there is often difficulty in the selectivity of the membrane in order to retain the catalyst completely whereas the product can pass through the membrane. In this process, the catalyst must have a very high retention rate[1] in order to avoid contamination with the product stream. Only with a retention >0.99 an effective recovery over several cycles can be achieved (Figure 5).

The entrapment of catalysts is typically based on covalent bonding to a solid support material, which can be separated by simple filtration of the reaction solution.[5] As a support, various organic polymers such as polystyrene, poly(ethylene glycol) and polyethylene or inorganic materials such as silica or zeolites are used. Some examples are shown in chapter 1.3. New approaches for immobilization of organocatalysts have been described by the research group of Prof. LIST, where organocatalysts are fixed by wet and photochemical methods on textile substrates (polyester, polyamide).[74] The catalysts bound to such textiles exhibited good activity over a hundred reaction cycles, and a high enantioselectivity was achieved. However, for this immobilization method the

[1] The retention (rejection) rate is calculated by: $R = 1 - \frac{c_P}{c_R}$

organocatalyst must have at least one double-bound, reducing the wide range of the applications.

Another alternative is the use of multiphase catalysis. The high potential is shown in two important industrial applications: the Ruhrchemie/Rhône-Poulenc Process[75] and the Shell Higher Olefin Process (SHOP).[76] Recent studies have focused on hydroformylation of long chain olefins (>C6) in multiphase systems. In particular, microemulsion systems provide catalyst recycling but also a selective reaction to linear aldehydes.[77] To overcome mass transfer limitations, switchable solvent systems can be used. The idea is initially to use a single-phase system for the catalytic reaction, which then devolves into a two-phase system by change of pressure, temperature, density, or pH value. With this concept, a simple and efficient separation of the catalyst is possible.[78]

All the presented methods, with their advantages and disadvantages, can be applied to the repeated use of a homogeneous catalyst without loss of activity and enantio-selectivity. The selection of the best separation technique is difficult and must be adapted for each catalyst/product/byproduct system. In general, the aim is to decouple the residence time of the catalyst and reactants so as to increase the TON. This is especially important in the field of organocatalysis, where high catalyst amounts are required to achieve high selectivities. Different approaches for this demanding task are described in the next chapters.

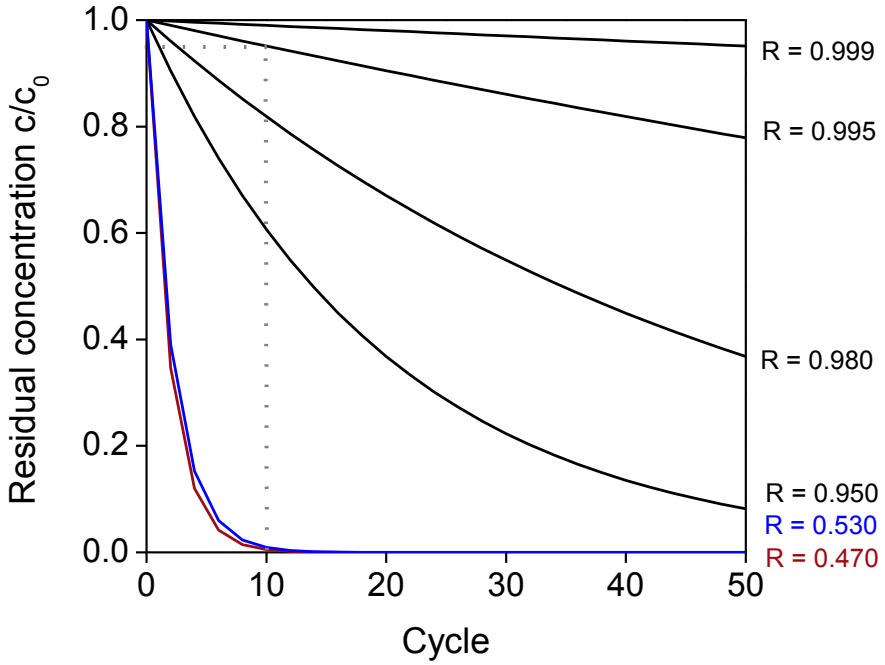


Figure 5. Normalized residual concentration as a function of the number of cycles for different retention rates.

2. Aim of This Work

A big disadvantage of organocatalytic reactions is the need for substoichiometric but still relatively high amounts of catalyst (1-30 mol%) to achieve high selectivities and reaction rates, and thus the industrial application is still limited. To overcome this disadvantage, this PhD project focused on the development and optimization of organocatalytic processes by considering three innovative concepts for catalyst removal to increase the productivity of the organocatalyst. In Figure 6, these three approaches for catalyst removal and simultaneous preparation of enantiomerically pure building blocks for active pharmaceutical ingredients (API) are highlighted. Generally, the enantiomerically pure product can be obtained after the reaction by column chromatography, wherein the precious organocatalyst is not obtained and can therefore not be reused. In this study, all the three approaches are also used to simplify the downstream process for obtaining the crude product without further purification steps, along with the simultaneous removal of the catalyst.

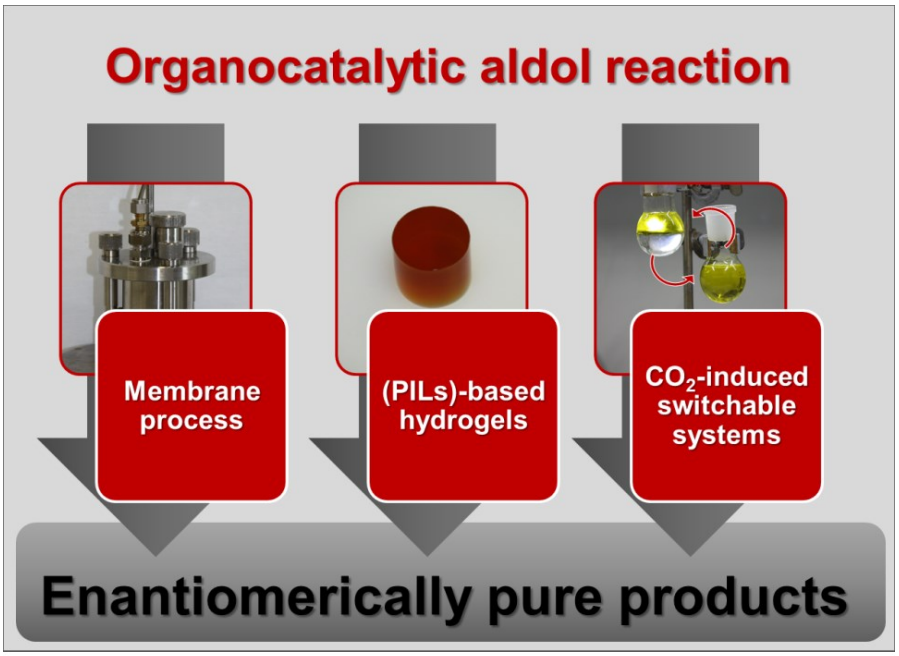


Figure 6. Three-pillar strategy for realization of efficient organocatalytic processes.

Based on preliminary work, a HENRY reaction was defined as a suitable organocatalytic aldol reaction for a test system. The three methods, which are novel approaches for catalyst removal and its recycling in the field of organocatalysis, have be investigated and compared. The challenge is to decouple the residence time of the reactants and catalyst, which will compensate for the weakness of the required high catalyst loadings.

First, the use of modern nanofiltration membranes for the rejection of an organocatalyst was targeted. In this stage, membrane characterization, increasing the size of the catalyst by chemical modification, catalyst recycling, and applicability to other systems are the

main tasks of this PhD project. In addition, the use of OSN for the purification of organocatalysts was investigated.

Another objective of this study is the development of novel immobilization techniques for organocatalysts without decreasing the selectivity while maintaining the advantages of homogeneous catalysis. Toward that goal, the embedding of the organocatalyst in polymerized ionic liquids (PILs)-based hydrogels should be tested and established. The influence of several parameters, such as water amount, gelation behavior, chemical and mechanical stability, or catalyst structure on the selectivity and catalyst removal was investigated and optimized.

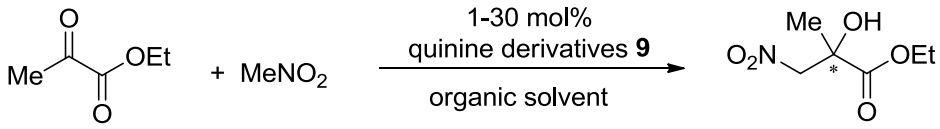
CO_2-induced switchable systems for catalyst removal represent the third approach for this study. The main challenge is to find a suitable switchable solvent system and to ensure complete catalyst/product separation without decreasing the catalyst activity. To optimize the downstream processing, microstructured devices such as falling-film microreactor and microextractor should be used.

3. Classification and Discussion of the Results

The background, motivation, and highlights of the **publications I-V** will be summarized in this chapter and compared with the literature. Beginning in the first chapter, the test reaction and the corresponding preliminary studies (not yet published) will be presented. **Publications I, II, IV** and **V** describe the different approaches for catalyst recycling, which will be compared and evaluated in chapter 3.6. Additionally, **publication III** shows another application of OSN for catalyst purification.

3.1. Organocatalyzed HENRY Reaction

The classical HENRY reaction, the coupling of a nitroalkane with a carbonyl compound in the presence of a base, is an important chemical reaction in organic synthesis since its discovery in 1895.[79] In turn, the enantioselective version of the HENRY reaction has had become a high impact in asymmetric catalysis, especially with biocatalysts and metal complexes.[37, 80] Several drawbacks of the reactions catalyzed by metal complexes lie in the costs and toxicity of the metal species. The organocatalyzed HENRY reaction catalyzed by quinine-derivatives, developed by LI and coworkers[40], was used as one example for this study (Scheme 6). The HENRY reaction is a C-C bond forming reaction providing access to small but highly functionalized building blocks.[39] Ethyl pyruvate and nitromethane are readily available educts and the product is a valuable starting material for the synthesis of aziridines and β-lactams, which are key intermediates for various pharmaceuticals.



6 **7** **8**

Scheme 6. Enantioselective HENRY reaction as a key example.

To promote the reaction with good performance, the organocatalytic structures must have a) a basic unit (or an external base); b) some unit capable of binding the nitro group such as through hydrogen bonding; and c) a unit capable of forming a hydrogen bond with the acceptor carbonyl.[81] Bifunctional organocatalysts represent an important class for the reaction. In order to obtain high yields and selectivities, the influence of modifications on the natural cinchona alkaloid quinine **9a**, reported in Figure 7, was studied using the test reaction with THF as the reaction solvent at 23 °C. The main focus was on both the synthesis of efficient organocatalysts and the improvement of the catalyst retention (**Publication I**) by introducing sterically demanding groups. As MARCELLI *et al.*[41, 82] reported that cinchona alkaloids bearing a phenol on the C-6' position (cupreines) are enantioselective bifunctional organocatalysts, the quinine derivatives

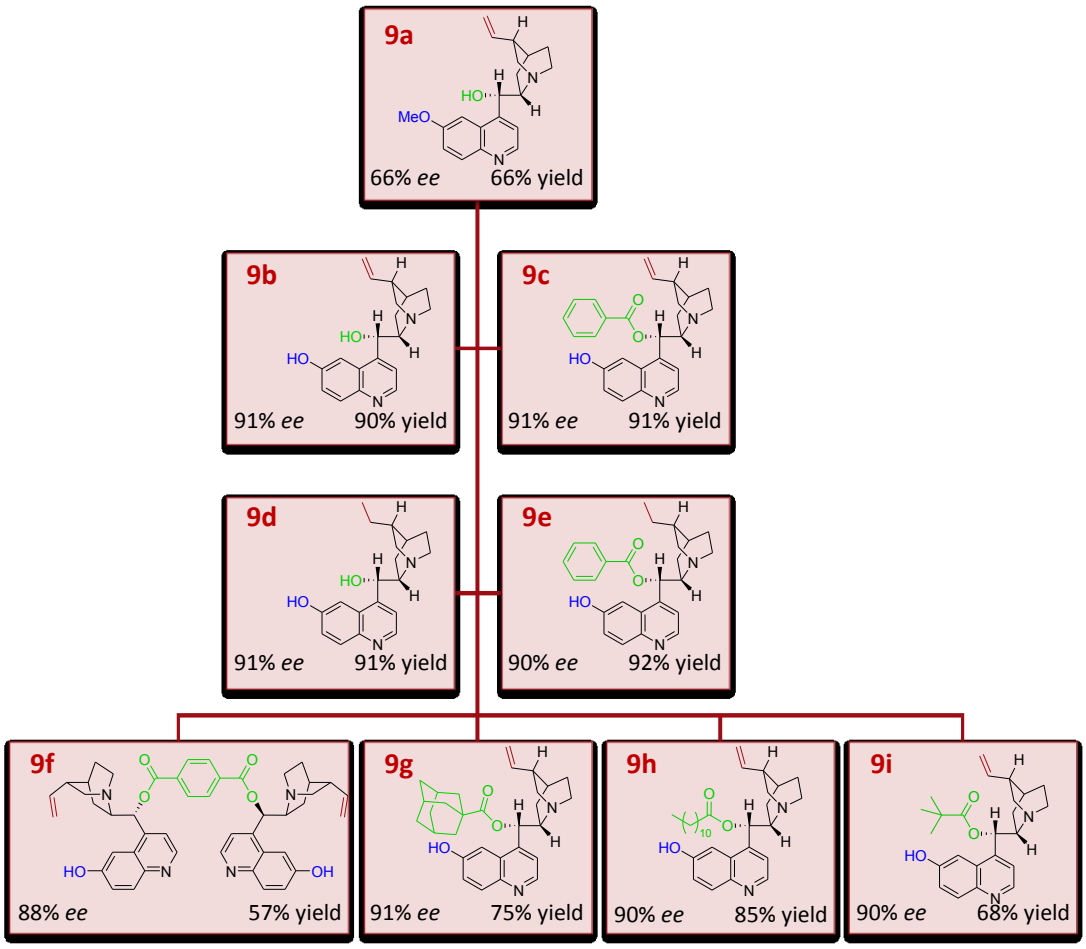


Figure 7. Quinine-derivatives synthesized and screened in this study. **9a** – quinine, **9b** – cupreine, **9c** – benzoyl cupreine, **9d** – hydro cupreine, **9e** – hydro benzoyl cupreine, **9f** –terephthaloyl cupreine, **9g** – adamantoyl cupreine, **9h** – lauroyl cupreine, **9i** – pivaloyl cupreine. (Synthesis procedure of catalyst **9b-9i** is shown in appendix).

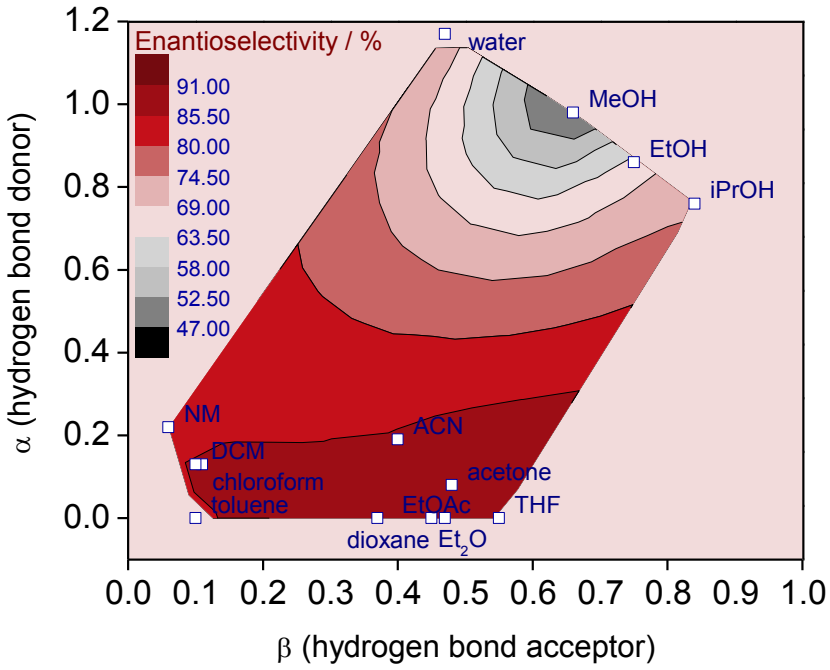
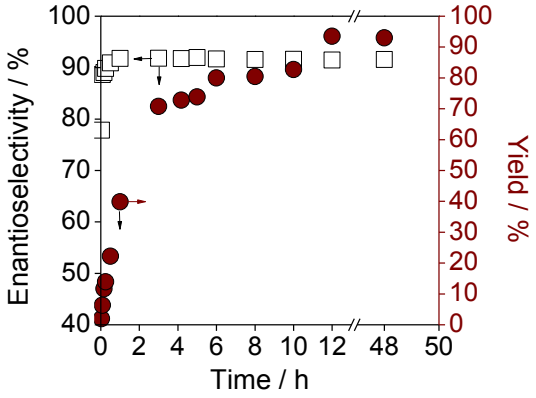


Figure 8. Dependency of different solvents on enantioselectivity for the HENRY reaction catalyzed by **9c**, examined with Kamlet-Taft parameters.

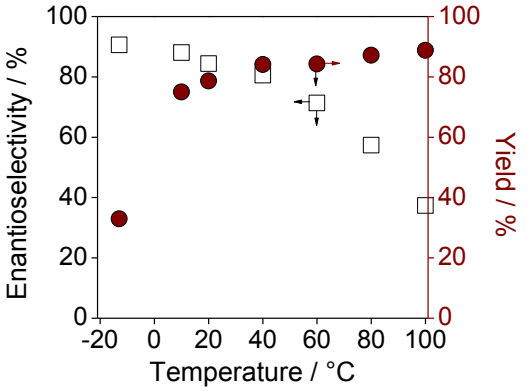
were converted into the corresponding cupreine derivatives **9b-i** (synthesis procedure is given in the appendix). In comparison to the quinine derivatives, which did not give the desired product in significant enantioselectivities (1-40% *ee*, data not shown), good enantioselectivities up to 95% *ee* (Figure 7) were achieved with the corresponding cupreine derivatives. To the best of my knowledge, the conformationally more rigid catalysts such as terephthaloyl-, adamantoyl- and lauroyl cupreine (**9f-h**) have not been reported in scientific literature before. Even if they show slightly lower yields, their enantioselectivities are comparable to the other catalysts. This suggested that the conformationally more rigid catalysts may not be crucial for successful catalysis. The best results were obtained with the catalysts bearing two hydroxy functionalities (**9b** and **9d**) and the catalysts bearing hydroxy and benzoyl functionalities (**9c** and **9e**). In addition, the catalysts **9d** and **9e** without the vinyl fragment of the quinuclidine (used in **Publication IV**) show nearly the same enantioselectivities and yields as their counterparts. This was also predicted in a density functional theory study by HAMMAR *et al.*[83] All these stable catalysts work remarkably well under the reaction conditions, with high yield and enantioselectivity. Nevertheless, catalyst **9c** was used for further optimization of the reaction conditions.

It was previously reported that the enantiomeric excess of the HENRY product is strongly dependent on the reaction medium.[84] Many research groups investigated the possible correlation of the solvents and the *ee* with physiochemical parameters such as dielectric constants; however, this led to no good relation. Therefore, the effect of various solvents on the *ee* for the test reaction was examined with the Kamlet-Taft parameters.[85] The enantioselectivity correlates quite nicely with the solvent α value (hydrogen bond donor), slightly with β (hydrogen bond acceptor), and randomly with π* (polarizability). To find an optimum of the solvent influence, the Kamlet-Taft parameters α and β are graphically drawn with the *ee*-values of various solvents (Figure 8). The optimum was found for solvents which have a very low α-value and a low to moderate β value. The graph shows that the hydrogen bond acceptor influences the *ee* too, but it is not as strong as the effect of the hydrogen bond donor. The π* value is apparently irrelevant (data not shown). It also suggests that solvent acidity (proticity) and solvent basicity both negatively affect the *ee* value, but acidity is more crucial to the enantioselectivity than basicity. It is important to note that solvents which have a higher α value than nitromethane (substrate in excess) lead to a decreasing enantioselectivity. The most suitable solvents are THF, acetone, dichloromethane, EtOAc, and diethyl ether, and low *ee*-values are obtained with protic solvents such as water and alcohols.

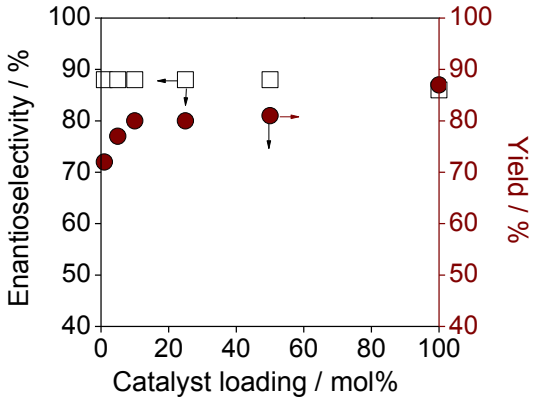
Further screening tests were performed with variation of temperature and catalyst loading catalyzed by **9c**. From these concentration-time-curves initial rates were obtained. In Figure 9a-c it can be seen that the reaction is finished after 12 hours and the temperature optimum is between 0 and 20 °C (75% yield, 88% *ee*). With increasing temperature the *ee* decreases dramatically, down to 37% *ee*. The use of different amounts of organocatalyst shows that when using lower amounts reaction time increases. However, the selectivity of the reaction remains remarkably high even when the amount of catalyst is reduced (1 mol% **9c**, 88% *ee*).



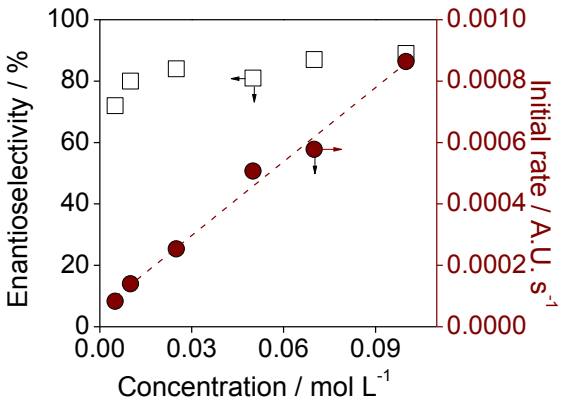
a) Temporal progress of the reaction.
Cond.: 1 M EP (5 mmol), 10 eq. NM,
5.0 mol% **9c**, THF, 23 °C.



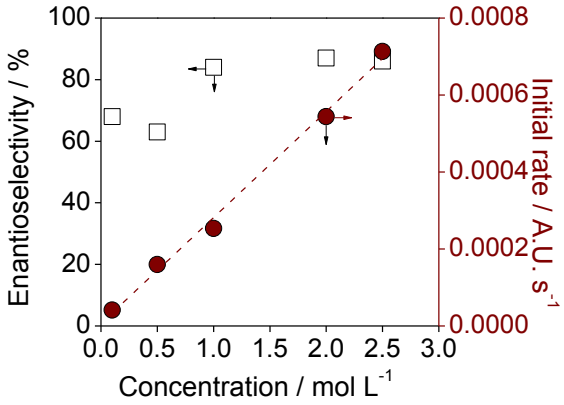
b) Dependency of temperature on ee/yield.
Cond.: 1 M EP (5 mmol), 10 eq. NM,
5.0 mol% **9c**, THF, 12 h.



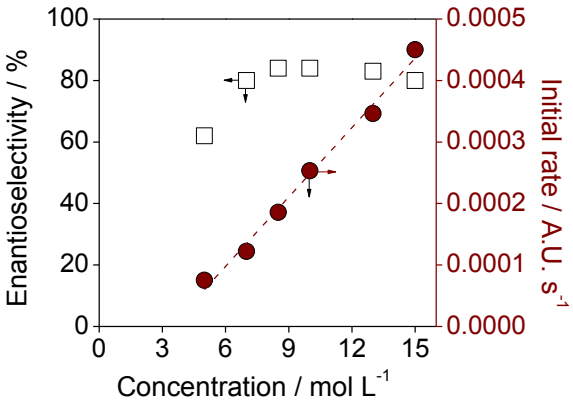
c) Dependency of catalyst amount on ee/yield.
Cond.: 1 M EP (5 mmol), 10 eq. NM,
cat. **9c**, THF, 23 °C, 12 h.



d) Kinetic parameters by variation of conc. cat.
Cond.: 1 M EP (7 mmol), 10 eq. NM,
cat. **9c**, THF, 23 °C, 15 min.



e) Kinetic parameters by variation of conc. EP.
Cond.: 10 M NM (0.07 mol), 2.5 mol% cat. **9c**,
THF, 23 °C, 15 min.



f) Kinetic parameters by variation of conc. NM.
Cond.: 1 M EP (7 mmol), 2.5 mol% **9c**,
THF, 23 °C, 15 min.

Figure 9. Screening results for HENRY reaction catalyzed by **9c**.

That leads to reduced costs for the process by reducing the catalyst loading and avoiding the use of excess catalyst. The reaction (Figure 9d-f) were determined by *in situ* IR monitoring of the consumption of nitromethane resulting in first-order kinetics in both substrates and catalyst. This measurements (Figure 9f) show that nitromethane will be used in large excess in comparison to the pyruvate derivative to ensure its complete conversion. This is not considered problematic due to the easy evaporation of excess nitromethane after reaction.

3.2. Catalyst Removal by Organic Solvent Nanofiltration

Short Introduction and Motivation

The principle of green chemistry guides the development and design of novel sustainable processes and products.[86] In this context, the development of energy efficient catalytic processes as well as efficient separation procedures plays an important role. A reliable separation process which is steadily growing in importance for the recovery and reuse of the catalyst is membrane technology, especially OSN. The separation of metal-based catalysts by OSN is well described in the literature, whereas the recovery of organocatalysts is still limited.[87] One of the first studies was the reduction of ketones by oxazaborolidines in a membrane reactor, where GIFFELS *et al.* showed the possibility of recycling a polymer-enlarged catalyst for enantioselective ketone reduction.[88] Furthermore, SIEW *et al.* reported the enlargement of a quinidine-based organocatalyst (M = 1044 g mol^{-1}) through polyalkylation and the recycling of them by OSN in 2013.[89] Simultaneously, the catalyst recycling by OSN has been reported in the example of benzoylcupreine (**Publication I**).[90]

First case study for catalyst recycling by OSN

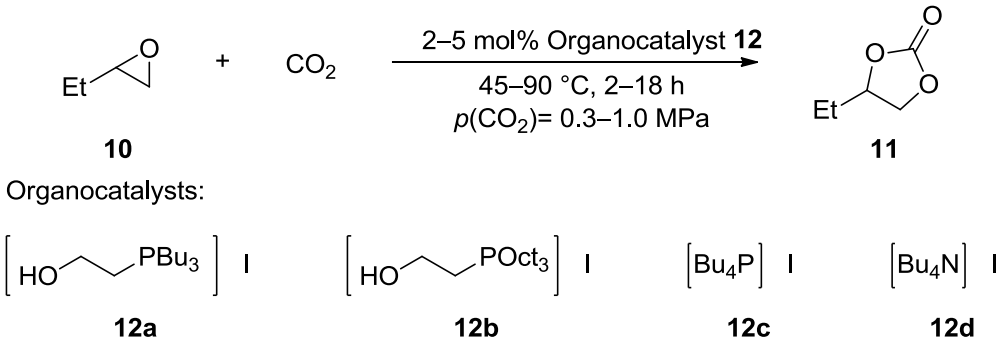
Prior to the recycling experiments, different membranes from DM series (Evonik MET Ltd., UK) were characterized. These solvent-resistant membranes consist of cross-linked polyimide prepared by phase inversion and are characterized by their nominal molecular weight cut-off (MWCO).[91] The manufacturer defined the MWCO as the molecular weight of the compound that is typically rejected by 90% for polystyrene oligomers when acetone is used as the solvent. In this case study, membranes with a MWCO between 150 and 500 g mol^{-1} were used in a stirred cell operating in a dead-end mode. Generally, the most used configurations are the dead-end and the cross-flow mode. The dead-end filtration mode[2], which was used for publication I, is characterized by easy handling, low prize, and low space requirements. The cross-flow filtration mode[3] was used in publication II and III, and its advantage is the minimization of concentration polarization by increasing shear rate over the membrane surface.

[2] Dead-end filtration mode is characterized by feed flow in the same direction as the permeate flow.
[3] Cross-flow filtration mode is characterized by a tangentially feed flow over the membrane and perpendicularly to the permeate flow.

The catalysts presented in chapter 3.1. have molecular weights between 310 and 751 g mol^{-1} and the synthesis product has a molecular weight of 177 g mol^{-1}. The molecular weight difference is approximately a factor of two, and the separation of the catalyst and product seems possible. Four membranes (DM 150, DM 200, DM 300 and DM 500) were used for the rejection tests with quinine **9a** (M = 324 g mol^{-1}) in THF due to its good availability (**Publication I**, Figure 1). As expected, with decreasing MWCO the retention increases from 0.80 for DM 500 up to 0.97 for DM 150 when performed in a stirred membrane cell (see also appendix). These retention rates correlate well with the manufacturer's prediction and the previous work reported here.[92] In addition, outstanding retentions of 0.97 for membrane DM 300 and 0.99 for membrane DM 150 are obtained with catalyst **9c** (M = 415 g mol^{-1}). On the other hand, the product is retained with 0.87 for DM 200 and 0.86 for DM 300, which is relatively high for an effective separation. Nevertheless, a discontinuous diafiltration should be possible to flush out effectively the product of the HENRY reaction. The catalyst recycling experiments were performed in a batchwise fashion (**Publication I**, Figure 5). The HENRY test reaction was performed in a reaction vessel, and after complete reaction the postreaction mixture was transferred into the filtration cell. Up to four discontinuous diafiltration steps were performed to flush out the product, followed by the subsequent reaction to examine catalyst activity (**Publication I**, Figure 6). These experiments show that the organocatalyst was still fully active (87-89% *ee*) after its removal and could easily be reused after the nanofiltration steps (four cycles). In addition, the product was obtained at a high purity (94%) without further purification steps. However, a decrease in product yield from 81% was obtained for batch I to 38% for batch IV, mainly due to the loss of catalyst during the diafiltration steps and retentate sampling. For this reason, in further work fresh catalyst was added after the discontinuous diafiltration steps (**Publication II**). Compared to this work, LIVINGSTON and coworkers used enlarged quinidine-based organocatalysts (MW = 1044 g mol^{-1}) which was retained to more than 0.99 by the membrane DM 300. They recycled this catalyst only once after the enantioselective MICHAEL ADDITION with little change in the catalytic performance.[89]

Second case study for catalyst recycling by OSN

To demonstrate the wide applicability of OSN for the recycling of organocatalysts, further experiments continued with the separation of phosphorus-based organocatalysts and their subsequent recycling (**Publication II**).[93] The background of this study was the development of sustainable processes, based on the example of the utilization of renewable resources such as CO_2 as a C1 building block. In this context, the atom-economic conversion of CO_2 and epoxides yielding cyclic carbonates has been intensively studied.[94] In **publication II**, the atom-economic conversion of butylene oxide with carbon dioxide has been chosen as a test reaction, producing the desired cyclic carbonate in excellent yields under mild conditions (Scheme 7). The obtained products are of great interest as solvents, building blocks, plasticizers, and for the synthesis of polymers.[95] Separation of the catalyst by distillation led unfortunately to partial thermal decomposition and thus loss of catalytic activity. As in publication I, catalyst and



Scheme 7. Reaction for publication II with phosphorus-based organocatalysts.

membrane screenings as well as parameter optimizations were performed prior to the recycling experiments. The catalysts **12a** and **12b** were prepared by alkylation, whereas the simple salts **12c** and **12d** were commercially available.[96] The bifunctional salts **12a** and **12c** showed much higher activity than **12c** and **12d**, yielding *1,2*-butylene carbonate **11** in 97 and 92% conversion, respectively. Further experiments were carried out with phosphonium salt **12a** with different membranes from the DM series in a stirred cell. The catalyst **12a** (374 g mol^{-1}) in EtOH solution (0.15 M) was rejected outstandingly well with a retention >0.99 for DM 150 and 0.96 for DM 300 (**Publication II**, Figure 2). The change from dead-end (RZ 75) to the cross-flow (FZ, see appendix) operating mode resulted in a flux that was twice as high. For sustainable chemistry purposes, the initial attempt was to filtrate the postreaction mixture under solvent-free conditions. Unfortunately, the filtration of catalyst **12a** in *1,2*-butylene carbonate (product **11**) gave no flux through the membrane. Notably, there is no clear correlation among the solvent properties[4], and the flux and retention. The used membranes are semihydrophobic; accordingly, polar solvents permeate preferably through the membranes.[97] As a result, the postreaction mixture was diluted with ethanol as the most suitable solvent since it exhibits the highest observed flux and is classified as a green solvent (**Publication II**, Figure 3).[98] The obtained high rejection of catalysts **12a-b** (0.96 and 0.98) regardless of their molecular weight is based on the hydroxyl group which binds to the relatively hydrophilic membrane, in comparison to catalysts **12c-d** (0.90 and 0.94).[99] The molecular weights of catalysts **12a** and **12c** are approximately a factor of three higher than that of **11** (M = 116 g mol^{-1}), and a separation by nanofiltration was assumed to be suitable. With a product rejection of 0.47, the product is theoretically washed out after 11 discontinuous diafiltration steps (see also Figure 5, chapter 1.6.). As shown in publication I, the reaction was carried out in a batchwise fashion (**Publication II**, Figure 5), though with a membrane cell operating in a cross-flow mode. If necessary, fresh catalyst was added to maintain the catalyst/substrate ratio. In each of the batches (four cycles), full conversion was achieved, and yields up to 99% were obtained. Moreover, excellent rejections up to 0.99 for **12a** were achieved, utilizing the same membrane for each diafiltration step.

[4] Typical solvent parameters to explain the different behavior are: M_{EtOH} = 46 g mol^{-1}, $logP_{EtOH}$ = -0.30 [-0.19 ± 0.18], $\eta(25°C)_{EtOH}$ = 1.08 mPa·s, $M_{acetone}$ = 58 g mol^{-1}, $logP_{acetone}$ = -0.24 [-0.16 ± 0.19], $\eta(25°C)_{acetone}$ = 0.32 mPa·s, M_{BC} = 116 g mol^{-1}, $logP_{BC}$ = [2.77], $\eta(25°C)_{BC}$ = 2.77 mPa·s. Log P in square brackets are obtained from ACD/Labs.

Furthermore, 26 g of *1,2*-butylene carbonate was isolated in high purity (>99%) without further purification steps. This study demonstrates the first application of OSN for phosphorus-based organocatalysts. Table 4 indicates the state of research in the field of organocatalysis and OSN and the classification of this new work.

Table 4. Examples of the application of OSN in the field of organocatalysis.

Year / Author	Organocatalyst	Membrane	MW / g mol^{-1}	Reaction
1997-1998 Giffels[35, 88] *et al.* and Felder[88] *et al.*	Polymer-enlarged oxazaborolidines	MPF-50	13 800	Ketone Reduction
2012 Grosseheilmann[92A] *et al.*	Quinine-based organocatalyst	DM 150 - 500	310 - 428	Michael-Addition
2013 Siew[89] *et al.*	Quinidine-based organocatalyst	DM 300 - 500	1044 - 1332	Michael-Addition
2013 Fahrenwaldt[90] *et al.*	Quinine-based organocatalyst	DM 150 - 500	310 - 428	Henry Reaction
2015 Grosseheilmann[93] *et al.*	Phosphorus-based organocatalyst	DM 150 - 500	370 - 430	Addition of CO_2 on epoxide

3.3. Purification of Organocatalysts by Organic Solvent Nanofiltration

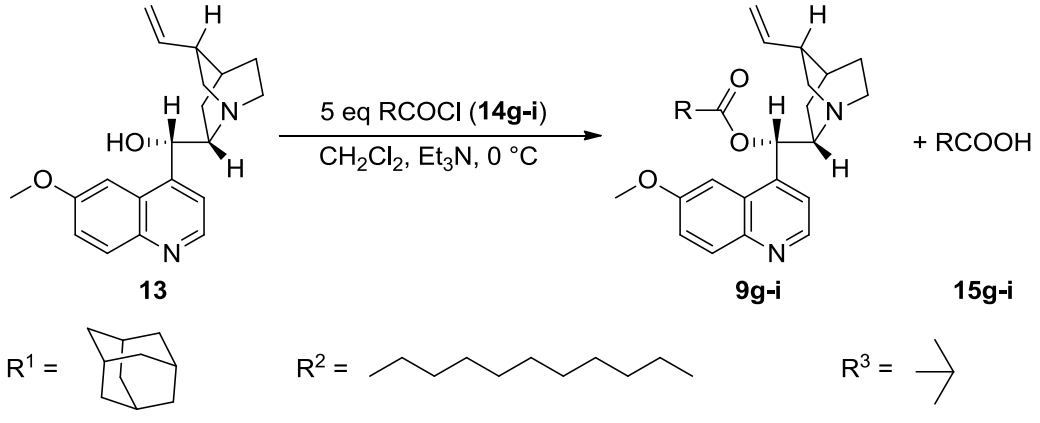
Short Introduction and Motivation

For many industrial processes, the majority of the production costs are created by downstream processing. Generally, processes such as distillation, solvent extraction, (fractional) crystallization, and chromatography are very time-consuming, expensive, and difficult to integrate into existing processes. These separation methods also have disadvantages on a laboratory scale. Therefore, the improvement of separation strategies is an attractive area for research and industry. OSN offers a sustainable alternative to conventional purification methods.[100] The main advantage is the separation of a given impurity from the product solution under relatively mild conditions directly from a solution.[101] The strength of this method, compared with other separation methods, lies in the simplicity of the process and the lower solvent consumption. During OSN, no further additives are required and no energy must be applied for phase transformations.[102] Another advantage of membrane applications is the possibility of concentrating the product during the separation process. As one example, in 1999 Dudziak *et al.* reported the successful purification of nucleotide sugars by using

nanofiltration in downstream processing for the desalination and concentration of nucleotide sugars.[103]

Case Study for Purification of Organocatalysts

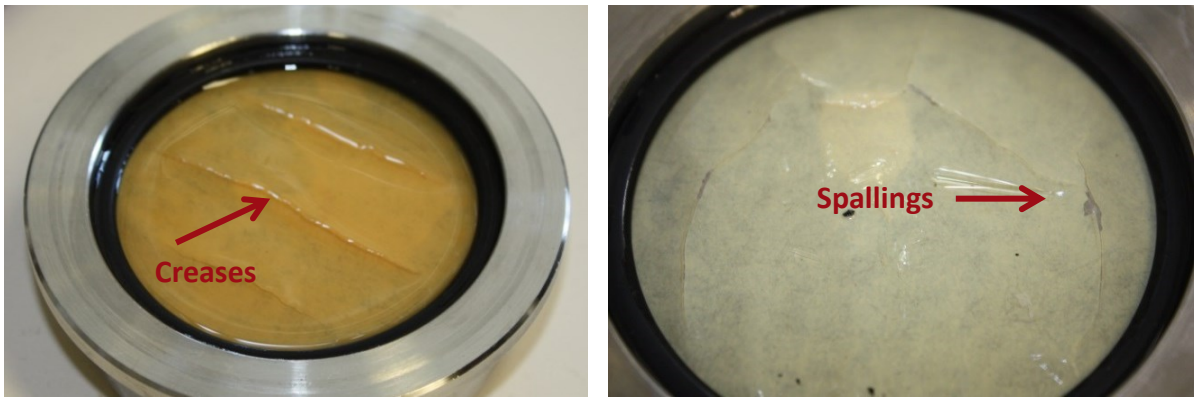
In this study, the successful use of OSN for the purification of three highly enantioselective quinine-based organocatalysts **9g-i** (see Figure 7) was demonstrated (**Publication III**).[104] Within their synthesis procedure (Scheme 8), suitable purification methods are essential and need to be finely tuned, as minor impurities may negatively affect the activity, stability, and even stereoselectivity of the catalyst. In this synthesis reaction, an excess amount of the acid chloride **14** was required to facilitate full conversion.[105] Chromatography, as the standard method which was used for the other catalysts **9b-f**, shows various limitations owing to the presence of structurally similar compounds. The main contaminant of the synthesized catalysts is the corresponding acids **15g-i**. Due to the different molecular weights of the catalysts and impurities, the impurity is washed out with continuous replacement of the solvent, whereas the catalyst remains in the filtration cell (**Publication III**, Scheme 2). As in publication I and II, DM membranes with a MWCO between 200 – 300 g mol^{-1} were used. All catalysts **9g-i** showed high retentions up to 0.99 (**Publication III**, Table 1), whereas the acids were significantly less retained (0.53 – 0.57). As calculated, 10 discontinuous diafiltration steps are necessary to flush out the impurity (see also Figure 5, chapter 1.6.). The purification of **9g** proved to be much more challenging, which seems to originate from the highly sterically demanding structure of the adamantyl side chain. In comparison, the purity of the organocatalyst **9i** was increased from 89.0% with column chromatography up to 99.8% with OSN. Similar results were obtained for **9h** on a gram scale. With these purified catalysts, high enantioselectivities up to 95% *ee* were achieved compared to the impure catalysts (87% *ee*).



Scheme 8. Reaction of quinine with different acid chlorides to the corresponding quinine-based organocatalysts. **14g**: R^1 = *1*-adamantyl , **14h**: R^2 = $Me(CH_2)_9Me$, **14i**: R^3 = *t*Bu.

Critical perspective

The three applications described above for catalyst separation and purification show the high potential of OSN. Nevertheless, applicability on a large scale is still limited due to the solvent and long-term stability as well as the high costs[5] of commercially available membranes.[91] The DM membranes used in this study consist of modified polyimide (PI) structures, which is an excellent polymer for membranes due to its high heat resistance and good mechanical and chemical strength.[106] Unfortunately, these membranes showed several limitations during this work. The first drawback is the decline of flux performance over time due to the compaction of the membrane's top layer, which was also reported by other research groups.[107] Secondly, the polymeric membranes show relatively low thermal (up to 40 °C) and chemical stability; for example, they are not stable in chlorinated solvents. In addition, the membranes show a lot of difficulties in the reproducibility of retention and flux between different charges which may be caused by the manufacturing process, such as the fact that DM 500 (Charge II) visually indicates a thicker protective layer. Furthermore, some membrane charges cannot be used due to missing stability during the filtration process. Figure 10 shows two broken membranes, which have creases and spallings after conditioning with EtOH at 20 bar. To overcome this drawback, the focus of this research is on the development on new membranes. In particular, specially combined organic/inorganic (mixed matrix) membranes have high potential due to the combination of the advantages of polymeric and ceramic membranes.[108]



a) b)

Figure 10. Membranes (a) Duramem™300 and (b) Duramem ™300(T1) after 12 h of filtration in EtOH.

[5] The unit price for one DM flat sheet membrane (210 x 297 mm) is 250.00€.

3.4. PILs-Supported Organocatalysts and Their Use in Organocatalysis

For the recycling of chiral organocatalysts, different methods such as heterogenization, membrane filtration, precipitation, or two-phase systems exist.[109] In this chapter, a novel strategy for the embedding of chiral catalysts in polymerized ionic liquids-based (PILs) hydrogels is presented.

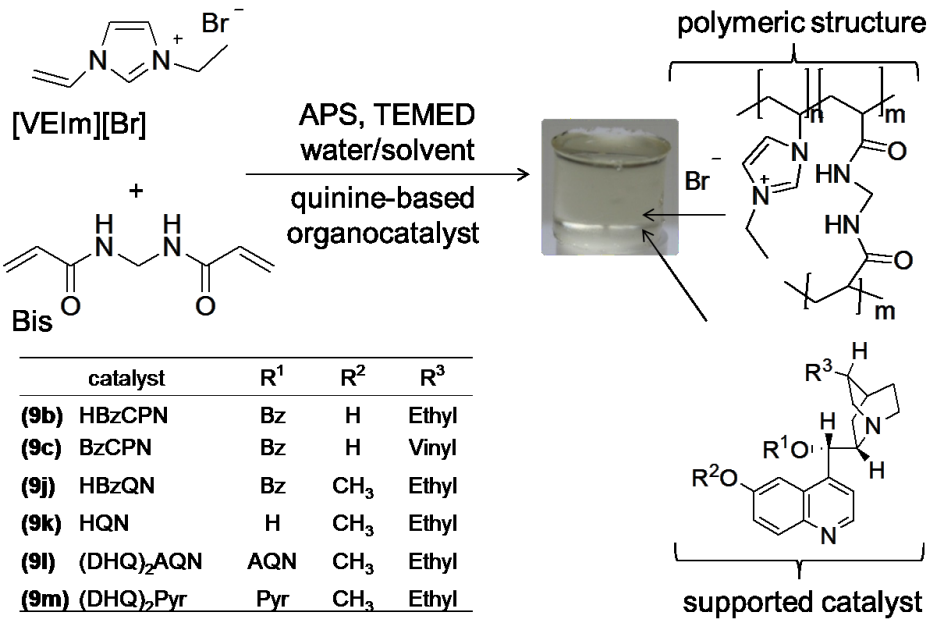
Short Introduction and Motivation

Polymerized/polymeric ionic liquids, also named "poly(ionic liquid)s", refer to a subclass of polyelectrolytes and have attracted increasing interest in the scientific literature since 1998. PILs are usually prepared by polymerization of ionic liquid monomers; as a result, they combine the advantages of ionic liquids (e.g., ionic conductivity, thermal and chemical stability, tunable solution properties) and the properties of polymers. Currently, there is a huge demand and potential for applications in catalysis, energy, and the environment, and in material science.[110] However, for PILs-based (hydro)gels there are only a few published reports, including thermo-responsive PILs-based hydrogels[111] or polymer gels containing amino acid ionic liquids (AAILs)[112]. The synthesis of novel hydrogels bases on polymerized ionic liquids and their applications are well investigated by the research group of Prof. KRAGL and recently described in the literature, in 2014.[113] Therefore, the motivation was to use these gel materials as a novel support for organocatalysts due to their great advantages, such as the enhanced mechanical stability, improved processability, flexibility, and durability.

Preparation and Investigation of Poly(ionic liquid)s-Supported Organocatalysts

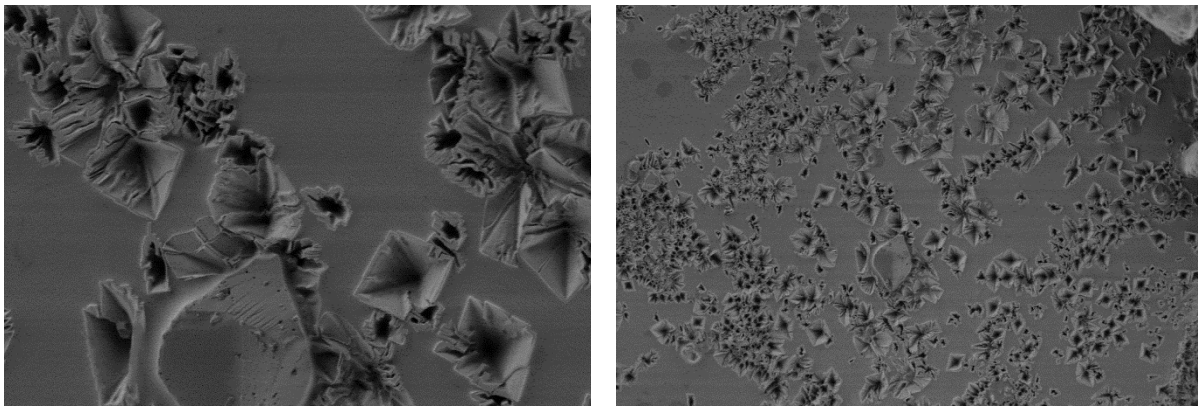
The synthesis of these very interesting gel materials was carried out by radical polymerization of imidazolium-based ionic liquids bearing a vinyl group with the crosslinker *N,N'*-methylenbisacrylamide yielding the PIL-network, as presented in Figure 11. In comparison to the previous report[113a], a catalyst in an organic solvent solution was added to encapsulate the applied organocatalyst. The investigated organocatalysts were dissolved in a suitable organic solvent and added to the radical polymerization of the hydrogel-precursors, yielding the final hydrogels with incorporated catalyst (see Figure 12). After evaporation of the organic solvent (during the drying process), catalyst crystallization occurred in the polymeric structure of the hydrogel. The presented SEM images clearly show a catalyst distribution on the surface (left) and inside the hydrogel (right). The poly(ionic liquid)-based catalyst does not act as an organo-catalyst as it has in other reports.[114] First, the initial concept was to decrease the leaching behavior of the catalyst bearing a vinyl group by anchoring the catalyst's vinyl group on the PIL-network during the polymerization process. Unfortunately, there was not only a decrease in leaching behavior but also a complete loss of activity. Therefore, further studies were conducted with catalysts bearing an ethyl group or by previous radicalization of the vinyl group. The gelation time and gel consistency depends on the

anion size and the alkyl chain length of the IL, crosslinker to IL ratio, organic solvent, and catalyst structure. Gelation tests were carried out with five organocatalysts with the IL monomer VEImBr (**Publication IV**, SI-Figure 3). The required gelation times were longer for cupreine derivatives bearing a hydroxyl group (120 min) in comparison to quinine derivatives (20 min). Nevertheless, stable hydrogels were observed with all incorporated catalysts. Furthermore, the gelation behavior was investigated in detail with the IL monomers VEImBr, VBImBr and VBImCl to compare the effect of the applied cation and anion. (**Publication IV**, SI-Table 1). In general, with increasing alkyl chain length the gelation time increases: VEImBr (20 min) < VBImBr (30 - 40 min), while with increasing size of the anion the gelation time also increases: VBImCl (25 - 35 min) < VBImBr (30 – 40 min). The organic solvent, required for the dissolution of the catalyst, also significantly influences the gelation time. The best gelation behavior was obtained with the organic solvents tetrahydrofuran and methanol, while an usage of ethanol and isopropanol resulted in very soft gels. In addition, gelation experiments were performed with different crosslinker to IL ratios (1.5, 1.7, 2.0, 2.5 and 3.0%). With an increasing cross-linker amount, the amount of free space for the catalyst decreases and more rigid gels are formed.



	catalyst	R^1	R^2	R^3
(9b)	HBzCPN	Bz	H	Ethyl
(9c)	BzCPN	Bz	H	Vinyl
(9j)	HBzQN	Bz	CH_3	Ethyl
(9k)	HQN	H	CH_3	Ethyl
(9l)	$(DHQ)_2AQN$	AQN	CH_3	Ethyl
(9m)	$(DHQ)_2Pyr$	Pyr	CH_3	Ethyl

Figure 11. Preparation of PIL-supported quinine-based organocatalysts; Radical polymerization of an imidazolium-based ionic liquid bearing a vinyl group, [VEtIm][Br] – 1-vinyl-3-ethylimidazolium bromide, and cross-linker *N,N'*-methylenebisacrylamide (Bis). APS– Ammonium peroxydisulphate, TEMED– *N,N,N',N'*-Tetramethylethane-1,2-diamine, AQN– anthraquinone-1,4-diyl diether, Pyr– 2,5-diphenyl-4,6-pyrimidinediyl diether.

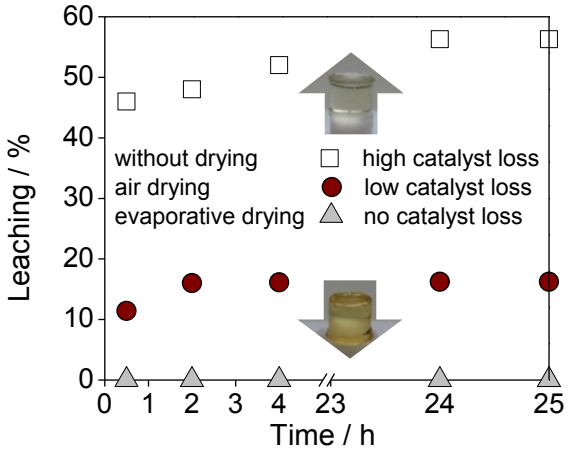


- 2 µm **- 10 µm**

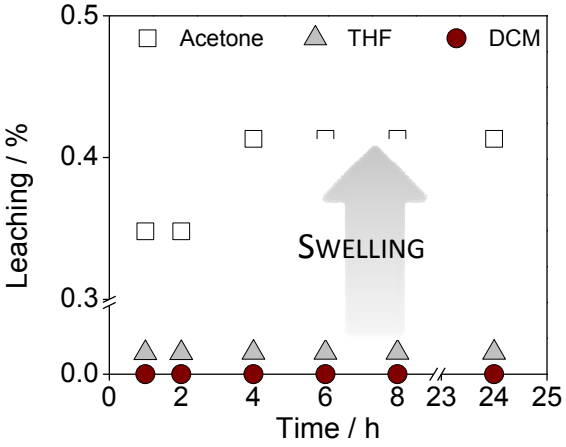
Figure 12. SEM images of crystalline catalyst **9b** on the surface (left) and inside (right) of the gel matrix VEImBr. (Cond. 10 mg catalyst **9b** in 300 µL THF, 11 µL H_2O, 0.3 g VEImBr, 353 µL BisA, 30 µL APS, 6 µL TEMED, evaporative drying).

Leaching behavior and catalyst activity

In order to be an economically viable process, complete recovery of the organocatalyst and an almost pure product without catalyst contamination is required. For this reason, leaching behavior with different drying methods, catalyst structures, water content, and solvents were investigated. The usage of fresh hydrogels resulted in a strong leaching effect of 56.3% in tetrahydrofuran (Figure 13a). By comparison, for less leaching and higher hydrogel stability, gels were dried in air and under evaporative conditions. During this procedure, shrinking of the polymeric structure occurred due to high water loss of up to 90%, but this was less pronounced than with other hydrogels such as polyacrylamide.[113a] This effectively reduced leaching to 16.2% (air-dried hydrogels) and 0.03% (evaporative procedure, 10^{-3} mbar), which represent a significant reduction. Different leaching behavior was observed with various solvents, as shown in Figure 13b; THF and dichloromethane led to shrinking and acetone led to strong swelling of the applied gels, and therefore to an increased leaching behavior (0.4% for acetone). In addition, an increase of polarity of the respective catalyst (HQN < HBzCPN < HBzQN < $(DHQ)_2$AQN < $(DHQ)_2$Pyr) also leads to an increase of leaching from 0.03 to 4.25%. In Figure 13d, the dependency on leaching behavior with different IL to crosslinker ratio is shown. As expected, with increasing crosslinker amounts the leaching of the catalyst also increases. Clearly, the stability of the hydrogel decreases with decreasing crosslinker amounts, so crosslinker amounts of 1.7 – 2.0% are preferred. In summary, further experiments were carried out with evaporative dried hydrogels and the use of solvents in which shrinking of the hydrogel occurred, catalysts with lower polarity but high enantioselectivity and crosslinker amounts of 2.0% due to the low leaching behavior.
The evaporative dried hydrogel-encapsulated catalyst **9e** (2.5 mol%) were used for the recycling experiments on the example of the HENRY reaction (**Publication IV**, Table 3). The first catalytic cycle led to a HENRY product with a yield of 62% and good enantiomeric excess of 88%, and no leaching of the catalyst was observed.

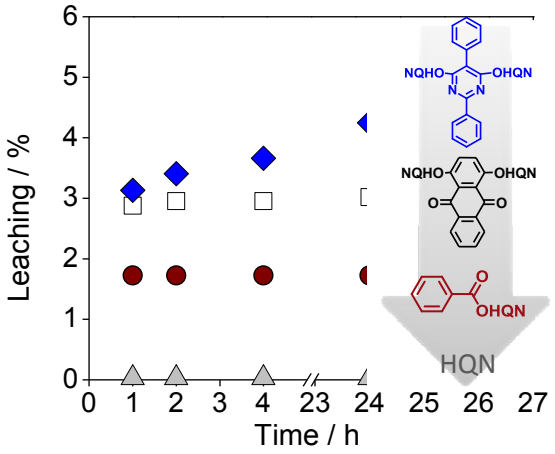


a) Leaching behavior for fresh, air dried and evaporative dried hydrogels.
Cond:. 10 mg HQN in 300 µL THF, 119 µL H_2O, 0.3 g VEIMBr, 245 µL BisA, 30 µL APS, 6 µL TEMED. Leaching in 5 mL THF.



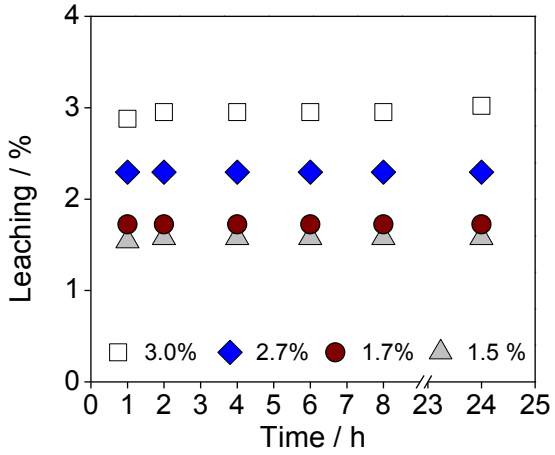
b) Leaching behavior for HQN in different solvents.

Cond:. 10 mg HQN in 300 µL THF, 119 µL H_2O, 0.3 g VEIMBr, 245 µL BisA, 30 µL APS, 6 µL TEMED. Evaporative drying. Leaching in 5 mL solvent.



c) Leaching behavior with different quinine-based organocatalysts.

Cond:. 10 mg catalyst in 300 µL THF, 119 µL H_2O, 0.3 g VEIMBr, 245 µL BisA, 30 µL APS, 6 µL TEMED. Evaporative drying. Leaching in 5 mL THF.



c) Leaching behavior with different crosslinker to IL ratio.

Cond:. 10 mg $(DHQ)_2AQN$ in 300 µL THF, x µL H_2O, 0.3 g VEIMBr, y µL BisA, 30 µL APS, 6 µL TEMED. Air drying. Leaching in 5 mL THF.

Figure 13. Leaching behavior of organocatalysts under different conditions.

As the catalyst is completely retained in the hydrogel, downstream processing of the product is simplified to a large extent. Simple evaporation of the solvent and remaining reactants leads to an almost pure product, with more than 98% purity. The catalyst was reused for four cycles without loss of enantioselectivity, although a significant decrease of reaction yield was noted in the third cycle (15%). Investigations showed that the decreasing yield is caused by partial adsorption of the product inside the polymer structure. Full recovery was facilitated by an additional extraction step with isopropanol, leading to an isolated yield of 76%. Remarkably, no catalyst leaching was observed during this extraction step. In conclusion, reuse of the catalyst will reduce its costs contribution to the overall product costs in the long run, together with savings during the downstream processing.

Critical Perspective

Reduced catalytic efficiency due to mass transport limitations is a typical problem in the field of catalyst immobilization. In this study, a significant decrease of reaction yield was noted in the third reaction cycle. Figure 14 depicts the effect of the reaction rate with different surface area to volume ratios of the applied hydrogel. As expected, in comparison to the homogeneously soluble catalyst, a reduced reaction rate was found for all immobilized catalysts. However, a good correlation between surface area and the ratio of the reaction rates was observed. With increasing surface area to volume ratio, the reaction rate increases. These primary experiments show that the immobilization matrix and procedure itself have an influence on the performance of the reaction. In particular, for immobilized catalysts, mass-transport limitations can easily be overcome by reaction engineering. Future work can concentrate for example on thin films or small particles of this hydrogel by performing the reaction in a *SpinChem* reactor.[115]

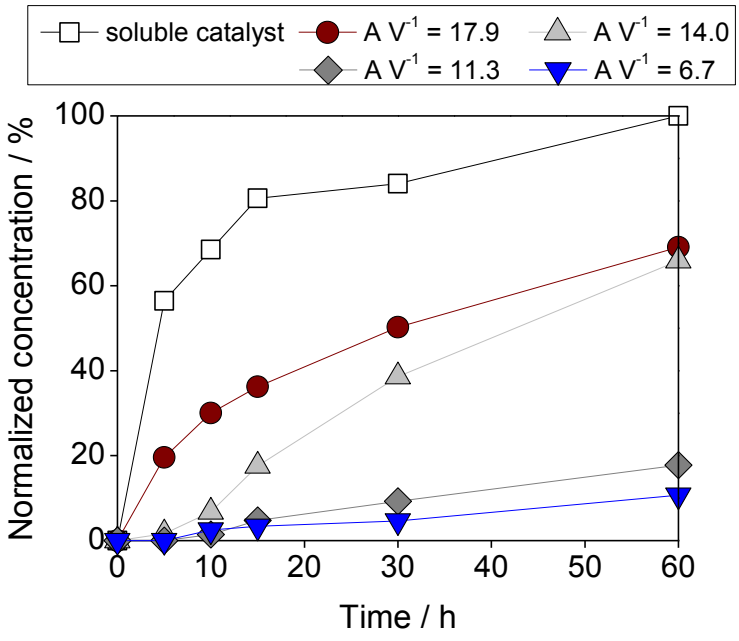


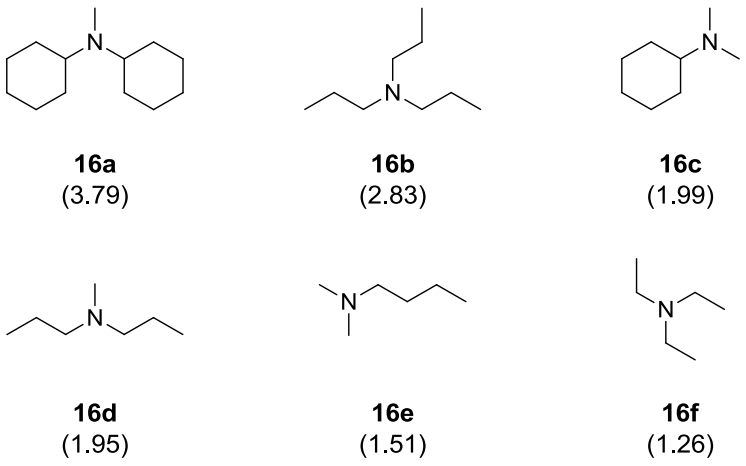
Figure 14. Correlation of apparent reactivity and surface to volume ratio of the applied hydrogels. Reaction conditions: 1 M ethyl pyruvate, 10 eq. of nitromethane, 2.5 mol% 9c in PILs with different surface areas, 1 h, 23 °C.

3.5. Switchable-Hydrophilicity Solvents for Product Isolation

Homogeneous catalysts offer many advantages, including high activity and selectivity, but they present problems at the separation stage of a process. Separation processes play a remarkable role in the chemical and pharmaceutical industries, where they account for 40-70% of operating costs. Multiphase systems present an effective solution for these problems, especially thermomorphic solvent systems (TMS),[116] fluorous biphasic systems (FBS),[5, 117] CO_2-based organic-aqueous tunable systems (OATS),[118] and microemulsions with nonionic surfactants (MLS)[116b, 119]. This chapter will illustrate switchable-hydrophilicity solvents (SHSs) as a novel approach for product isolation and separation in the field of organocatalysis.

Switchable-Hydrophilicity Solvents

SHSs are solvents which can switch reversibly between a water-miscible state to a state that forms a biphasic mixture with water.[120] The one form, which has a high miscibility with water in the presence of CO_2, is hydrophilic, and the other form, which has a low miscibility with water in the absence of CO_2 is hydrophobic. CO_2 is preferred as a trigger due to its non-toxicity, low price and easy removal. JESSOP and coworkers identified that amidine/CO_2, guanidine/CO_2, and tertiary amine/CO_2 can be used as SHSs.[121] These solvents have been studied for applications such as the extraction of lipids and hydrocarbons from microalgae,[122] the extraction of soybean oil from soybean flakes,[121b] and the extraction of hemicellulose from spruce.[123] In this study, tertiary amine SHSs are used because they are commercially available or very easy to synthesize, and also stable under the investigated conditions. The compounds which were used and previously identified as SHSs are shown in Scheme 9.



Scheme 9. The amines used in this study. The number in brackets is the predicted log K_{ow}, while the number in bold font is the compound number.

The change in phase behavior is caused by the reaction of CO_2 and water with the SHS yielding the water-soluble bicarbonate salt of the protonated SHS (Eqn 5).

$$NR_3 + CO_2 + H_2O \leftrightarrows [NR_3H^+][HCO_3^-] \quad (5)$$

Objective of this project

During a research stay as part of the research group of Prof. JESSOP at the Queen's University in Canada, the combination of organocatalysis and switchable solvent systems was investigated. The motivation was to perform the reaction in a monophasic solvent and thereby maintain the advantages of homogeneous catalysis, even through product separation is easily performed by a biphasic system. So far, this concept was restricted to the recycling of metal-based homogeneous catalysts.[124] In this study, using the enantioselective HENRY reaction catalyzed by cinchona alkaloids, switchable amine-based solvents were screened and the potential for organocatalytic reactions evaluated. This combination shows some difficulties so far. First, the reaction performed with racemate-forming substances such as amine or water yielded a low enantiomeric excess. Secondly, the measured solubilities for catalyst and product in different solvents are very similar and a separation seems to be very difficult. Third, temperatures up to 50 °C are usually required to obtain a biphasic system by expelling CO_2. As shown in Chapter 3.1., high temperatures led to the product in its racemic form. How these three challenges have been solved is described in **publication V**.

SHS as an extraction media

For the extraction of the postreaction mixture the SHSs are used in their monophasic and hydrophilic forms. To obtain a monophase of the bicarbonate salts in carbonated water by the addition of CO_2 depends on various parameters such as amine/water ratio, sample size, and the method of addition of CO_2. These parameters were previously experimentally tested and theoretically calculated for the requisite amines **16a-f** by Prof. JESSOP and coworkers.[120, 125] With all chosen amines, a single phase was obtained but with a different water amount and required time (**publication V**, Table 2). With increasing hydrophobicity of the amine, more water is needed, and the time for CO_2 addition also increases simultaneously. The water-soluble bicarbonate salt of the protonated SHS (the hydrophilic monophasic form) was tested as an extraction solvent for the postreaction mixture (catalyst **9c**, HENRY product **8**, and ethyl acetate as the reaction media). The intention was to use the carbonated water/amine mixture to extract the hydrophilic **8** (log K_{OW} = -0.05) and the hydrophobic **9c** (log K_{OW} = 4.69) remains in the reaction solvent. In comparison, with pure water or pure amine **16** as extraction solvent, neither the product nor the catalyst is selectively extracted from the postreaction mixture. The ability of carbonated water/amine mixtures to extract the product or catalyst from the postreaction mixture is shown in publication V. Generally, many factors, such as hydrophobicity of the amine, polarity, water/amine ratio, and ionic strength influence the extraction efficiency. With increasing hydrophobicity of the amine, the extraction efficiency for the catalyst increases and for the product decreases. With the most hydrophobic amine **16a** the catalyst was fully extracted, while only 15% product was obtained. The pH value of the carbonated water/amine could also influence the extraction behavior. The best extraction efficiency for **9c** was observed when the pH value was low and therefore the protonation of the catalyst was high. The lower pH value in the carbonated water/amine mixture could help the catalyst to be extracted into the

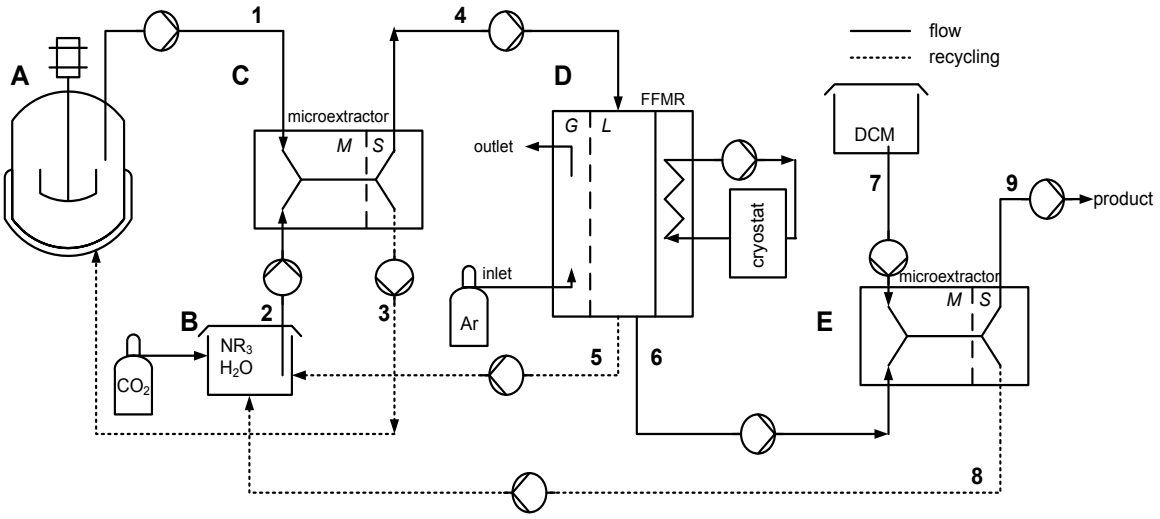
SHS/carbonated water phase because the protonated catalyst would be more hydrophilic than the neutral catalyst. This effect is also shown for cinchona alkaloids as phase-transfer catalysts. However, **16a** was rejected due to the difficulties in isolating the catalyst from the SHS amine. The best result was obtained with a carbonated water/amine **16e** mixture with a ratio of 1:1; no extraction of catalyst **9c** into the SHS phase was observed, and 78% of product **8** was extracted. If some of the product remained in the ethyl acetate phase, this would not be considered a significant problem since the ethyl acetate phase can be reused, and the residual product would be extracted in the next cycle. Therefore, further study continued exclusively with compound **16e**.

Optimization by microstructured devices

Microreaction technologies offer many advantages, such as high heat and mass transfer rates, shorter mixing times, the ability to work under aggressive conditions, and small liquid hold-ups.[126] A microextractor (see also appendix) was used for a faster product extraction due to optimize mass-transfer via larger surface-to-volume ratios. The extraction of the product from the ethyl acetate phase into the SHS amine/water mixture takes place within the microstructures of the microextractor. After mixing, the ethyl acetate phase and the carbonated amine/water phase are separated in the integrated settler. Product **8** was extracted with 86% yield, and no catalyst leaching into the SHS amine carbonated phase was observed. Remarkably, with this technique, the SHS extraction solvent consumption was minimized by 20% for a 10 mL postreaction mixture. Furthermore, product **8** was isolated with a high enantiomeric excess of >89% by using the microextractor due to the fast extraction time (only five minutes).

After the effective extraction and recycling of the catalyst, the carbonated amine-water solution must be separated into two phases by expelling CO_2. Previous work has shown that CO_2 removal can be difficult and time-consuming, depending upon the applied methods.[120] In this study, a continuous bubble-free operating falling-film microextractor (FFMR) was used to optimize the removal of CO_2 in comparison to conventional methods.[127] In publication V, the FFMR (see appendix) was compared, with regards to the conversion time, mass loss and racemization of the product, with classical heating, bubbling an inert gas through the solution with a gas dispersion tube, and sonication with a sonicator or sonication bath (**publication V**, Table 3). After complete conversion, the formed enantiomer easily (89% *ee*) racemizes when heating or a sonicator is applied for CO_2 removal. Furthermore, with this method a high mass loss of up to 53% was observed, due to volatility of the amine. In addition, with a gas dispersion tube and a sonication bath, no separation into two phases was observed after four hours. Very short exchange times at ambient temperatures in the FFMR was obtained with microstructured devices, while the racemization reaction was effectively suppressed. With this method, the conversion time to obtain a phase separation was decreased from four hours down to 15 minutes. A mass loss of only 9% for the carbonated amine/water mixture and a good enantiomeric excess of 89% was obtained. The CO_2-removal to obtain a phase split was optimized by application of a FFMR. With this very efficient technique, racemate-forming substances such as amine and water can also be used for downstream processing.

Catalyst Recycling and Product Isolation



Scheme 10. Schematic setup used for organocatalyst recycling and product isolation. A – Reaction performed in a reaction vessel; B – Preparation of SHS as extraction solvent (protonation of **16e** by carbonic acid resulted into water-soluble bicarbonate salts); C – Extraction of product **8** facilitated by a microextractor with integrated settler; D – Removing CO_2 by using an FFMR; E – Extraction of **8** facilitated by a microextractor with integrated settler; 1 – Postreaction stream containing **9c**, **8** and ethyl acetate; 2 – protonated hydrophilic SHS stream containing **16e**, H_2O and CO_2; 3 – Recycling of **9c** in ethyl acetate; 4 – SHS stream enriched with **8**; 5 – Recycling of **16e**; 6 – Aqueous stream enriched with **8**; 7 - Dichloromethane as extraction solvent; 8 – Recycling the aqueous phase; 9 – **8** in dichloromethane. *M* – micromixer; *S* – settler; *G* – gas; *L* – liquid.

Scheme 10 shows the setup used for the catalyst and product separation experiments from the postreaction mixture. The reaction was carried out in a batchwise fashion. The reaction was repeated four times, and the results for each cycle are summarized in **publication V**, Table 4. In all of the batches, outstanding yields of up to 99% were achieved. Moreover, excellent enantiomeric excess of 91% was obtained in all cycles. In all of these cycles, the catalyst was fully active after extraction with SHS and could be reused several times. In addition, with the use of microstructure devices, the ability to work with typically racemate-forming substances such as amine and water has been demonstrated. The extraction efficiencies are in agreement with the screening results. After all downstream process steps, the product was isolated with a yield of up to 73% and a high purity of 98% (89% *ee*) after evaporation under reduced pressure. Furthermore, the isolation of the product and the catalyst removal using this technique could be completed in a reasonable amount of time. It is an economically viable process, because all substances (such as catalyst, amine and water), were recovered and reused. After the final downstream process step, 87% of the amine and 93% of the water were recovered. In conclusion, the combination of SHSs with microstructured devices is introduced as an eco-friendly and sustainable alternative to existing methods for product and catalyst separation as well as catalyst recycling in organocatalysis.

Critical perspective

In this case study, amines and water were used which affect negatively the enantioselectivity of the used HENRY reaction. Here, we compensated this disadvantage by using microstructured devices. Nevertheless, future work can concentrate on novel switchable solvent systems where switchable quinine-based organocatalysts will be used (Figure 15). The idea is to perform the reaction in a suitable organic solvent (*n*-heptane, diethyl ether, dichloromethane, etc.) so that the advantage of homogeneous reaction conditions are maintained. After complete reaction, an aqueous solution is added, so that a two-phase system is formed. By CO_2 addition the catalyst is transferred into the aqueous phase because of the higher affinity for the aqueous phase since its protonation at the nitrogen atom. After phase separation, the product is isolated from the organic phase. Fresh solvent is added and the catalyst is transferred to the organic phase by CO_2 removal. Due to the CO_2 induced switching, the catalyst can be selectively "activated" and "deactivated/immobilized".

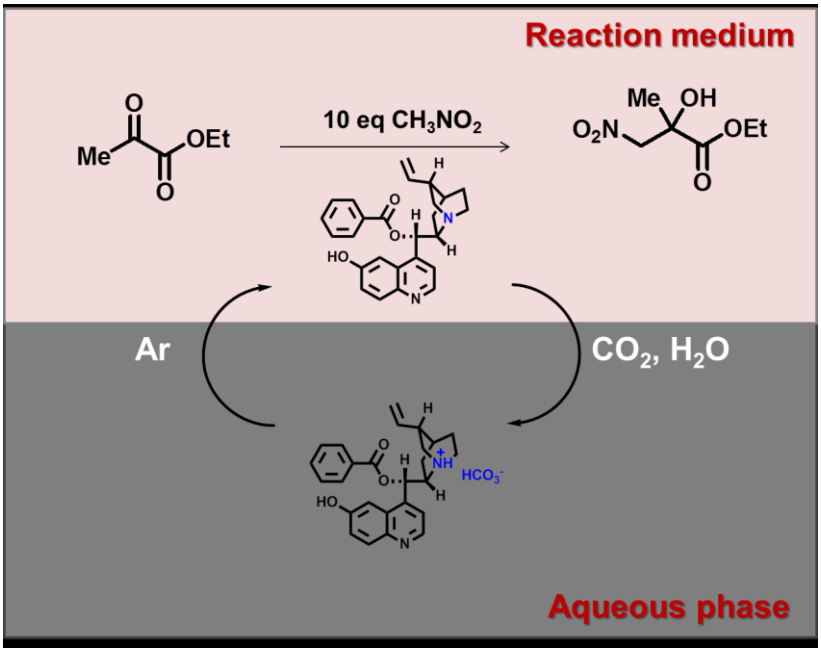


Figure 15. Switchable quinine-based organocatalyst by addition/removal of CO_2.

3.6. Discussion and Outlook

In the previous chapters three innovative approaches for the catalyst and product separation and the catalyst recycling are described. In this chapter, these methods will be compared and evaluated using an analysis of their strengths, weaknesses, opportunities, and threats (SWOT).

To judge the potential for the first approach — OSN — and to identify areas where further research is needed, a SWOT analysis is given in Figure 16. The greatest opportunity is to perform the reaction at very high catalysts loading. This will lead to increased productivity, while decoupling the residence time of catalyst and reactants will reduce the product specific catalyst consumption at the same time. In addition, with the development of novel organic solvent resistant membranes the coupling of the catalyst on supports such as polymers or dendrimers is no longer required, in comparison with attempts published more than a decade ago. Another great advantage, especially for industrial applications, is the eco-friendly lower energy consumption in comparison with conventional methods such as distillation or crystallization. In addition, this process can be easily integrated into existing processes and a scale-up can be easily carried out. However, the largest threat is the limited availability of membranes which are stable against harsh solvents such as chlorinated solvents and reactive reagents. Furthermore, the occasionally low reproducibility and membrane stability could cause problems for a wide applicability. Future work may overcome these problems with ceramic membranes or polymeric mixed membranes, which could offer much lower MWCOs and better-defined ranges.

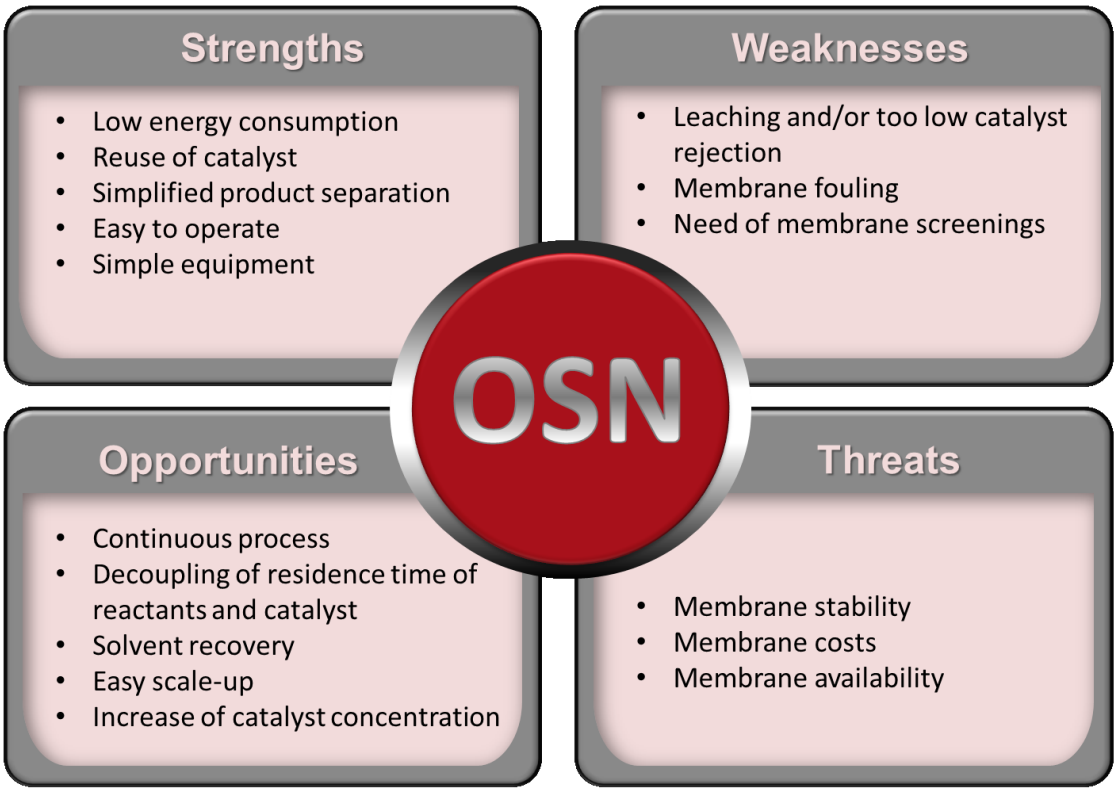


Figure 16. SWOT-Analysis for OSN.

For further applications in the field of homogeneous catalysis, the catalyst can be improved by simple derivatization to increase the rejection. With this simple method, the leaching of the catalyst can be decreased and the product obtained in very high purity. OSN has shown tremendous advantages within downstream processing and catalyst recycling and proved its significance within the chemist's toolbox.

The second approach — PILs-supported organocatalysts (SWOT analysis in Figure 17) — shows a novel strategy for the embedding of organocatalysts. The great advantages of these materials are the high mechanical and chemical stability in common solvents, which may allow novel reactor concepts with integrated product separation as well as other novel applications. For a scale-up, small hydrogel particles can be used in a fixed-bed reactor or as a thin film in a continuously operated plug-flow reactor. With this concept, mass-transport limitations can be overcome by reaction engineering. This will allow to make use of different concentration-time and concentration-place behaviors of the batch-reactor or continuously operated plug-flow reactor or stirred-tank reactor. The disadvantage of high catalyst leaching in the field of immobilization can be overcome with this unique method by controlling the water content. The immobilization process allows for the use of low amounts of the catalyst (2.5 mol%) because the active molecules are better distributed in the supporting polymer material. However, the catalyst may have no "free" double bond (such as a vinyl group), which would limit the wide range of the applications. In this study, a reaction was chosen where small amounts of water would negatively affect the catalyst activity. Therefore, a complete removal of water by different drying methods was required. For future work, the potential of these methods can perhaps be better shown in other organocatalyzed reactions, ones where water does not interfere with the catalyst's activity. In addition, the decrease of yield by adsorption of product in the polymer structure has to be overcome with a reaction solvent in which the reaction can be carried out with high selectivity, so that there is no leaching of the catalyst but high leaching of the product. With such a solvent, an additional washing step may be avoided.

The combination of organocatalysis and SHSs as the third approach (SWOT analysis in Figure 18) was the greatest challenge in this study due to the use of amines, water, and high temperatures for the enantioselective HENRY reaction. This problem was successfully overcome by using microreaction technology, in which a series of tertiary amine SHSs were identified for extraction of the hydrophilic product from the postreaction mixture. This concept can be adapted to other reactions with the wide range of tertiary amine SHSs, but must be fine-tuned to catalysts and products with different hydrophobicities. Nevertheless, this concept has been introduced as an eco-friendly and sustainable alternative to existing methods for product and catalyst separation in organocatalysis. The disadvantage of high catalyst loading required for organocatalytic reactions was compensated by decoupling the residence time of the reactants and catalysts. For future work, this concept can be applied to other reactants, as well as to switch the organocatalyst bearing a tertiary amine by introducing and removing CO_2 for an easy separation process.

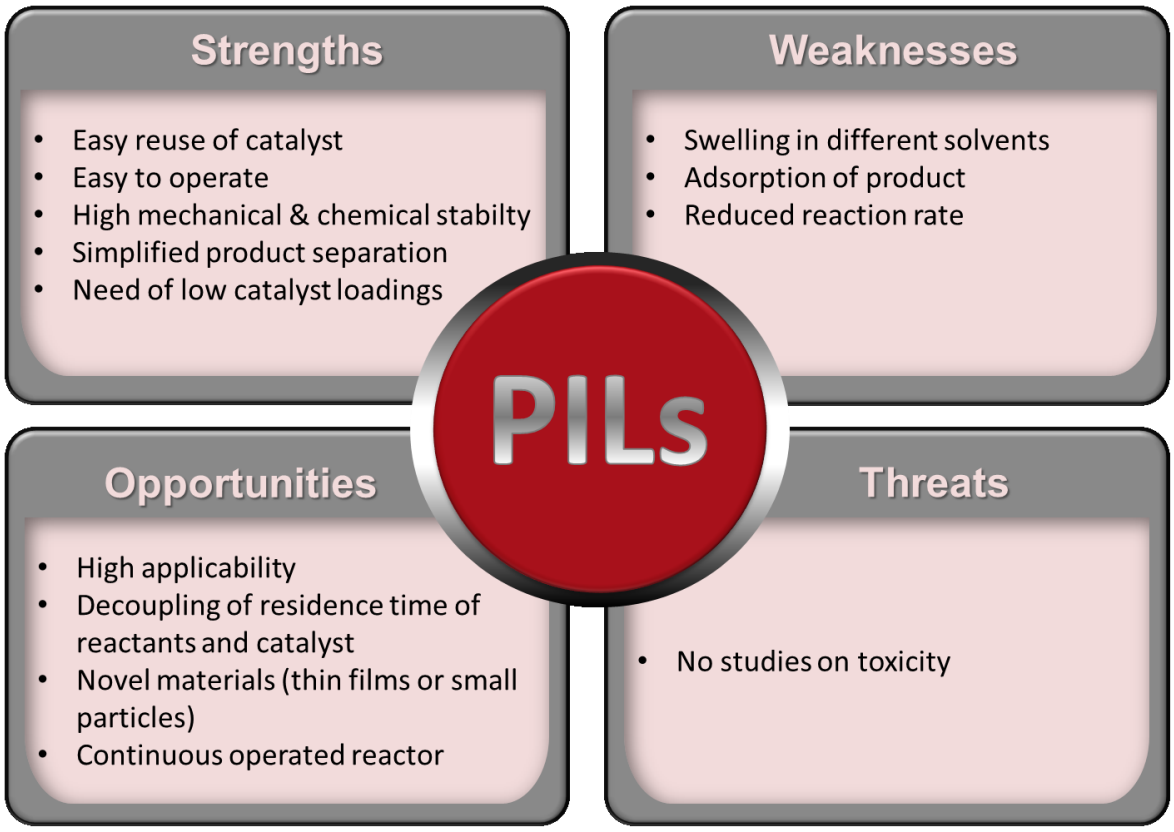


Figure 17. SWOT-Analysis for PILs-supported organocatalysts.

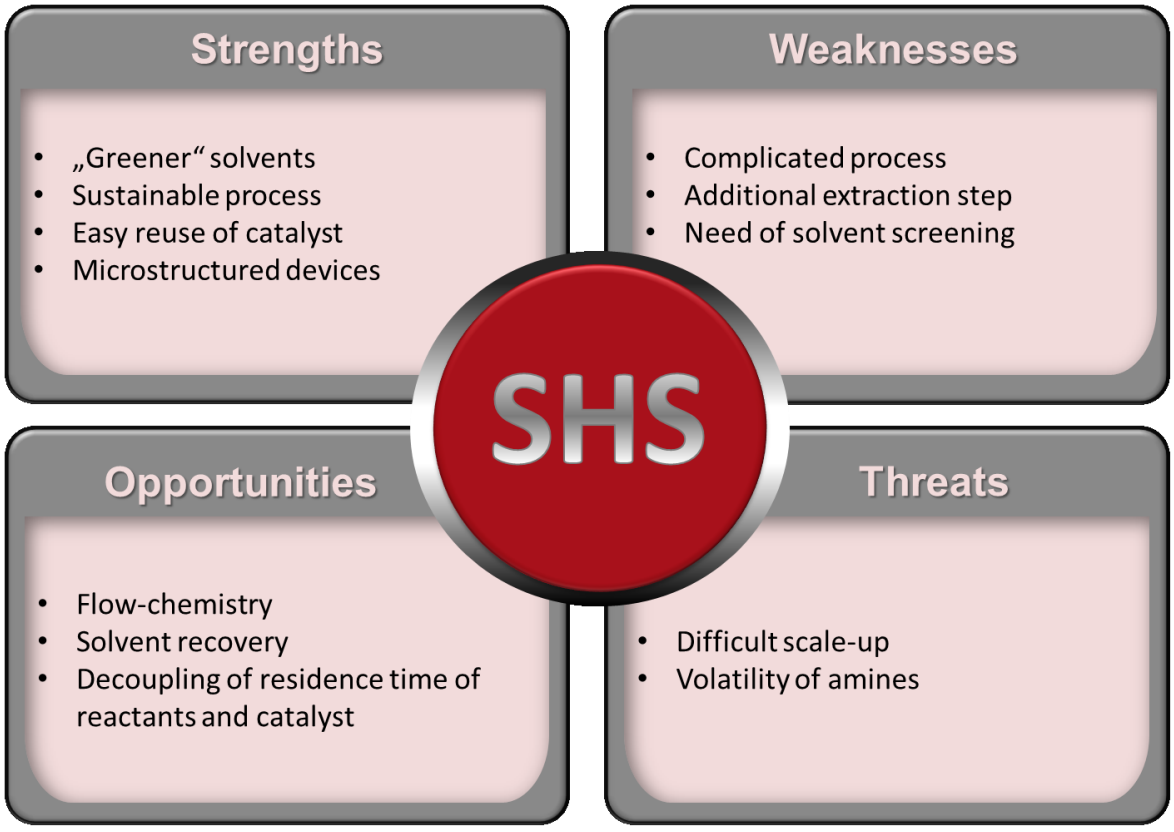


Figure 18. SWOT-Analysis for SHS.

In comparison (Table 5), OSN seems to be the most promising approach for an application on a large scale, at least when the solvent THF is replaced by a "greener" solvent such as ethyl acetate. An additional membrane stage for solvent recovery would be necessary for a sustainable process. PILs show the most advantages, such as low solvent consumption, simple equipment, and low time consumption for an industrial process. The use of SHS is shown as an effective separation method due to the high TON of 156, the use of green solvents, and the high catalyst activity over four cycles. Nevertheless, the large number of stages in the downstream process for product isolation, the difficulties in the transferability to other reactions, and the high equipment requirements make this process currently only of interest for academic research.

In conclusion, all approaches for catalyst recovery described here, as well as the use of "greener" solvents, along with continuous flow and microreactor techniques, are already contributing to make organocatalytic processes more sustainable.

Table 5. Comparison of the three approaches for catalyst and product separation.

	OSN	PILs	SHS
Catalyst loading / mol%	10	2.5	2.5
Substrate amount / mmol	25	10	10
Enantioselectivity / %	89	88	91
Yield / %	81	62	99
Recycling Number	4	4	4
TON	27	58	156
Reaction Solvent	THF	THF	EtOAc
Solvent Consumption	High	Low	Moderate
Time consumption	Moderate	Low	Moderate
Equipment effort	Moderate	Low	High
Transfer to other reactions	Easy	Moderate	Difficult

4. Summary

Within this PhD study, three innovative approaches for product and catalyst separation were investigated in the field of organocatalysis. With publication I and II, organic solvent nanofiltration was shown as a versatile tool for mild and energy-saving downstream processing. In this method, the catalyst was recycled up to four times without a significant loss of activity and the product was isolated in high purity. Furthermore, excellent retentions of up to 0.99 for the organocatalyst in the recycling experiments were obtained. The enantioselective HENRY reaction and the atom-economic conversion of butylene oxide with carbon dioxide were used to demonstrate the high potential of this technique. In addition, this technique was used for the purification of three highly enantioselective quinine-based organocatalysts as an efficient alternative to column chromatography (publication III). These catalysts are obtained in high purity of over 99% after 10 discontinuous diafiltration steps.

The second approach was introduced as a novel strategy for the embedding of quinine-based organocatalysts in polymerized ionic liquids-based hydrogels (publication IV). With this technique, the encapsulated organocatalyst was successfully recovered and reused for four cycles without any loss of enantioselectivity. Furthermore, the high catalyst leaching was significantly reduced by controlling the water content. The downstream processing was simplified to a large extent and the product was obtained in high purity without any further purification steps.

Switchable-hydrophilicity solvents have been studied as the third approach for product/catalyst separation as well as catalyst recycling (publication V). With this method, the product was isolated with high extraction efficiencies (>84%) and low extraction rates for the catalyst (<0.1%) in high purity (>98%). At the same time, the catalyst was reused without any loss of activity (>91% *ee*, >99% yield) four times. Furthermore, the extraction efficiency was optimized by working with a microextractor, and with the use of a falling-film microreactor, the product was obtained with high enantioselectivity in a reasonable amount of time.

5. Publications

		Contribution
I	Fahrenwaldt, T.; Großeheilmann, J.; Erben, F.; Kragl, U., Organic Solvent Nanofiltration as a Tool for Separation of Quinine-Based Organocatalysts. *Organic Process Research & Development* **2013**, *17* (9), 1131-1136.	Full Paper **40%**
II	Großeheilmann, J.; Büttner, H.; Kohrt, C.; Kragl, U.; Werner, T., Recycling of Phosphorus-Based Organocatalysts by Organic Solvent Nanofiltration. *ACS Sustainable Chemistry & Engineering* **2015**, *3* (11), 2817-2822.	Full paper **50%**
III	Großeheilmann, J.; Fahrenwaldt, T.; Kragl, U., Organic Solvent Nanofiltration-Supported Purification of Organocatalysts. *ChemCatChem* **2016**, *8*, 322-325.	Communication **80%**
IV	Großeheilmann, J.; Bandomir, J.; Kragl, U., Preparation of Poly (ionic liquid) s-supported Recyclable Organocatalysts for the Asymmetric Nitroaldol (HENRY) Reaction. *Chemistry–A European Journal* **2015**, *21*, 18957-18960.	Communication **80%**
V	Großeheilmann J., Vanderveen R. J., Jessop G.P., Kragl U. Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis. *ChemSusChem* **2016**, DOI: 10.1002/cssc.201501654	Full paper **60%**

Publication I

Full paper *Org. Process Res. Dev.*, **2013**, *17*, 1131-1136.

Organic Solvent Nanofiltration as a Tool for Separation of Quinine-Based Organocatalysts

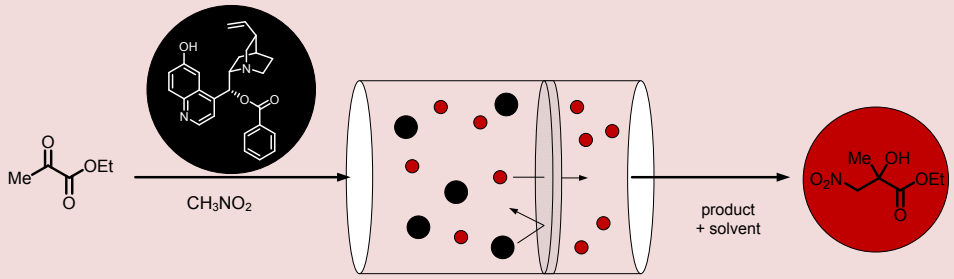
Dr. Thomas Fahrenwaldt (40%), Julia Großeheilmann (40%), Dr. Friedrich Erben (10%) and Prof. Dr. Udo Kragl (10%)*

Received 11th February 2013, Accepted 21th August 2013

DOI: 10.1021/op400037h

Table of contents

Modern nanofiltration membranes offer the possibility to separate organocatalysts from reaction mixtures with high retention rates. The enantioselective Henry reaction of ethyl pyruvate and nitromethane catalysed by benzoyl cupreine was used to demonstrate the potential of this technique for preparative use.



My main **contribution** to this work (**40%**):

I performed all screening tests during my diploma thesis. In the beginning of my PhD thesis I carried out the recycling experiments. Thomas Fahrenwaldt and Prof. Dr. Udo Kragl had the initial idea and T. Fahrenwaldt has written the main part of the manuscript. Prof. Dr. Udo Kragl revised the manuscript through final corrections.

Publication II

Full paper *ACS Sustainable Chem. Eng.*, **2015**, *3(11)*, 2817-2822.

Recycling of Phosphorus-Based Organocatalysts by Organic Solvent Nanofiltration

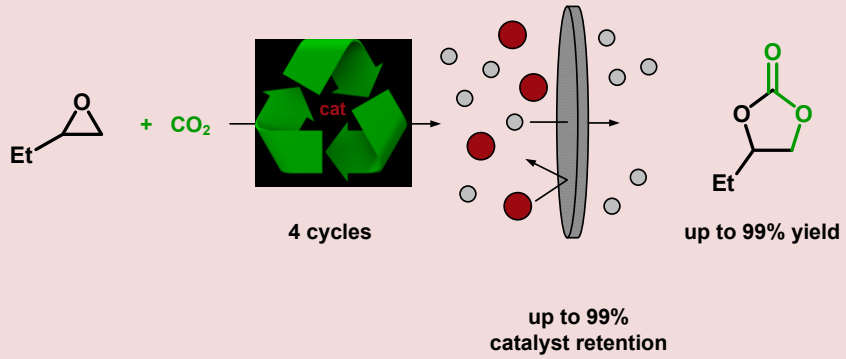
Julia Großeheilmann (50%), Hendrik Büttner (15%), Dr. Christina Kohrt (15%), Prof. Dr. Udo Kragl* (10%) and Dr. Thomas Werner* (10%)

Received 22 July 2015, Published 20 September 2015

DOI: 10.1021/acssuschemeng.5b00734

Table of contents

Organic Solvent Nanofiltration (OSN) proved to be a sustainable method for separation and recycling of bifunctional phosphonium salts. The atom-economic conversion of butylene oxide with carbon dioxide has been chosen as a test reaction, yielding the desired cyclic carbonate in excellent yields under mild conditions.



Contribution (50%):

In the context of a joint project (P-Campus) between Leibniz Institute for Catalysis and the University of Rostock all experiments were performed in cooperation by H. Büttner and myself. My contribution to this work: screening experiments (choice of membrane, catalyst and filtration cell); recycling experiments, writing the majority of the manuscript. Dr. T. Werner and Prof. Dr. U. Kragl had the initial idea for this cooperation and clarified the text by critical considerations.

Publication III

Communication *ChemCatChem*, **2016**, *8*, 322-325.

Organic Solvent Nanofiltration-Supported Purification of Organocatalysts

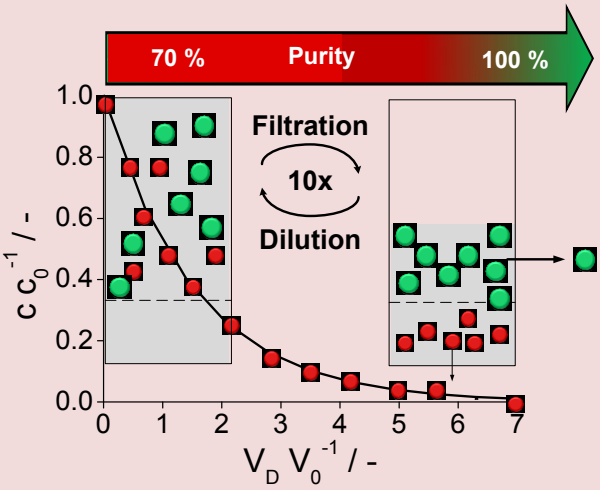
Julia Großeheilmann (80%), Dr. Thomas Fahrenwaldt (10%) and Prof. Dr. Udo Kragl* (10%)

Received 12 August 2015, Accepted 12 November 2015

DOI: 10.1002/cctc.201500902

Table of contents

Pure and simple: Organic Solvent Nanofiltration proves to be an efficient alternative to column chromatography for the purification of quinine-based organocatalysts. These catalysts are obtained in a high purity of >99% after 10 discontinuous diafiltration steps at a gram scale.



Contribution (80%):

I've written the manuscript and performed all experiments during the end of my diploma thesis and the beginning of my PhD work. Dr. T. Fahrenwaldt supervised the first experiments during my diploma thesis. Prof. Dr. U. Kragl revised the manuscript through final corrections.

Publication IV

Communication *Chem. Eur. J.,* **2015**, *21*, 18957-18960.

Preparation of Poly(ionic liquid)s-Supported Recyclable Organocatalysts for the Asymmetric Nitroaldol (Henry) Reaction

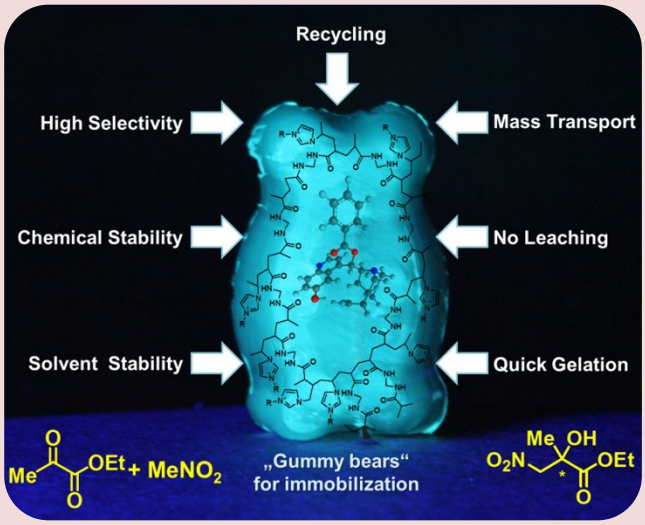
Julia Großeheilmann (80%), Dr. Jenny Bandomir (10%) and Prof. Dr. Udo Kragl* (10%)

Received 26 October 2015, Accepted 03 November 2015

DOI: 10.1002/chem.201504290

Table of contents

"Gummy bear"-like hydrogels for the immobilization of organocatalysts. With a novel strategy for the embedding of benzoylcupreine in a polymerized ionic liquids-based hydrogel, the catalyst was recovered for four times after the Henry reaction without loss of enantioselectivity (up to 91% *ee*). High catalyst leaching was significantly reduced (<0.01%) by controlling the water content.



Contribution (80%):

The idea for the combination of organocatalysis with poly(ionic liquid)s was created by Dr. J. Bandomir and myself. I performed all experiments. In the writing process we contributed unequally to this manuscript (20% by Dr. J. Bandomir and 80% by myself). At the end Prof. Dr. Udo Kragl helped to focus the main idea of catalyst removal.

Publication V

Full paper *ChemSusChem,* **2016**, *9*, 696-702 (VIP-paper).

Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis

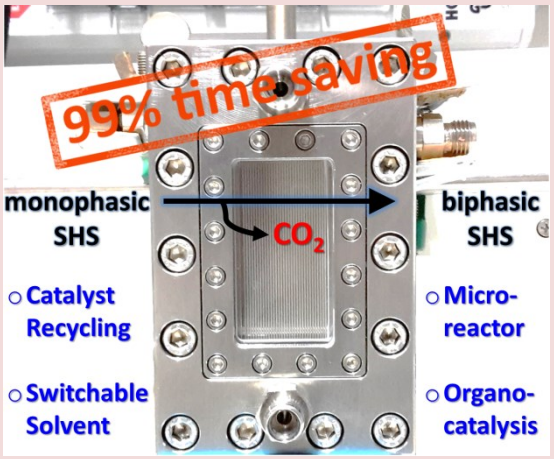
Julia Großeheilmann (60%), Jesse R. Vanderveen (20%), Prof. Dr. Philip G. Jessop (10%) and Prof. Dr. Udo Kragl* (10%)

Received 16 December 2015, Accepted 09 February 2016

DOI: 10.1002/cssc.201501654

Table of contents:

Switchable-Hydrophilicity Solvents was used as a sustainable method for product isolation (>84% yield, 98% purity) and catalyst recycling (>91% ee for four cycles). The downstream processing was simplified to a large extent by using a microextractor and a falling-film microreactor.



Contribution (60%):

During my research stay in Jessop's working group we combined organocatalysis with switchable solvent systems for catalyst removal. J.R. Vanderveen and I performed some screening experiments to identify the best system. In addition, I performed the recycling experiments with the micro technology and I have written the manuscript. At the end Prof. Dr. U. Kragl and Prof. Dr. P. G. Jessop revised the manuscript through final corrections.

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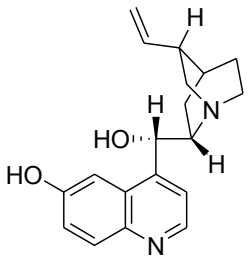
Appendix

A1 Synthesis Procedure for Organocatalysts

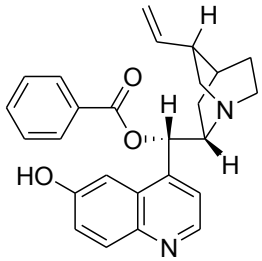
General. Moisture-sensitive catalyst syntheses were carried out under standard Schlenk conditions. All chemicals and starting materials were obtained from Sigma-Aldrich, Acros Organics, TCI and Merck KGaA and were used without further purification. NMR spectra were recorded on Bruker AVANCE 250, 300 and 500 spectrometers (University of Rostock, Institute of Chemistry).

Catalysts quinine **QN**, hydroquinine **HQN**, hydroquinine anthraquinone-1,4-diyl diether **$(DHQ)_2$AQN** and hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether **$(DHQ)_2$Pyr** were purchased from Sigma Aldrich and utilized without further purification.

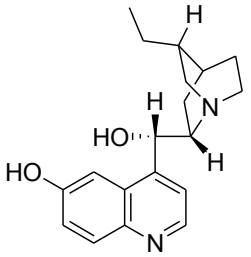
Synthesis of Cupreine 9b. Quinine (13.0 g, 0.04 mol) was dissolved in 160 mL dry DMF under argon atmosphere. NaSEt (13.5 g, 0.16 mol) were added and stirred at 105 °C for 16 h. The reaction was stopped with the addition of 200 mL NH_4Cl at room temperature. The reaction mixture was neutralized with 1 N HCl. Both phases were separated and the aqueous phase was washed with dichloromethane. The combined organic phases were washed with a NaCl-solution and dried with Na_2SO_4. Evaporation under reduced pressure yield the product **9b** (4.2 g, 32% yield). ^{1}H NMR (300 MHz, DMSO, δ): 0.73-0.94 (m, 1H), 0.97-1.17 (m, 1H), 1.31-1.81 (m, 6H), 2.21 (s, 1H), 2.74-3.13 (m, 3H), 4.81-5.25 (m, 3H), 5.64 (s, 1H), 5.73-5.95 (m, 1H), 7.23-7.30 (dd, J_1 = 6.4 Hz, J_2 = 11.7 Hz, 1H), 7.38-7.47 (m, 2H), 7.81-7.89 (d, J = 9.1 Hz, 1H), 8.57-8.61 (d, J = 4.3 Hz, 1H).



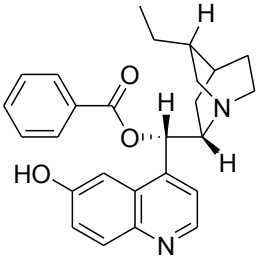
Synthesis of Benzoyl cupreine 9c. Quinine (8.78 g, 0.027 mol) was dissolved in 270 mL dry CH_2Cl_2 under argon atmosphere. PhCOCl (16.20 mL, 0.135 mol) and 37.80 mL 30% NaOH solution were slowly added at room temperature and the mixture was stirred for 4 h. Water and dichloromethane were added and the phases were separated. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. Benzoyl quinine was obtained as a white solid by column chromatography (EtOAc/NEt_3, 50:1) after evaporation of the solvent. This solid (11.14 g, 0.026 mol) was dissolved in 520 mL dry CH_2Cl_2 and cooled at -75 °C. 100 mL BBr_3 solution (in CH_2Cl_2, 1 M, 4 equiv.) was slowly added. After addition, the reaction solution was first stirred at room temperature for 1 h followed by heating under reflux at 40 °C for 1 h. The solution was cooled at 0 °C and a 40% NH_4OH solution was added. Water and dichloromethane was added and the phases were separated. The aqueous phase was extracted with 1-butanol. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/Et_3N/MeOH, 50:1:2) and product **9c** was obtained (4.2 g, 39% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.42-1.85 (m, 4H), 1.88-1.92 (m, 1H), 2.23 (br, 1H), 2.68-2.77 (m, 2H), 2.80-2.83 (m, 1H), 2.97-3.16 (m, 1H), 3.39-3.52 (m, 1H), 4.90-5.05 (m, 2H), 5.72-5.82 (m, 1H), 6.75-6.86 (m, 1H), 7.22-7.33 (d, 2H), 7.34-7.62 (m, 4H), 7.62-7.72 (m, 1H), 7.94-8.13 (dd, J_1 = 8.3 Hz, J_2 = 33.9 Hz, 3H), 8.63 (d, J = 4.5 Hz, 1H).



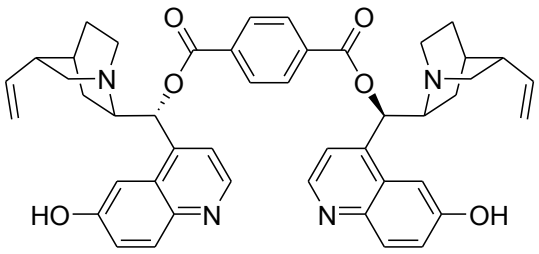
Synthesis of Hydrocupreine 9d. Hydroquinine (13.0 g, 0.04 mol) was dissolved in 160 mL dry DMF under argon atmosphere. NaSEt (13.5 g, 0.16 mol) were added and stirred at 105 °C for 16 h. The reaction was stopped with the addition of 200 mL NH_4Cl at room temperature. The reaction mixture was neutralized with 1 N HCl. Both phases were separated and the aqueous phase was washed with dichloromethane. The combined organic phases were washed with a NaCl-solution and dried with Na_2SO_4. Evaporation under reduced pressure yield in product **9d.** ^{1}H NMR (250 MHz, DMSO, δ): 0.96-1.12 (m, 3H), 1.29-1.37 (m, 2H), 1.39-1.65 (m, 6H), 2.29-2.35 (m, 4H), 2.70-2.91 (m, 1H), 4.73-4.98 (m, 1H), 5.72 (s, 1H), 5.81-5.99 (m, 1H), 7.24-7.35 (m, 1H), 7.43-7.54 (m, 2H), 7.89-7.94 (m, 1H), 8.56-8.63 (m, 1H).



Synthesis of Hydrobenzoylcupreine 9e. Hydroquinine (8.78 g, 0.027 mol) was dissolved in 270 mL dry CH_2Cl_2 under argon atmosphere. PhCOCl (16.20 mL, 0.135 mol) and 37.80 mL 30% NaOH solution were slowly added at room temperature and stirred for 4 h. Water and dichloromethane were added and the phases were separated. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. Benzoyl quinine was obtained as a white solid by column chromatography (EtOAc/NEt_3, 50:1) after evaporation of the solvent. This solid (11.14 g, 0.026 mol) was dissolved in 520 mL dry CH_2Cl_2 and cooled at -75 °C. 100 mL BBr_3 solution (in CH_2Cl_2, 1 M, 4 equiv.) was slowly added. After addition, the reaction solution was first stirred at room temperature for 1 h followed by heating under reflux at 40 °C for 1 h. The solution was cooled at 0 °C and a 40% NH_4OH solution was added. Water and dichloromethane was added and the phases were separated. The aqueous phase was extracted with 1-butanol. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/Et_3N/MeOH, 50:1:2) and product **9e** was obtained (4.2 g, 39% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.93-1.12 (m, 3H), 1.20-1.29 (m, 2H), 1.33-1.67 (m, 4H), 1.741.82 (m, 1H), 2.34 (br, 1H), 2.72-2.79 (m, 2H), 2.80-2.86 (m, 1H), 3.02-3.26 (m, 1H), 3.42-3.59 (m, 1H), 6.82-6.89 (m, 1H), 7.35-7.44 (d, 2H), 7.49-7.59 (m, 4H), 7.68-7.82 (m, 1H), 7.91-8.23 (dd, J_1 = 7.9 Hz, J_2 = 35.8 Hz, 3H), 8.77 (d, J = 4.3 Hz, 1H).



Synthesis of 1,4-Bis(9-*O*-cupreinyl)terephthalate 9f. Cupreine **9b** (7.2 g, 23.4 mmol) was dissolved in 120 mL dry DMF under argon atmosphere. 8.1 mL triisopropylsilyl chloride TIPSCl (2 eq) was added at room temperature and the reaction solution was stirred for 14 h. The reaction mixture was dissolved in 800 mL EtOAc and washed with $NaHCO_3$ and NaCl solution. The crude product was obtained as white solid after purification by column chromatography (EtOAc/MeOH/Et_3N, 10:1:0.25) after evaporation of the solvent. This solid (3.3 g, 7 mmol) reacted with 2 mL NEt_3 and 0.5 equiv. terephthaloyl chloride. After 18 h reaction time the crude product was purified by column chromatography (EtOAc/MeOH, 10:1). 30 mL CH_3CN were added and the solution was cooled at 0 °C followed by the addition of 1.5 mL HF-solution (48%). $NaHCO_3$-solution was added and the reaction mixture



was extracted with ethylacetate. The obtained solid was recrystallized with acetone which yields the product **9f**. 1H NMR (300 MHz, DMSO-d_6, δ): 10.16 (s, 2H), 8.61 (d, J = 4.5 Hz, 2H), 8.22 (s, 4H), 7.90 (d, J = 9.1 Hz, 2H), 7.55 (br, 2H), 7.51 (d, J = 4.5 Hz, 2H), 7.36-7.29 (m, 2H), 6.45 (d, J = 7.5 Hz, 2H), 6.02-5.87 (m, 2H), 5.07-4.93 (m, 4H), 3.54-3.42 (m, 2H), 3.17-3.00 (m, 2H), 2.96-2.79 (m, 2H), 2.42 (br, 2H), 2.30-2.15 (m, 2H), 2.04-1.87 (m, 2H), 1.78 (br, 2H), 1.74-1.37 (m, 6H).

Synthesis of Adamantoylcupreine 9g. Quinine (5.0 g, 15.4 mmol) was dissolved in 154 mL dry CH_2Cl_2 under argon atmosphere. The reaction solution was cooled at 0 °C followed by the addition of 30.8 mL Et_3N and adamantoyl chloride (3.0 g, 15.4 mmol). After 24 h stirring water was added and the both phases were separated. The organic phase was washed with NH_4Cl. The crude product was obtained under reduced pressure. Adamantoyl quinine was obtained by purification with organic solvent nanofiltration (DM 200, EtOH, discontinuous diafiltration). This solid was dissolved in dry CH_2Cl_2 and cooled at -75 °C. BBr_3 solution (in CH_2Cl_2, 1 M, 4 equiv.) was slowly added. After addition, the reaction solution was first stirred at room temperature for 1 h followed by heating under reflux at 40 °C for 1 h. The solution was cooled at 0 °C and a 40% NH_4OH solution was added. Water and dichloromethane was added and the phases were separated. The aqueous phase was extracted with 1-butanol. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/MeOH, 10:1) and product **9g** was obtained . ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.10-1.37 (m, 1H), 1.76-2.15 (m, 19H), 2.09-2.84 (m, 3H), 2.95-3.28 (m, 2H), 3.36 (s, 1H), 4.83-5.17 (m, 2H), 5.64-5.91 (m, 1H), 6.48 (s, 1H), 7.11-7.58 (m, 3H), 7.86-8.15 (m, 1H), 8.61 (s, 1H).

Synthesis of Lauroylcupreine 9h. Quinine (5.0 g, 15.4 mmol) was dissolved in 154 mL dry CH_2Cl_2 under argon atmosphere. The reaction solution was cooled at 0 °C followed by the addition of 30.8 mL Et_3N and lauroyl chloride (3.66 mL, 15.4 mmol). After 24 h stirring water was added and the both phases were separated. The organic phase was washed with NH_4Cl. The crude product was obtained under reduced pressure. Lauroyl quinine was obtained by purification with organic solvent nanofiltration (DM 200, EtOH, discontinuous diafiltration). This solid was dissolved in dry CH_2Cl_2 and cooled at -75 °C. BBr_3 solution (in CH_2Cl_2, 1 M, 4 equiv.) was slowly added. After addition, the reaction solution was first stirred at room temperature for 1 h followed by heating under reflux at 40 °C for 1 h. The solution was cooled at 0 °C and a 40% NH_4OH solution was added. Water and dichloromethane was added and the phases were separated. The aqueous phase was extracted with 1-butanol. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized in acetone and the product **9h** was obtained. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 0.74-0.95 (m, 3H), 1.18-1.37 (s, 17H), 1.46-1.98 (m, 7H), 2.18-2.52 (m, 3H), 2.54-2.85 (m, 2H), 2.98-3.42 (m, 3H), 4.84-5.14 (m, 2H), 5.57-5.87 (m, 1H), 6.44-6.63 (d, J = 5.2 Hz, 1H), 7.15-7.34 (m, 2H), 7.69-7.70 (d, J = 2.5 Hz, 1H), 7.90-7.99 (d, J = 9.1 Hz, 1H), 8.63-8.71 (d, J = 4.4 Hz, 1H).

Synthesis of Pivaloylcupreine 9i. Quinine (5.0 g, 15.4 mmol) was dissolved in 154 mL dry CH_2Cl_2 under argon atmosphere. The reaction solution was cooled at 0 °C followed by the addition of 30.8 mL Et_3N and pivaloyl chloride (1.86, 15.4 mmol). After 24 h stirring water was added and the both phases were separated. The organic phase was washed with NH_4Cl. The crude product was obtained under reduced pressure. Pivaloyl quinine was obtained by purification with organic solvent nanofiltration (DM 200, EtOH, discontinuous diafiltration). This solid was dissolved in dry CH_2Cl_2 and cooled at -75 °C. BBr_3 solution (in CH_2Cl_2, 1 M, 4 equiv.) was slowly added. After addition, the reaction solution was first stirred at room temperature for 1 h followed by heating under reflux at 40 °C for 1 h. The solution was cooled at 0 °C and a 40% NH_4OH solution was added. Water and dichloromethane was added and the phases were separated. The aqueous phase was extracted with 1-butanol. The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The product **9i** was obtained by column chromatography (EtOAc/EtOH/Et3N, 7:3:0.5). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.71-0.96 (m, 1H), 1.24 (s, 9H), 1.50-1.96 (m, 5H), 2.45 (s, 1H), 2.59-2.96 (m, 2H), 2.99-3.46 (m, 3H), 4.84-5.09 (m, 2H), 5.55-5.85 (m, 1H), 6.39-6.67 (m, 1H), 7.14-7.43 (m, 2H), 7.82 (s, 1H), 7.93-8.05 (d, J = 9.1 Hz, 1H), 8.65-8.70 (d, J = 4.5 Hz, 1H).

A2 Materials & Methods

A2-1 Membranes & Filtration cells

Membranes

DuraMem Membranes (DM) were purchased from Evonik MET, Ltd., UK, with a molecular weight cut-off (MWCO) in a range of 150-500 g mol^{-1} as flat sheets. The membranes consisting of modified polyimide are stable in solvents such as acetone, THF, alcohols, ether and ester. Also mixtures of aqueous and organic solvents are suitable. They are temperature stable up to 50 °C and pressure stable up to 6.0 MPa. All membranes were conditioned before use with pure solvent at 3.0 MPa pressure (2.0 MPa pressure for DM 500) and ambient temperature (23 °C) to flush out any preserving agents, e.g. poly(ethylene glycol). According to the manufacturer, a minimum of 40 L of solvent / m² of membrane was used. All investigated solvents for filtration experiments were distilled before use. The flux during conditioning was monitored by determination of the permeate volume over time.

Dead-End-Filtration Cell

The Berghof Cell (Eningen, Germany) operating in dead-end mode (Figure A2-1) was used for publication I. This stainless-steel filtration cell with a volume of 200 mL can be used with a pressure up to 10 MPa. The membrane area amounts to 44.2 cm², but only 35.4 cm² are effectively used. The cell has a refill reservoir having a volume of 50 mL in order to refill solvent during the filtration process without reducing the pressure. The pressure is generated by a nitrogen gas cylinder. An integrated magnetic stirrer was used to avoid concentration polarization.

Cross-Flow-Filtration Cell

The filtration experiments for publication II and III were performed in a cross-flow operating stainless-steel cell, which was manufactured inhouse (Figure A2-2). The volume of the feed solution can be selected (dead volume – 20 mL) and the feed reservoir is depressurized. The membrane area amounts to 25.5 cm² with an effective area of 17.5 cm². The pressure is applied by a micro-annular gear pump (HNP-mzr-4605) with a maximum pressure of 10 MPa. The monitored flow rate is kept constant at 70 mL min^{-1}. The adjustment of the transmembrane pressure is set by a needle valve. A sintered metal plate is used to stabilize the membrane.

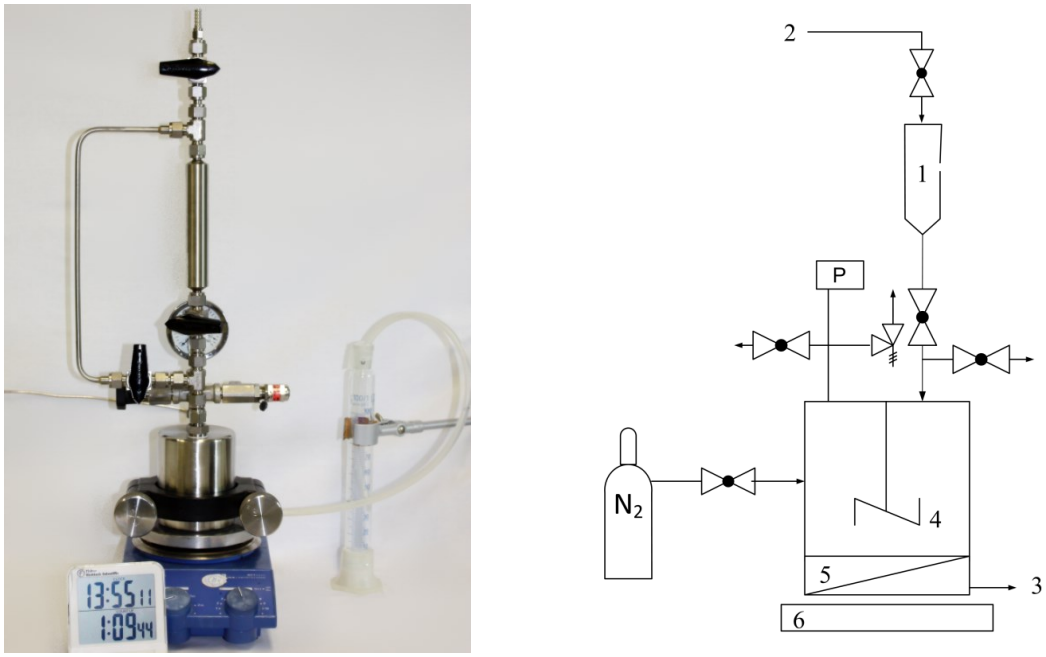


Figure A2-1. a) Dead-End Filtration Cell. b) Flow-Scheme: 1 – Refill reservoir, 2 – Feed stream, 3 – Permeate stream, 4 – Stirrer, 5 – Retentate stream, 6 – Magnetic stirrer.

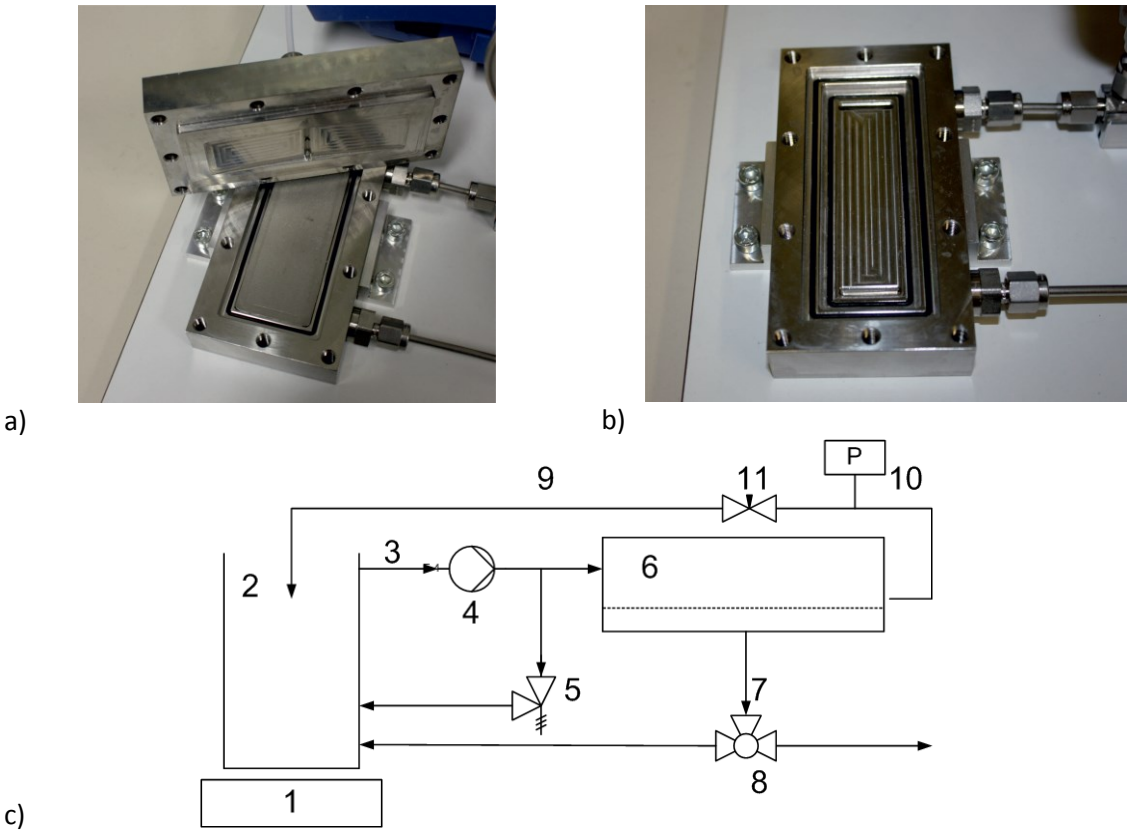


Figure A2-2. Cross-Flow Filtration Cell. a) Top of the cell with sintered plate. b) Bottom of the cell. c) Flow-Scheme: 1) Magnetic stirrer, 2) Reaction vessel (depressurized), 3) Feed stream, 4) micro annulear gear pump, 5) Overflow valve, 6) Membrane modul, 7) Permeate stream, 8) Sampling valve, 9) Retentate stream, 10) Manometer , 11) Needle valve.

A2-2 Microreaction devices

Microextractor

The extraction experiments were carried out with a microextractor (Little Things Factory) consisting of an integrated mixer and settler (Figure A2-3). The total volume amounts to 4.5 mL, of which 1/100 is the mixing zone and the residue for the separating part. The solvents were pumped via two microannular gear pumps (HNP, mrz-2942). The microextractor has two outlets on the separation unit for the organic and the aqueous phase. The mixing section can not be varied. The extraction and the separating process was carried out at ambient temperatures.

Figure A2-3. Microextractor.

Falling-film Microreactor

For removal of CO_2, a standard falling-film microreactor (IMM, Mainz, Germany) was used (Figure A2-4). The gas-liquid contact was facilitated by a vertical microstructured reaction plate (16 parallel open microchannels; width X thickness: 1200 x 400 µm) with a size of 76 x 25.6 mm². For each plate, a constant liquid flowrate (70 mL min^{-1}) was utilized by using two microannular gear pumps (HNP, mrz-2942). The argon flow (100 mL min^{-1}) was set by a digital mass-flow controller (Bronkhorst, El-Flow Select F-201CV) and controlled by a prepressure regulator (Parker, Porter 4000, 0-60 psi). The temperature of the plate was kept constant using a cryostat (Huber, CC3). The reactor top plate contained a glass window for flow inspection.

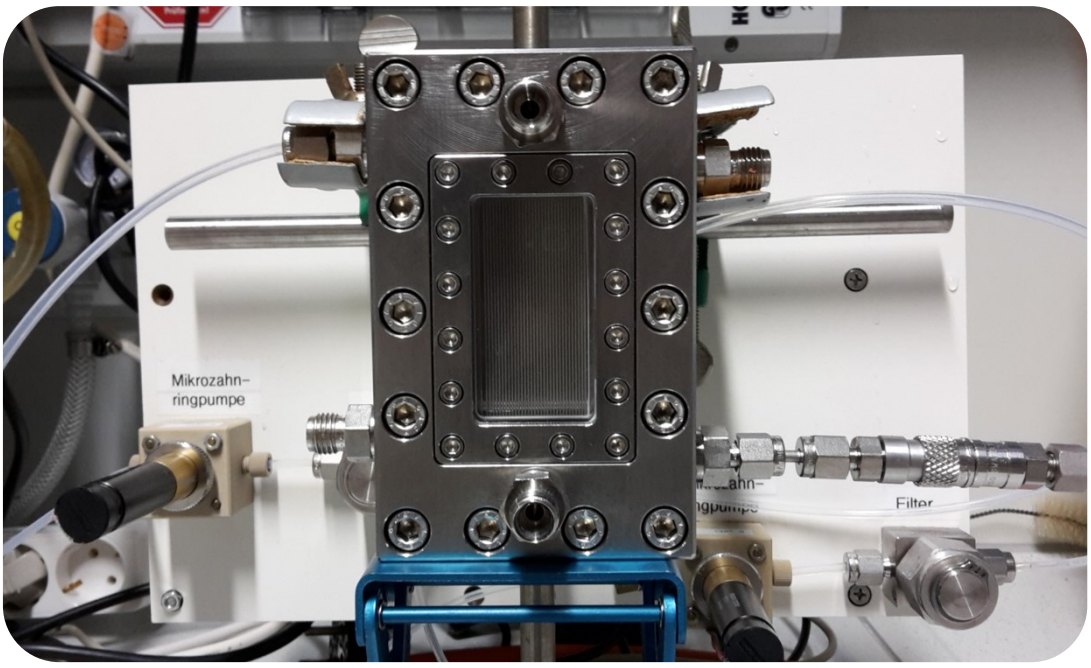


Figure A2-4. Falling-film microreactor used in this study.

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A3 Supporting Information

Preparation of Poly(ionic liquid)s-Supported Recyclable Organocatalysts for the Asymmetric Nitroaldol (Henry) Reaction

Julia Großeheilmann, Jenny Bandomir, and Udo Kragl*[a]

chem_201504290_sm_miscellaneous_information.pdf

Supporting Information

TABLE OF CONTENTS

CHEMISTRY & SUSTAINABILITY
CHEMSUSCHEM
ENERGY & MATERIALS

A4 Supporting Information

Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis

Julia Großeheilmann, Jesse R. Vanderveen, Philip G. Jessop, and Udo Kragl*[a]

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an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von ~~Frau~~/Herrn

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