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Dissertation

DESIGN OF CHIRAL IONIC LIQUIDS: STRUCTURAL INVESTIGATION TOWARDS CHIRAL RECOGNITION

Ausgeführt zum Zwecke der Erlangung des akademischen Grades eines

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Dedicated to my grandmother Aurelia (Titi)

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Abstract

The present work focuses on the synthesis and characterization of novel enantiomerically pure ionic liquids derived from the chiral pool. These chiral ionic liquids were specially designed to fulfil the desired properties for application in synthesis and separations.

The chiral recognition properties of amino alcohol-derived chiral ionic liquids were evaluated to get an insight into the influence of ionic liquid structure towards recognition strength. Moreover these chiral ionic liquids could be applied as novel shift reagents in NMR spectroscopy.

Furthermore target-made coordinating chiral ionic liquids with amino alcohol structure were designed and efficiently applied in asymmetric alkylation reaction and in transition metal catalyzed asymmetric transfer hydrogenation. By taking advantage of the tunable properties of ionic liquids, the performance of these supported chiral ligands was adjusted to demonstrate the positive effect of chiral ionic liquids in asymmetric synthesis.

Finally the application of achiral and chiral ionic liquids in gas chromatography as stationary phase was investigated. After development of suitable coating protocols, different ionic liquid-based stationary phases could be produced and evaluated for their separation properties.

Kurzfassung

Die vorliegende Arbeit befasst sich mit der Synthese, Charakterisierung und Anwendung neuer chiraler ionischer Flüssigkeiten ausgehend von enantiomerenreinen Naturprodukten. Anhand der außergewöhnlichen Eigenschaften dieser Substanzklasse konnten diese chiralen ionischen Flüssigkeiten speziell für Anwendungen im Bereich der Synthese und Trennung entwickelt und anschließend eingesetzt werden.

Die Stärke der chiralen Wechselwirkungen der synthetisierten enantiomerenreinen ionischen Flüssigkeiten wurde untersucht um den Einfluss unterschiedlicher Grundkörper und Kopfgruppen zu evaluieren. Diese chiralen ionischen Flüssigkeiten konnten anschließend als chirale Trennreagentien in der NMR-Spektroskopie eingesetzt werden.

Weiters wurden neuartige chirale ionische Flüssigkeiten mit Aminoalkohol-Struktur entwickelt und erfolgreich in der asymmetrischen Alkylierungsreaktion und in der Übergangsmetall-katalysierten asymmetrischen Transferhydrogenierung eingesetzt. Durch Wahl geeigneter Gegenionen konnten die Eigenschaften optimiert und den gewünschten Reaktionsbedingungen angepasst wurden, wodurch der Vorteil dieser immobilisierten chiralen Liganden in der asymmetrischen Synthese demonstriert wurde.

Im letzten Teil dieser Arbeit wurde die Verwendung chiraler und achiraler ionischer Flüssigkeiten als stationäre Phase in der Gaschromatographie untersucht. Die Beschichtung mehrerer Säulen konnte mit unterschiedlichen ionischen Flüssigkeiten durchgeführt und deren Trennleistung evaluiert werden.

I Introduction

I 1 Ionic Liquids

The concept of liquids consisting solely of ions has been known in history for a long time: First publications on this matter date back to 1888 when Gabriel *et al.* described ethylammonium nitrate with a melting point of 52-55 °C.[1] Another low melting salt was reported in literature by Paul Walden[2] in 1914 and is often considered as the hour of birth of "modern" ionic liquids (ILs), although the term and the definition of ionic liquids as "salts with a melting point under 100 °C" was created much later in the 1990s. Ionic liquids commonly consist of organic cations such as on ammonium or phosphonium structures in combination with organic or inorganic anions and therefore exhibit ionic conductivity (Figure 1). The bulky and asymmetric structure of the cations in combination with a good charge distribution in the anions results in rather low melting points.[3]

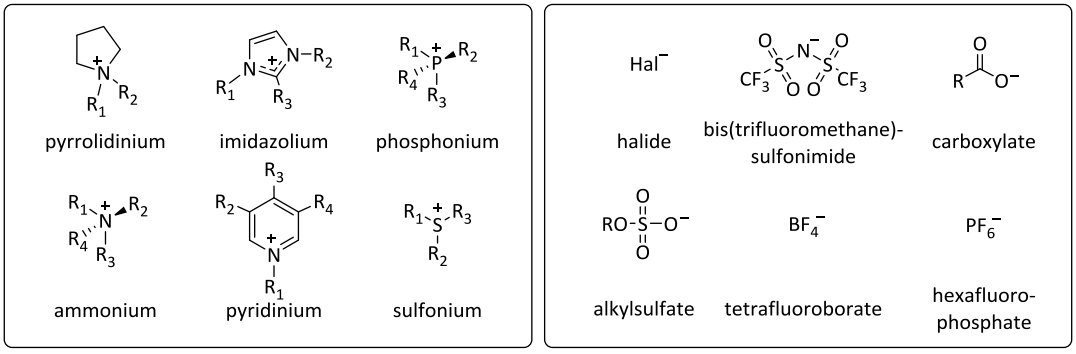


Figure 1: Example of commonly used cations and anions

Even though ionic liquids became widely popular only in the past 20 years, the awareness of the extraordinary properties of low melting salts was realized earlier. It was already in 1951 when Hurley and Wier[4] introduced the application of low melting chloroaluminate salts for electroplating of aluminium and forced the interest in electrochemical applications until today. A major drawback for the application of these ILs, which are considered as the first generation of ILs, is their hygroscopic nature and the formation of corrosive HCl when reacted with water. It was an important breakthrough for the application of ILs when Wilkes and Zaworotko published the first air- and water-stable IL based on 1-ethyl-3-methylimidazolium tetrafluoroborate in 1992.[5] Unlike chloroaluminate ILs these liquid salts based on tetrafluoroborates or hexafluorophosphates could be prepared and safely stored outside an inert atmosphere.

The discovery of stable ILs was the start for popular application of ILs in different areas. It was already in 1986 when Fry and Pienta proposed the use of ionic liquids as solvent in organic synthesis based on their unique solving properties for the first time.[6]

The applications of ionic liquids are however not limited to the mere use as solvents. An overview of their unique properties and the resulting applications is given below, indicating the tremendous possibilities in ionic liquid research (Figure 2).

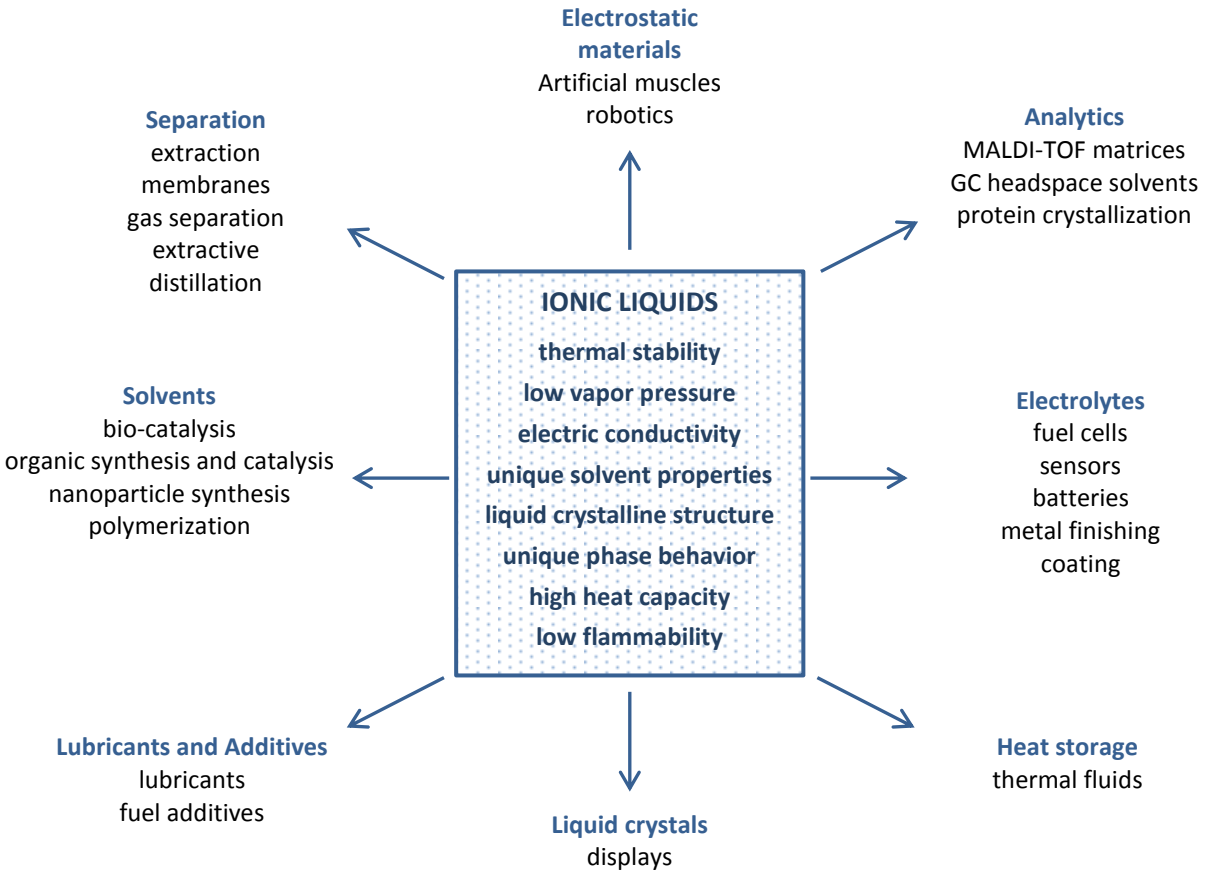


Figure 2: Properties and applications of ionic liquids[i]

Due to the variable structure of ionic liquids there is a wide range of possibilities to influence their properties: different combinations of cations and anions lead to changes in melting point, phase behaviour, crystallinity, thermal stability and conductivity. Ionic liquids are therefore often considered as "designer solvents", as the proper selection of ions allows fine-tuning of their properties and the design for a specific application. To date there is a constantly increasing number of different ILs reported in literature and the estimated number of possible combinations of known ions with low melting point is in the order of 1 billion, as published by Earle and Seddon.[7]

[i] http://www.sigmaaldrich.com/technical-documents/articles/chemfiles/ionic-liquids0.html, last accessed 1st August 2014.

Regarding this wide field of applications, it is not surprising that the interest in ionic liquids has been growing nearly exponential in the last 23 years, indicating the need of improvement of existing methods and materials by the application of novel techniques (Figure 3). The trend can be observed regarding the number of academic papers as well as new patents applications.[8]

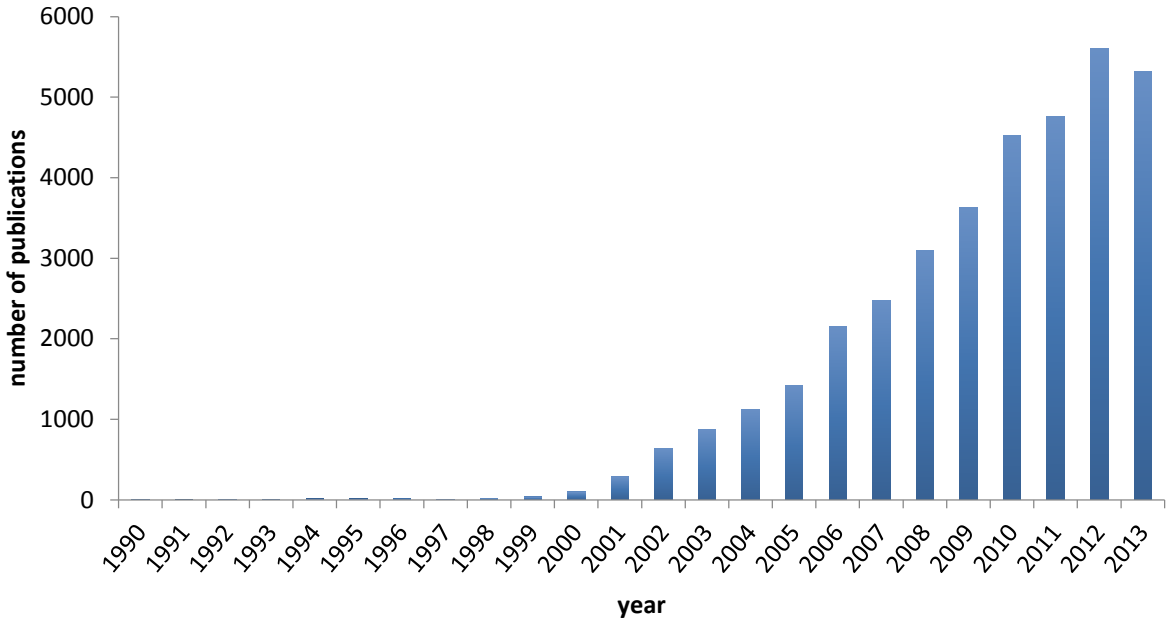


Figure 3: Evolution of scientific papers published on the issue "ionic liquids" from 1990 to 2013 (source Sci-Finder™ on 4th April 2014)

In the area of synthesis and catalysis ILs can be applied in various ways: they can be used as solvent, co-catalyst or catalyst, support or ligand, but can also fulfil multiple roles: With regard to industrial processes their low volatility in comparison to conventional organic solvents is one of the most significant features.[9] The tuneable phase behaviour enables liquid-liquid biphasic catalysis which opens the possibility to recycle the catalyst system and to avoid catalyst leaching to the product, which is a general concern in industrial catalysis.[10]

Due to their high viscosity, ionic liquids can also influence diffusion characteristics and alter reaction rates.[11] Furthermore ILs are able to participate in the catalytic process when used as solvent by stabilizing intermediates or transition states and influence the selectivity and outcome of a reaction.[12]

When used as catalyst or ligand in catalysis one of the most advantageous property of ILs is the possibility to adapt their solubility to the given reaction conditions. Based on the choice of anion ILs can be recovered from reaction mixtures by extraction with a suitable solvent.

Since 2000 several industrial applications of ionic liquids in synthesis and catalysis have been reported. One of the earliest and best known process applications is the BASIL process (*B*iphasic *A*cid *S*cavenging utilizing *I*onic *L*iquids) introduced by BASF in 2002 (Figure 4). In this process for the production of alkoxyphenylphosphines methylimidazole replaces triethylamine as acid scavenger. The formation of a protic ionic liquid 1-methylimidazolium chloride that is liquid at the reaction temperature

facilitates the removal of the generated salt *via* simple phase separation and allows isolating the product in multi-ton scale without further purification. Furthermore the starting material 1-methylimidazole can be recovered by treatment of the protic IL with base.

The introduction of the BASIL process and the development of a specific reactor technology could increase the space/time yield of the reaction by a factor of 80.000 in comparison to the conventional industrial process for alkoxyphenylphosphines with triethylamine.[ii13]

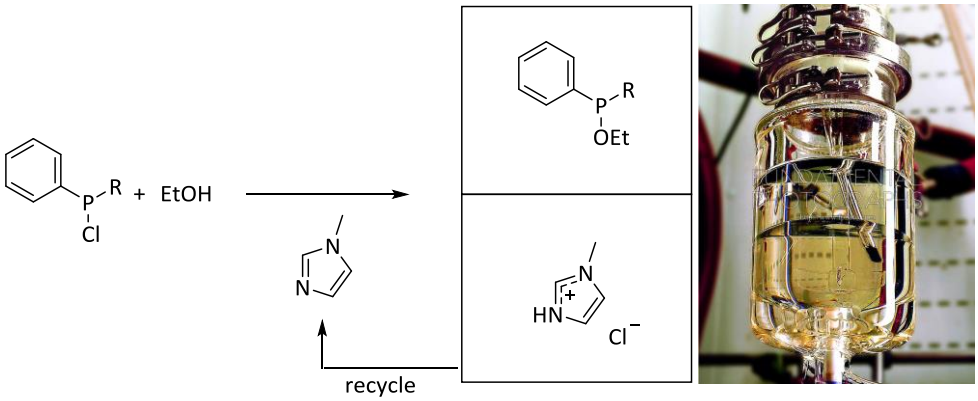


Figure 4: BASIL process by BASF[iii]

The same principle of product separation using biphasic mixtures with ILs was applied in the Dimfasol™ process by the French Petroleum Institute (IFP), with the additional benefits of a Lewis-acidic and catalytically active IL. The common Dimersol™ process is used in industry since the mid-1970s to dimerize light olefins into branched octans that are starting materials for the synthesis of intermediates in the plasticizer industry, *e.g. iso*-nonanol. For the Dimersol™ process Ziegler-type catalysts containing nickel and alkyl-aluminum co-catalyst are currently used under solvent-free conditions.[14] By adaptation of the Dimersol™ protocol using chloroaluminate based IL as solvent and co-catalyst under the name Difasol™ could be significantly improved. Using the IL as solvent the nickel complex could be immobilized without the need of additional co-catalysts and the products could be isolated by simple decantation as they are poorly soluble in the IL. After phase separation of the product, the catalyst phase could be reused without further purification. The introduction of the Difasol™ process allowed a more efficient overall catalyst utilization and an increase in yield of octenes by about 10 wt%.[3]

[ii] http://www.basf.com/group/corporate/de/innovations/publications/innovation-award/2004/basil, last accessed 1st August 2014.
[iii] http://fphoto.photoshelter.com/image/I00002QBEWYqF02o, last accessed 1st August 2014.

Molten salts also find application in the pharmaceutical industry as reported by Eli Lilly in 2004 for the demethylation of 4-methoxyphenylbutyric acid, an important key substrate in medicinal chemistry.[15] In this process, the molten salt pyridinium hydrochloride is used as catalyst for the demethylation reaction and the products are isolated by solvent extraction in very high yield and purity in 190 L scale.

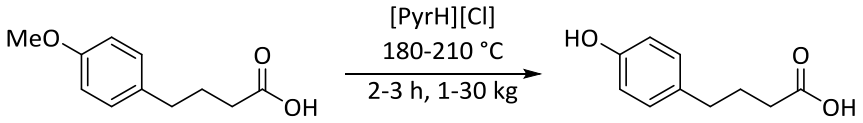


Figure 5: Synthesis of 4-hydroxyphenylbutyric acid by Eli Lilly

To date, the largest industrial process based on ionic liquids with 65.000 tons per year plant is operated by PetroChina under the name of "Ionikylation" for the alkylation of isobutene. Isobutene alkylation is currently used to produce reformulated gasoline and is currently run using corrosive sulphuric acid and hydrogen fluoride as catalyst, which not only perform moderately but also faces severe security issues. The novel Ionikylation process features a strongly Lewis acidic IL based on aluminium(III)chloride with the addition of cuprous chloride to further enhance the acidity of the IL.[16] The use of this IL inhibits undesirable side reactions such as isomerisation and cracking, and circumvents safety issues with the former catalyst. PetroChina was able to demonstrate an 8-month stability of the catalyst and an olefin conversion of 99%, thus improving the process unit capacity and economics immensely.

I 2 Chirality and Chiral Ionic Liquids

Chirality plays an overwhelming role in nature since living organisms are composed of chiral biomolecules such as amino acids, sugars and nucleic acids. Because of this phenomenon, living organisms show different biological responses to enantiomers in drugs and other chiral compounds. In particular the effects of two different enantiomers of a chiral drug can be significant as they might have different pharmacological activities, as well as different pharmacokinetic and pharmacodynamic effects and can dramatically harm the human body if the wrong enantiomer is administered.[17]

Based on historic incidents with chiral drugs, the U.S. Food and Drug Administration issued a guideline in 1992 regarding the therapeutic effects of chiral compounds and introduced the official demand of separate studies for each enantiomer, including pharmacological and metabolic pathways.[iv] In case of the administration of racemic drugs, a rigorous justification must be given. Given the fact that over 86% of the most sold drugs in the US are chiral and 44% are administered in enantiomeric pure form, chirality is a major concern in modern pharmaceutical chemistry.[v]

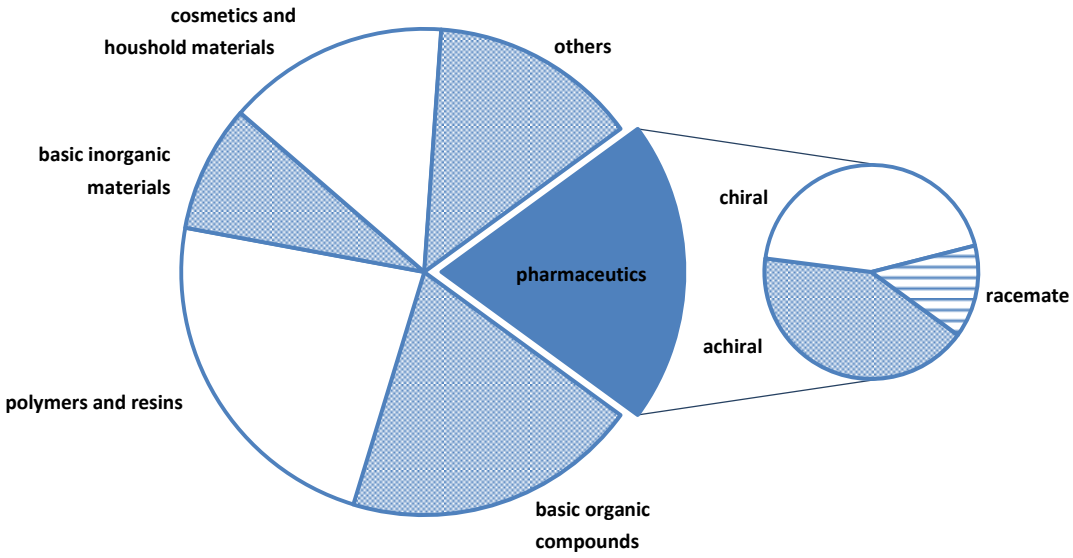


Figure 6: Market share of pharmaceutics[vi]

The introduction of chirality in synthetic organic chemistry in particular in drug development is accessible over three pathways:

- Chiral starting material – ex-chiral pool synthesis
- Chiral catalyst, auxiliaries or solvents – asymmetric synthesis
- Resolution of racemates – separation

[iv] http://www.fda.gov/default.htm, last accessed 1st August 2014.
[v] http://www.medscape.com/viewarticle/820011, last accessed 1st August 2014.
[vi] http://www.census.gov/, www.drugdiscoverytoday.com, last accessed 1st August 2014.

Chiral starting materials are mostly based on the use of compounds emerging from the chiral pool (Figure 7).[18] The chiral pool is a library of compounds found in nature that strictly consist of one single enantiomer and are typically available in large amounts. While this is an attractive and convenient feature for the manufacturing of chiral products, the major drawback of this approach is the limited variety of starting materials. Several synthetic steps are usually required to convert the chiral pool analogue to the desired product, while stereochemistry must be preserved.

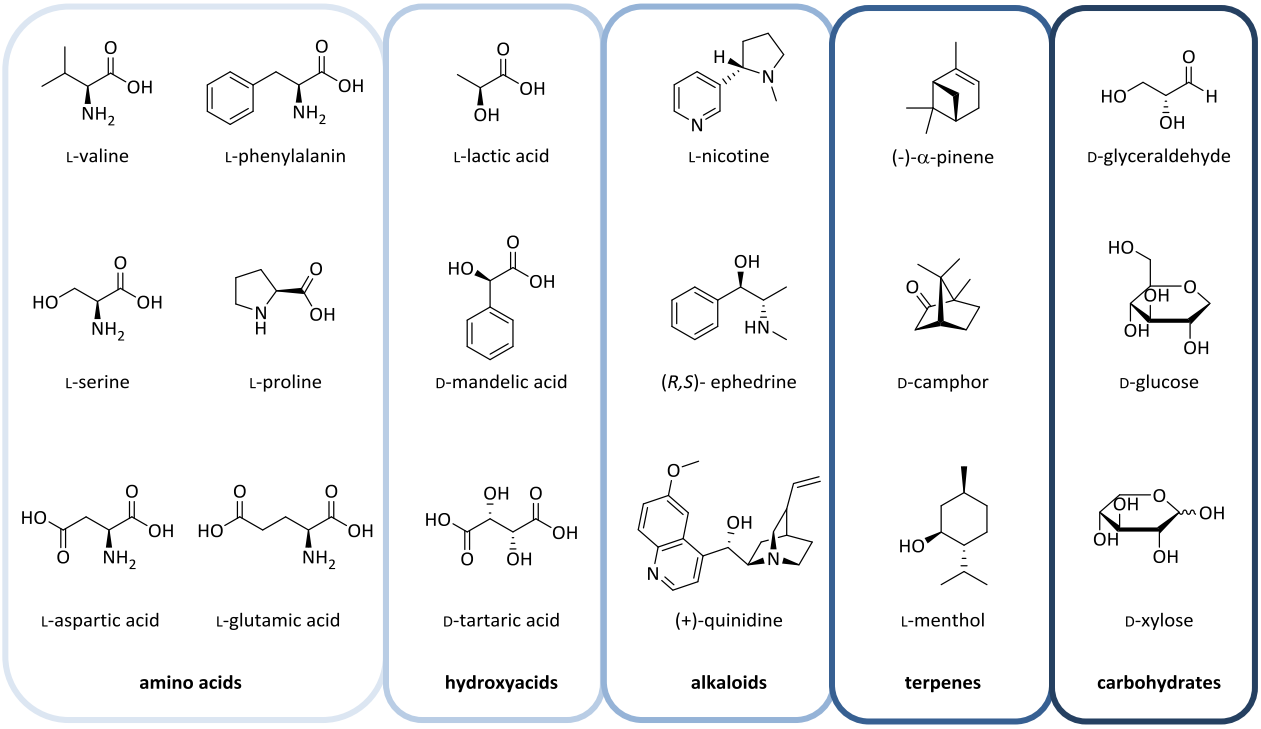


Figure 7: The chiral pool

The industrial production of pharmaceuticals is mainly based on asymmetric synthesis in combination with chiral resolution.[19] In asymmetric synthesis the field of catalysis is particularly interesting, since this strategy is by far the most atom-efficient in comparison to the use of chiral solvents or auxiliaries. Because of this reason and the permanent demand to reduce the amount of often expensive chiral catalyst amount, a lot of effort is put into the investigation of novel catalytic systems.

The role of ionic liquids in the manufacturing of chiral products can be widespread: While the ex-chiral pool strategy starting from chiral substrates or asymmetric synthesis of prochiral substrates with chiral reagents can be done in conventional ionic liquids, it is also possible to immobilize chiral catalysts within ionic liquids or to synthesize chiral ionic liquids (CILs) which can act as solvents, catalysts or auxiliaries themselves (Figure 8). The major advantage of these approaches, in comparison to conventional methods in asymmetric synthesis, is the possibility to immobilize and recover the chiral active species and therefore reduce the amount of catalyst. Additionally, the tuneable properties of ionic liquids are a valuable tool for the design of functionalized and tailor-made solvents, catalysts or auxiliaries and hence improve and positively influence asymmetric reactions.

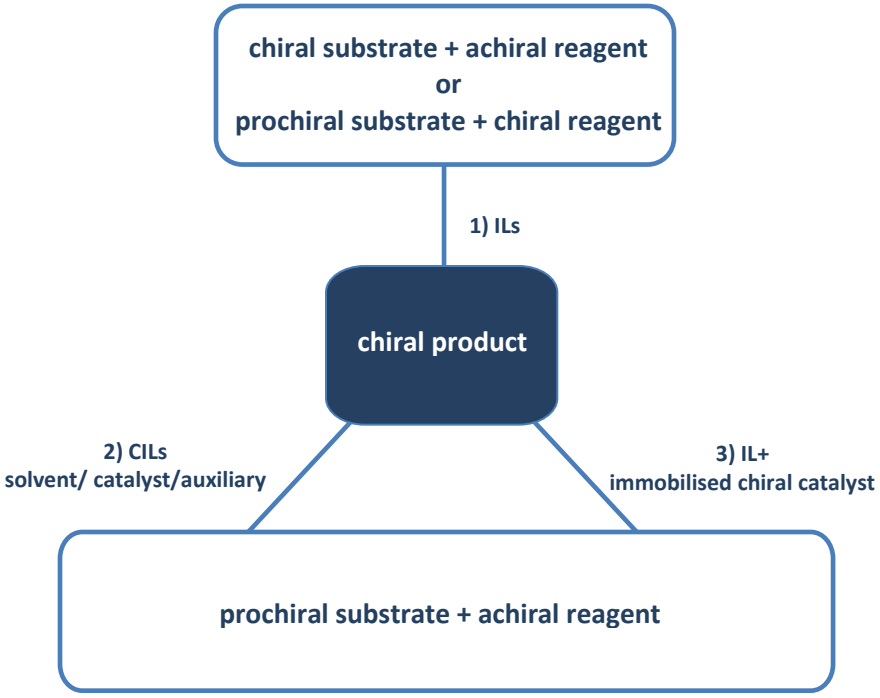


Figure 8: Application of chiral ionic liquids in asymmetric synthesis

Since the first example of a CILs was reported in 1997 by Howarth *et al*. the number of publications dealing with CILs grew rapidly, and nowadays a large pool of chiral ionic liquids bearing either chiral cations, anions or seldom both with a wide variety of functionalities is available (Figure 9).[20]

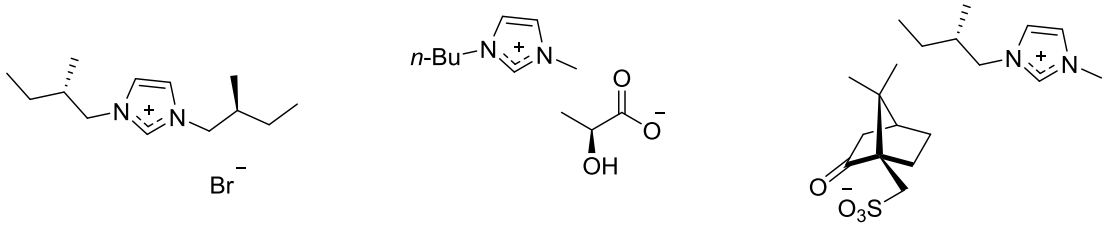


Figure 9: Examples for chiral ionic liquids with chiral cation (left), chiral anion (middle) or both (right)

It was soon realized that enantiopure natural products from the chiral pool provide a unique and indispensable source for ionic liquids and allow the resource-efficient design of CILs. Chiral amino acids are particularly attractive, since they can be converted to both cation and anion due to their inherent amine and carboxylic acid moiety. Furthermore they can be used in their native form, where the amino acid can be deprotonated or protonated with the corresponding base or acid to give the desired CIL. Alternatively the amino acid can be modified prior to the application as CIL.

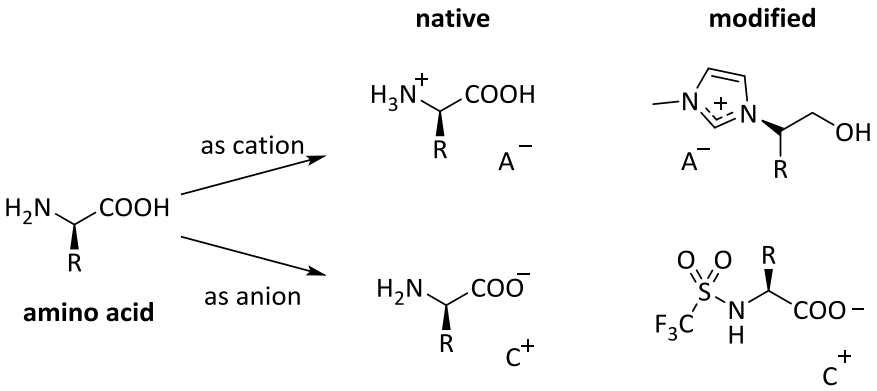


Figure 10: Application of amino acids in the synthesis of chiral ionic liquids

Consequently, the overwhelming majority of all CILs owe their existence to natural amino acids.[21] Similarly chiral alcohols such as menthol, terpenes (*e.g.* camphor or camphorsulfonic acid), chiral amines or alkaloids provide a common source for the design of chiral ionic liquids, whereas about a third of all chiral ionic liquids reported in literature are derived from non-chiral pool sources (Figure 11)

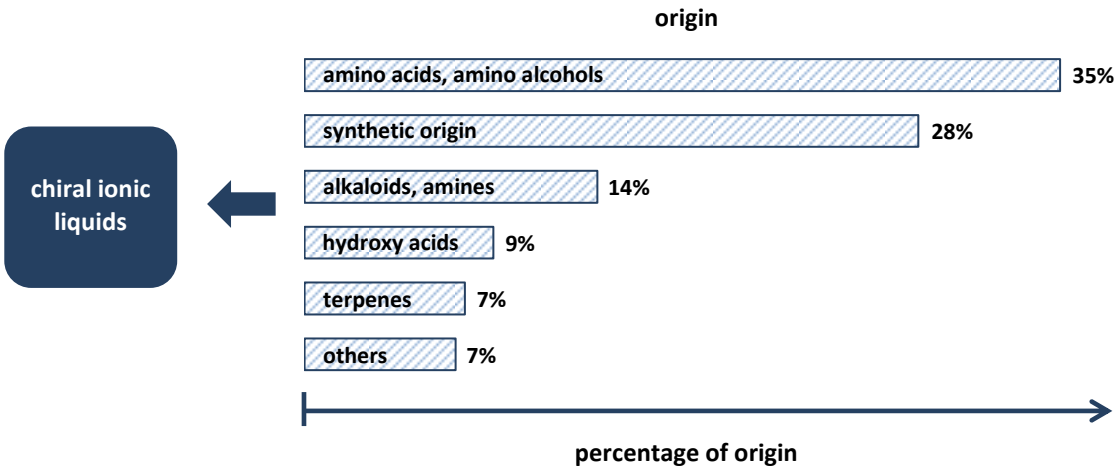


Figure 11: Literature survey for origin on the issue "chiral ionic liquids" from 1990 to 2013 (source Sci-Finder™ on 4th of August, 2013)

II Application of Chiral Ionic Liquids

The ionic structure, high degree of organization and hydrogen bonded supramolecular network inherent to ionic liquids was early promoted as novel aspect of chiral solvents that might allow a significant transfer of chirality for asymmetric synthesis as well as for separation (Figure 12).[22] It was particularly the wide field of asymmetric organocatalysis that gave access to highly enantioselective reactions catalysed by chiral ionic liquids, with the special benefit of a simple recycling of the chiral catalyst.[23] Soon applications in other asymmetric reactions followed, and successful examples for the use of chiral ionic liquids as catalyst, solvent or ligand include reactions as diverse as asymmetric hydrogenations,[24] sulfoxide oxidations[25] or alkylation reactions.[26]

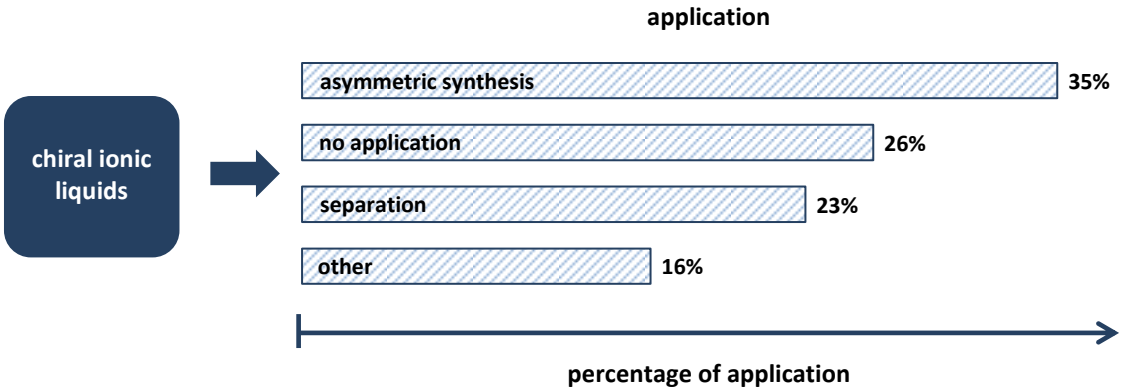


Figure 12: Literature survey for application on the issue "chiral ionic liquids" from 1990 to 2013 (source Sci-Finder™ on 4th of August, 2013)

II 1 Chiral Ionic Liquids in Asymmetric Synthesis

Although the number of chiral ionic liquids based on different starting materials and synthetic strategies was rapidly growing as soon as their potential was discovered,[27] it was not until 2005 that the first successful application of an CIL in asymmetric synthesis was demonstrated by Vo-Thanh *et al.* in Baylis-Hillman reaction.[28] From this starting point numerous applications in asymmetric synthesis were published using CILs either as solvent, organocatalyst, as ionic liquid-supported ligand or as additive for the induction of chirality (Figure 13). In the following chapters a short overview of these applications will be given.

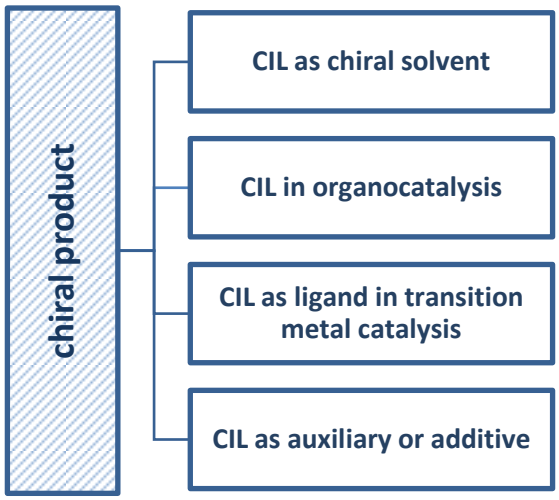


Figure 13: Application of chiral ionic liquids in asymmetric synthesis

II 1.1 Chiral Ionic Liquids as Chiral Solvent

The original motive in the use of CILs for asymmetric synthesis is their application as chiral solvent to minimize several disadvantages that occur with conventional chiral solvents.[29] The high degree of organization in CILs and their ability to form H-bonds allows strong interactions and therefore good transmission of chiral information. Furthermore the possibility of recycling the CIL compensates for the often high price of chiral solvents. Apart from these facts the common advantages of ILs as solvents as for *e.g.* their wide liquid range, their unique dissolving behaviour, the possibility of "designing" the properties *via* the choice of anion and their ability to stabilize charged intermediates make them interesting alternatives as solvents in asymmetric synthesis and some examples are given in the following chapters.

II 1.1.1 Chiral Ionic Liquids in Asymmetric Diels Alder Reactions

In 1998 the group of Earle performed the first Diels Alder reaction of cyclopentadien and three different dienophils in ionic liquids, amongst others also in L-lactate based CIL ([C_4mim][lactate]).[30] The authors could demonstrate an increased reaction rate in comparison to the established reaction in lithium perchlorate-diethyl ether mixtures. Furthermore they could show a higher impurity tolerance and recyclability for the IL solvents and thus the advantage for the use of IL in comparison to the conventional method. Unfortunately no enantioselectivity could be observed when L-lactate-based CILs were used as reaction media.

The first successful application with regard to enantioselectivity of a CIL in Diels Alder reactions was published by Vo-Than and co-workers in a series of publications starting from 2006. Several CILs were used as reaction media in asymmetric aza-Diels-Alder reaction between Danishefsky's diene and a chiral imine without addition of organic co-solvents or other Lewis-acidic catalysts.[31] Applying novel CILs they could achieve moderate to high yields (up to 76%) and good diastereoselectivity (up to 72%). In a subsequent publication, the design and application of isosorbide based ionic liquids was further investigated for the same reaction with comparable results (Figure 14).[32] The authors could demonstrate that the use of CILs is not only favorable with regard to reaction rate but also profitable for the enantiomeric outcome. The asymmetric induction is transmitted by strong intermolecular interactions, *e.g.* electrostatic attraction and hydrogen bonding between the ionic species and the transition states of the diastereoselective reaction.

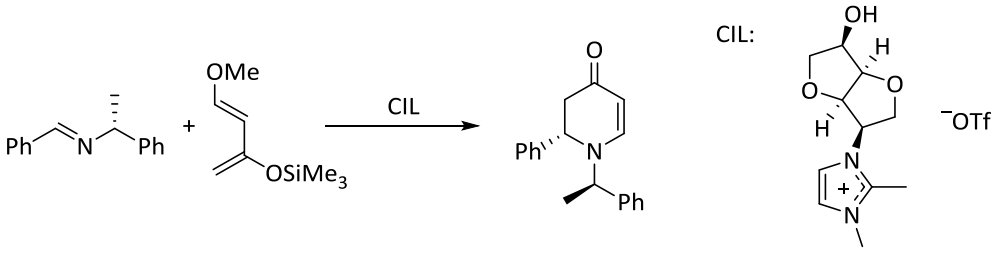


Figure 14: Chiral ionic liquids in asymmetric aza-Diels-Alder reaction

In the same year Bica *et al.* presented camphor-derived CILs with either cationic or anionic camphor moiety and applied theses CILs in asymmetric Diels Alder reaction between cyclopentadiene and acrylic acid as reaction media and single source of chirality.[33] Since the starting materials and the product were soluble in the ionic liquid no additional solvent was required. Additionally, the reaction could be performed without further addition of Lewis acid. Under these conditions excellent yields up to 99% could be achieved but unfortunately only moderate diastereoselectivities (7.3:1) and no enantioselectivity could be achieved, although recycling was possible over 5 runs.

II 1.1.2 Chiral Ionic Liquids in Photochemical Reactions

In 2005, Armstrong and co-workers were the first to report CILs as solvent and sole source for chiral induction in a photochemical reaction when used as solvent (Figure 15).[34] When investigating the photodimerization of different dibenzobicyclo[2.2.2]octatriens Armstrong *et al.* found that only a diacid was isomerized in an enantioselective way. This indicates that the observed chiral induction results through an ion pair effect with the ephedrinium-derived chiral ionic liquid, and up to 94% yield with an enantioselectivity of 12% ee were obtained. Screening of different chiral and achiral bases as additives showed no influence in the stereoselective outcome of the reaction, which supports the presumption that chirality transfer can be traced back to strong ion interactions with the chiral solvent, although addition of base is still essential for the dimerization reaction.

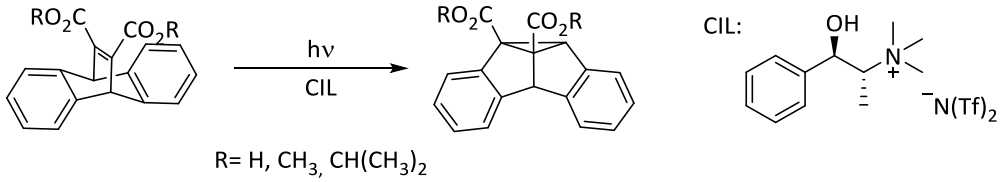


Figure 15: Chiral ionic liquids in photochemical reactions

In 2010 and 2011 Fukuhara *et al.* published the application of a CIL as solvent and chiral inductor in a photoinduced [4+4]cyclodimerization of 2-anthracencarboxylic acid and its lithium salt (Figure 16).[35] In case of the lithium salt as starting material no enantiomeric excess could be detected. However, when the free carboxylic acid was reacted in the presence of CIL in acetate form and dichloromethane, the head-to-head products C and D where formed in 98% selectivity with an enantiomeric excess of 14% for the *anti*-product C, indicating the formation of a dual complex of two 2-anthracencarboxylic acids through electrostatic and hydrogen-bonding interactions. To further investigate this phenomenon different counter anions were examined, leading to an inverse stereoisomer ratio when bis(trifluoromethane)sulfonimide ion was used and an enantioselectivitiy of up to 41% ee for the *syn*-head to tail product B.

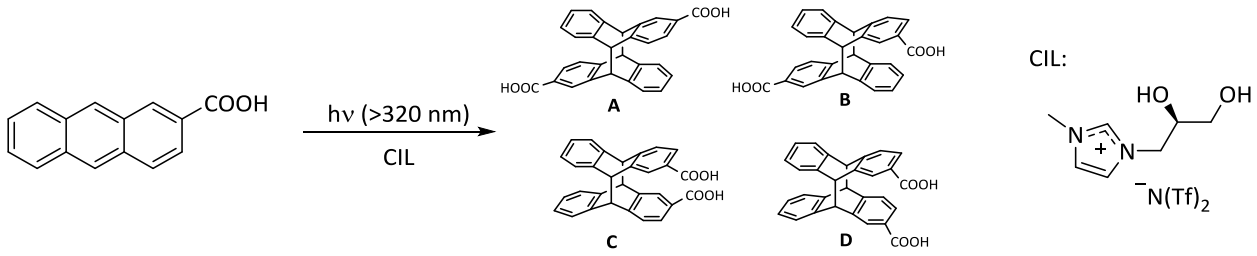


Figure 16: [4+4] Cyclodimerization in Chiral ionic liquids

II 1.1.3 Chiral Ionic Liquids in Heck Reactions

In 2003 Kiss *et al.*[36] reported the first asymmetric Heck reaction in the presence of a chiral imidazolium based ionic liquid as both reaction media and chiral ligand (Figure 17). Although the CIL could actively form a chiral carbene ligand in this reaction due to its imidazolium moiety in the presence of Ag_2CO_3 as base, both yield and selectivity remained very low (13% yield, 5% ee). When triphenylphosphine was introduced as additional ligand the yield increased to 28%. However, selectivity was lost completely, indicating that the chiral ligand was completely exchanged in favour of the palladium phosphine complex and that the solvation of CIL had no influence on selectivity.

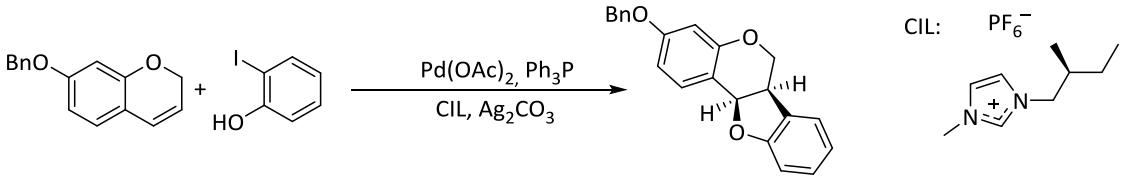


Figure 17: Chiral ionic liquids in asymmetric Heck reaction

The application of CILs as solvent in Heck arylation of aza-endocyclic acrylates was investigated by Correia *et al.* in 2010.[37] A set of novel room temperature CILs with a chiral imidazolium or imidazolinium core and deactivated carbene position was synthesized. A strong influence of the counterion was observed since the best results were achieved with hydrophobic ionic liquids based on the bis(trifluoromethane)sulfonimide anion (Figure 18). Although good conversion (up to 100%) and selectivity towards the ester product (96:0) was reported, no chiral induction could be obtained.

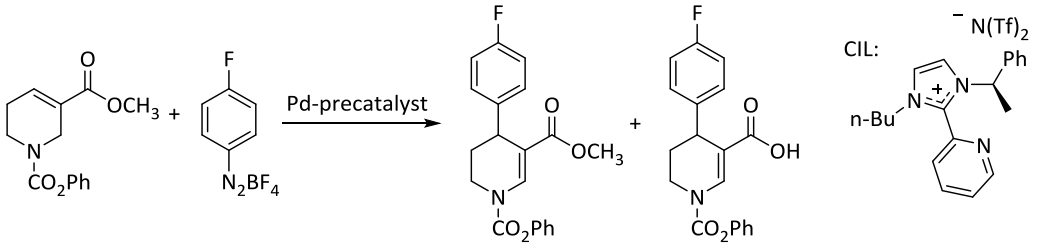


Figure 18: Chiral ionic liquids in asymmetric Heck reaction

The first truly successful application of a CIL as reaction media in the asymmetric Heck reaction was published in 2013 by Morel *et al.*[38] based on some preliminary results in 2011.[39] The influence of different chiral anions based on L-prolinate and L-lactate in combination with non-chiral quartanary ammonium cations on the palladium catalyzed enantioselective Heck arylation of 2,3-dihydrofurane with aryl iodides was reported (Figure 19).

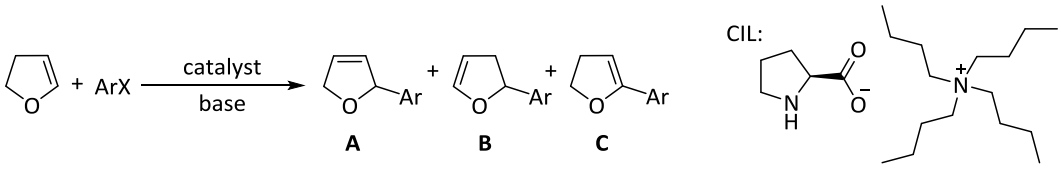


Figure 19: Chiral ionic liquids as solvent in asymmetric Heck reaction

In case of the CIL tetrabutylammonium prolinate as chiral inductor the asymmetric Heck arylation of 2,3-dihydrofurane with $Pd(OAc)_2$ as Pd source proceeded with good conversion (83%), moderate regioselectivity (52% yield for product C) and excellent enantioselectivity (>99% ee). Additional investigations on the influence of the cation revealed that a bulkier cation results in better enantioselectivities. The authors claim that this trend can be traced back to electrostatic effects of the cation with the negatively charged surface of Pd(0) nanoparticles that are formed during the reaction and which were confirmed *via* TEM analysis.

II 1.1.4 Chiral Ionic Liquids in Asymmetric Baylis-Hillman Reactions

An early example of asymmetric Baylis-Hillman reactions was reported by the group around Vo-Than in 2004. This was also one of the first applications of CIL as single source of chirality in asymmetric reactions.[40] An IL with a chiral ephedrinium cation and variable anions was applied as reaction medium in the reaction between benzaldehyde and methyl acrylate in the presence of DABCO as Lewis-base (Figure 20).

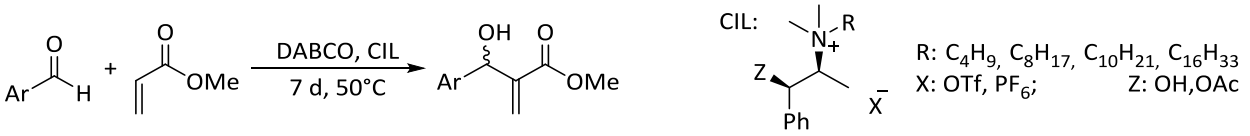


Figure 20: Asymmetric Baylis-Hillman reaction in chiral ionic liquids

The authors were to not only able to enhance conversion from 78% to 85% when using CILs in comparison to the ephedrine-derived non-charged ligand but also improve enantioselectivity from 9% ee to 44% ee. Interestingly, when the alcohol moiety in the CIL was replaced by an acetyl group enantioselectivity was lost, indicating that the alcohol moiety is participating *via* hydrogen bonding with a carbonyl function from either benzaldehyde or methyl acrylate and thus responsible for the chiral interaction.

The same reaction conditions for this benchmark reaction were applied by Headley *et al.* in 2008 using a set of novel chiral ionic liquids based on three different core structures, all of them bearing two chiral centers in a C-2-functionalized imidazolium cation.[41] The use of these bistereogenic CIL resulted in good yields (up to 90%) but unfortunately gave only moderate enantioselectivities (24% ee). Although a better enantioselectivity through the coordination *via* hydrogen bonding of the substrate to the solvent was expected, this chirality transfer could not be confirmed and is still under investigation.

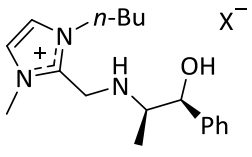


Figure 21: Example of bistereogenic chiral ionic liquids designed by Headley *et al.*

In 2006 Leitner and co-workers published an elegant strategy for the asymmetric aza-Baylis-Hillman reaction using chiral ionic liquids with chiral anions as reaction medium and single source of chiral

induction. The reaction of α,β-unsaturated ketone and an imine in the presence of triphenylphosphine as nucleophilic catalyst proceeded with excellent enantioselectivity (84% ee) and high yields.[42] The authors specifically designed an ionic liquid which can stabilize the zwitterionic intermediate to circumvent racemization. At that time, this outstanding paper reported highest enantioselectivity ever known that was induced solely by a chiral solvent. The obtained values where comparable with the results published with well-designed catalyst for asymmetric aza-Baylis-Hillmann reactions (Figure 22).

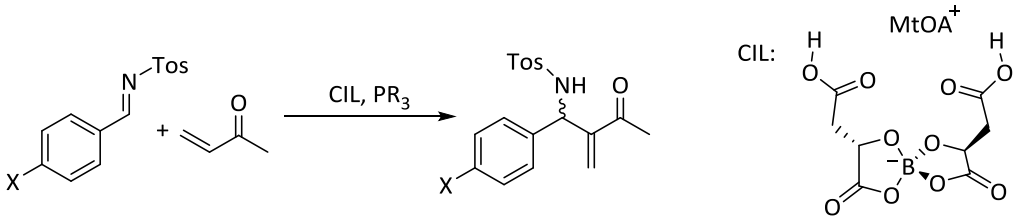


Figure 22: Asymmetric aza-Baylis-Hillmann reaction in chiral ionic liquid

II 1.1.5 Chiral Ionic Liquids in Asymmetric Michael Addition

Bao *et al.* published the application of CILs as reaction media and single source of chirality for the enantioselective Michael addition of diethyl malonate to 1,3-diphenylprop-2-en-1-one in 2005.[43] Although they were able to synthesise novel imidazolium based CILs, starting from commercially available L-diethyl tartrate and L-ethyl lactate, enantioselectivities were rather low (25%-10% ee).

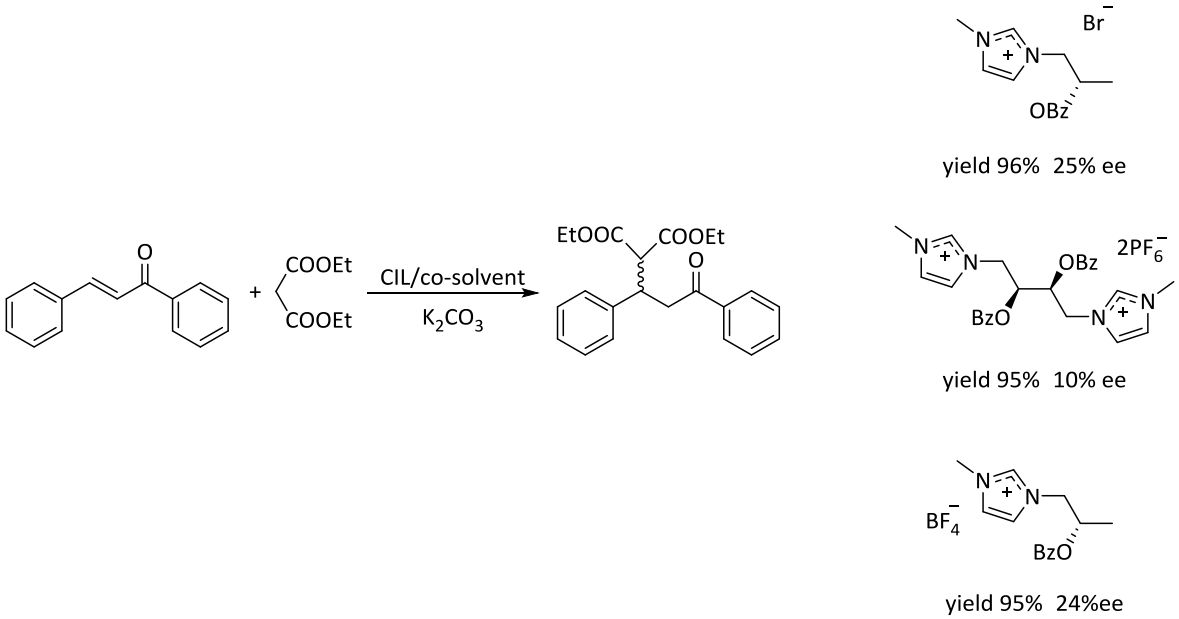


Figure 23: Chiral ionic liquids as reaction media for asymmetric Michael addition

The concept of CILs for the simultaneous use as ligand and reaction media was applied by Malhotra *et al.* in a copper catalyzed 1,4-addition of diethylzinc to α,β-unsaturated enones.[44] A chiral *α*-pinen-based ionic liquid with a quarternized oxazolin moiety and tetrafluoroborate anion was developed and applied as reaction media. Optimum conditions were presented with 35 mol% $Cu(OTf)_2$, and enantioselectivities of up to 76% ee and yields up to 90% could be achieved.

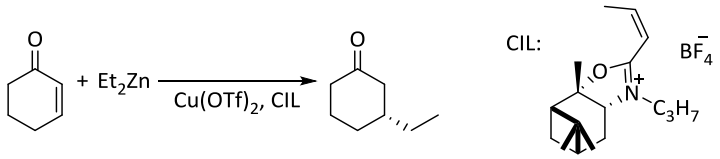


Figure 24: Asymmetric alkylation by Malhotra *et al.*

II 1.1.6 Chiral Ionic Liquids in Sharpless Dihdroxylation

Branco *et al.* published a novel class of room temperature CILs based on tetra-alkyldimethylguanidinium cations in combination with simple chiral anions based on D-lactate, L-mandelate, D-quinic acid and D-camphersulfonate.[45] The group proofed the high thermal stability of these CILs and applied them successfully as reaction media for Rh(II) mediated asymmetric C-H-insertion and asymmetric dihydroxylation.

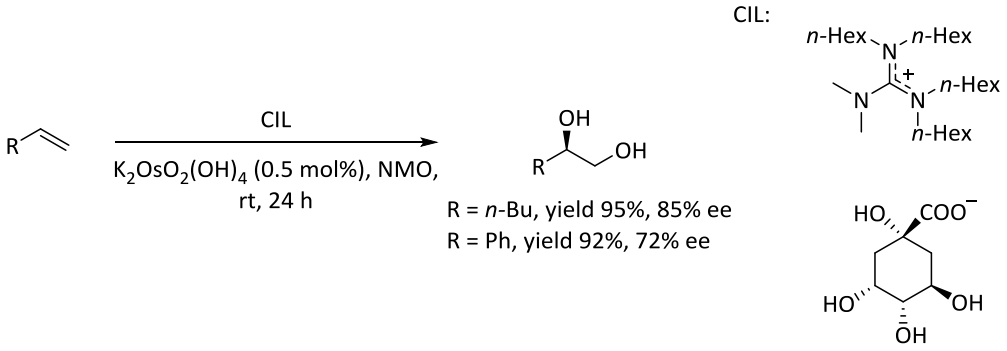


Figure 25: Chiral ionic liquids in Sharpless dihydroxylation

When these CILs were used as reaction media for the asymmetric osmium mediated Sharpless dihydroxylation with NMO as co-oxidant, no further chiral ligand was necessary to obtain the diols in good yield and good enantioselectivity (Figure 25). Furthermore the addition of the olefin, which is usually added slowly to the reaction mixture to allow active complex formation, could be accelerated when the CIL was used.

II 1.1.7 Chiral Ionic Liquids in Biginelli Reaction

In 2008 Yadav *et al.* reported the first diastereo- and enantioselective three-component Biginelli reaction of polyfunctionalized perhydropyrimidines (Figure 26) in CILs as reaction medium.[46] A set of amino acid-derived CILs was designed including the protic ionic liquids L-prolinium sulfate and L-alaninium hexaflurophosphate. Among these systems, L-proline-derived CILs were most successful, and a variety of functionalized perhydropyridines could be isolated as single diastereomers in good yields (up to 93%) and excellent enantioselectivities (up to 95% ee).

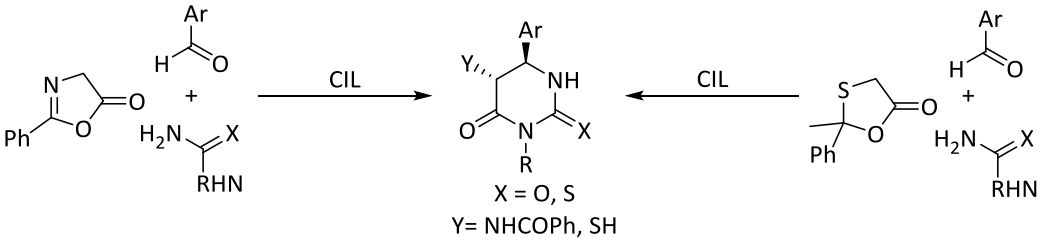


Figure 26: Chiral ionic liquids in asymmetric Biginelli reaction

II 1.1.8 Chiral Ionic Liquids in Biotransformations

Although the use of ionic liquids as solvents in biotransformations has found broad application, CILs are less explored for this purpose. There are only a few examples of CILs in biocatalysis, the most significant being published by the group around Zhao in 2006.[47] The authors investigated the enzymatic hydrolysis of phenylalanine methyl ester as model reaction to examine protease activity and enantioselectivity in different ω-amino acid based CILs with [C_2mim] cation to stabilize the enzyme (Figure 27). For this purpose they investigated the influence of different concentration of CIL in water or deuterium oxide and the effect of different ω-amino acid based anions. The group was able to demonstrate that high concentrations of CILs destabilized the enzyme but that the presence of the dissociated ions in water can enhance the enzyme activity at low concentrations. Furthermore they were able to show that the CILs based on D-amino acids are more favourable than those based on L-amino acids.

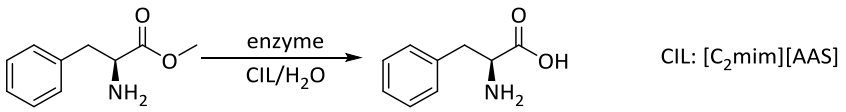


Figure 27: Chiral ionic liquids as solvent in biotransformation

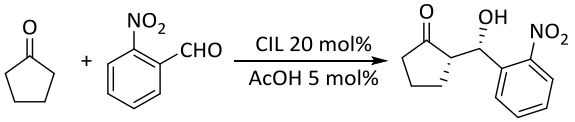
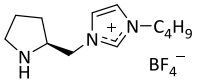
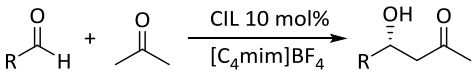
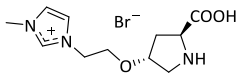
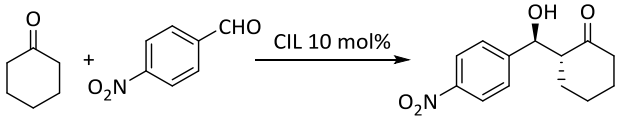
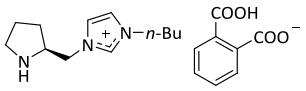
II 1.2 Chiral Ionic Liquids as Organocatalysts

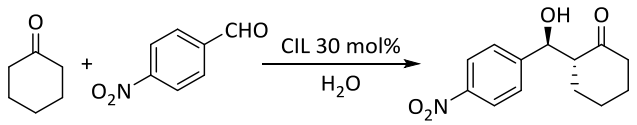
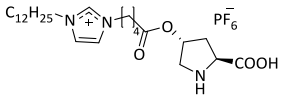
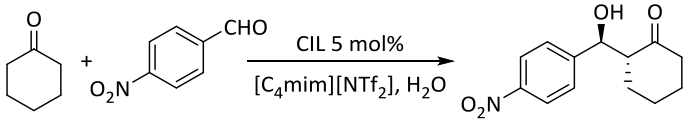
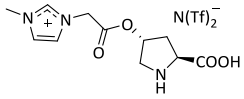
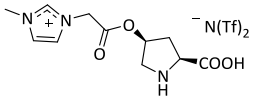
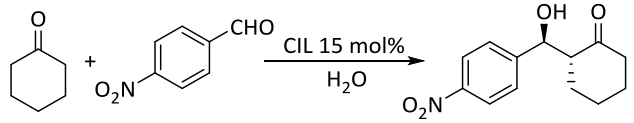
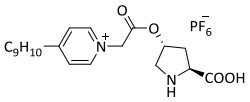
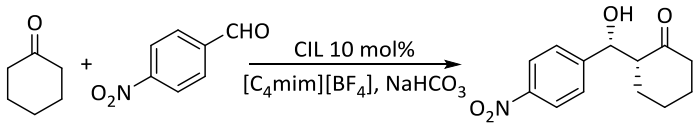
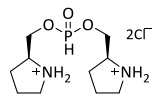
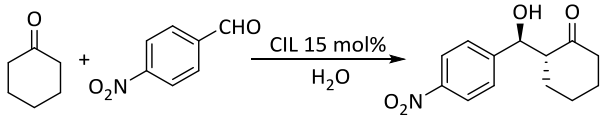
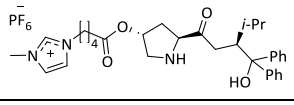
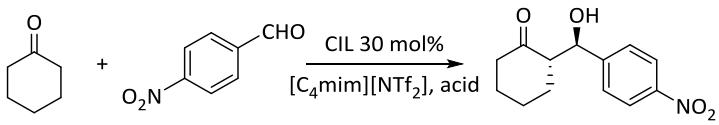
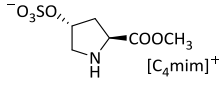
II 1.2.1 Chiral Ionic Liquids in Asymmetric Aldol Reaction

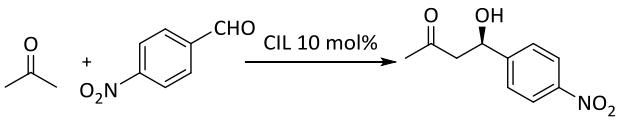
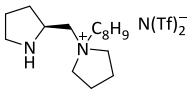
Enantioselective aldol reactions catalyzed by small organic molecules provide a unique and booming methodology in asymmetric C-C bond forming reactions. Proline-like cyclic five-membered secondary amine structures have been recognized as privileged organocatalysts, as they catalyze reactions *via* an enamine-type transition state and favour the attack from one side.[48]

Chiral ionic liquids can be designed to meet this criteria by keeping the structural motives which are important for the active catalyst, but offer also the possibility to adjust the hydrophilicity thus allowing "in water" reactions. Consequently a lot of effort has been put into the development of CILs suitable for aldol reactions which resulted in a couple of noteworthy publications and a short overview is given in Table 1. Since 2007 many different CILs, mostly based on a proline or hydroxyproline core, have been designed and applied in the asymmetric aldol reaction. Research has often focused on the optimization of tuneable solubility of the ionic liquid-based organocatalyst for the use under aqueous conditions and for recycling protocols of the active organocatalyst.

Table 1: Chiral ionic liquids in asymmetric aldol reactions

entry	reaction				ref.
	CIL	yield (%)	ee (%)	dr	
1					Luo[49] 2007
		92	11	5:1	
2					Zhou[50] 2007
		94	84	-	
3					Zhang[51] 2007
		94	55	70:30	

4					Siyutkin[52] 2008
		95	99	97:3	
5					Lombardo[53] 2009
		37	99	94:6	
		87	99	92:8	
6					Zlotin[52] 2008
		97	97:3	99	
7					Xu[54] 2010
		99	84	99:1	
8					Larionova[55] 2011
		90	70	24:76	
9					Schmitzer[56] 2012
		72	52	75:25	

10					Vasiloiu[26] 2013
		94	72		

The first successful example for the application of a proline-functionalized CIL for aldol reactions was published in 2007.[49] Luo *et al.* investigated the influence of different proline-derived CILs with hydrophilic and hydrophobic counter anions and different imidazolium-based ionic headgroups (Table 1, entry 1). Furthermore the group showed that the addition of acid to the CIL, especially acetic acid prevents the formation of the undesired elimination side product. Although only moderate enantio- and diasteroselectivities were observed, they could nevertheless demonstrate the possibility of recycling using the CIL catalyst in 6 consecutive runs with excellent conversions, although losses in enantioselectivity were observed. The authors suggest that the rather low enantioselectivities are caused by a certain space shielding for the participating aldehyde acceptor by the ionic liquid moiety.

The group of Siyutkin designed a novel L-proline based CIL for a highly enantio- and diastereoselective aldol reaction in water and demonstrated its reuse in 5 consecutive runs without any loss in selectivity and yield (Table 1, entry 4).[52] After completion of the reaction the product was extracted with diethyl ether and fresh starting materials were added without the need of isolation or purification of the catalyst.

Lombardo *et al.* published a series of investigations on the improvement of asymmetric aldol reaction using "ion-tagged L-prolins" from 2007-2009 (Table 1, entry 5).[57] Investigations regarding the influence of the anion revealed that lipophilic bis(trifluoromethane)sulfonimide improves the reaction in comparison to the tetrafluoroborate anion. Additionally, aqueous biphasic conditions instead of the neat ionic liquid [C_4mim][NTf_2] were identified as optimum, and no additional organic solvent was required.[58] Fine-tuning of the catalyst was achieved by adapting the catalyst geometry from *trans*- to *cis* geometry at the proline subunit. This could improve the yield from 37% in case of the *trans* catalyst to 87% with the *cis* catalyst. With this system exceptionally high turnover numbers of 196 could be achieved together with excellent enantioselectivities.

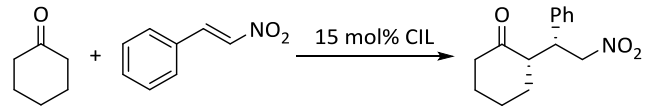
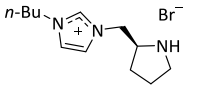
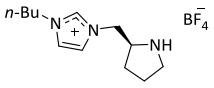
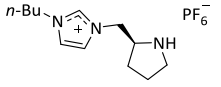
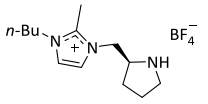
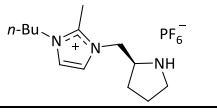
Recently our group designed a novel set of CILs that was specifically designed to replace trifluoroacetic acid in enamine-based organocatalysis for asymmetric C-C bond formation (Table 1, entry 10). Chiral pyrrolidinium-based CILs with permanent charge could replace the active protonated species in organocatalytic aldol additions and thus circumvent the use of corrosive acids.[26] The asymmetric aldol reaction of 4-nitrobenzaldehyde and acetone was performed with good yields and selectivities up to 80% ee without additional acid.

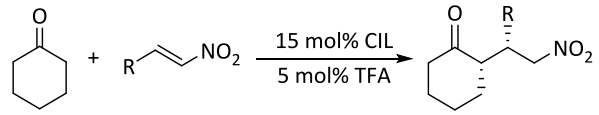
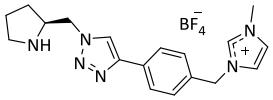
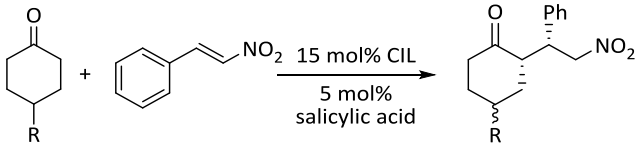
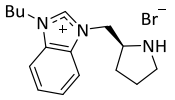
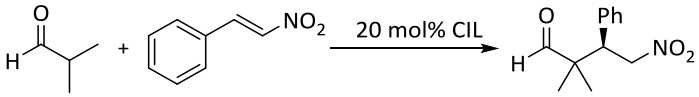
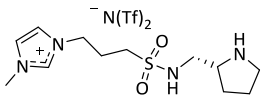
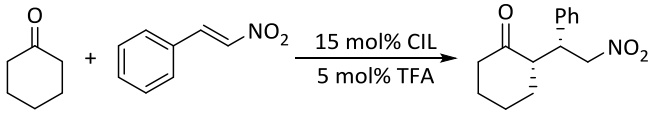
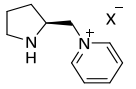
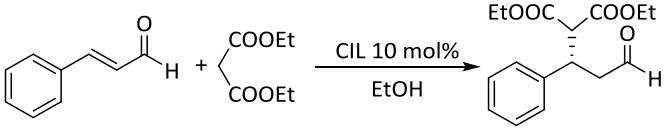
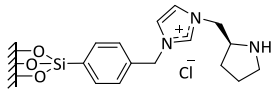
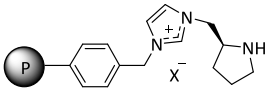
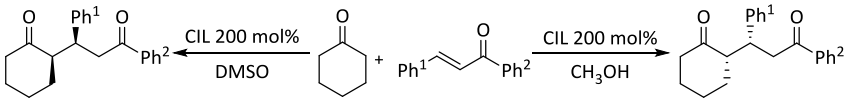
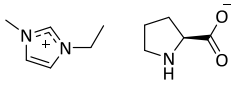
II 1.2.2 Chiral Ionic Liquids in Asymmetric Michael Addition

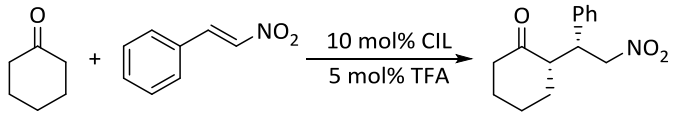
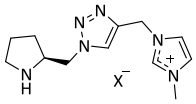
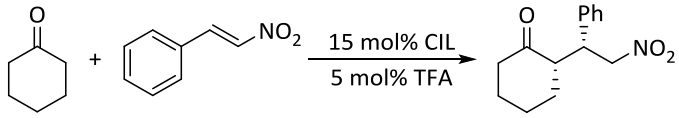
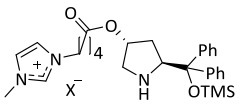
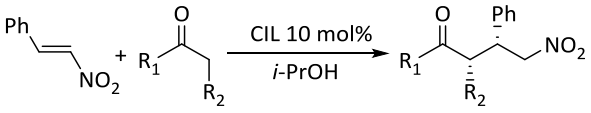
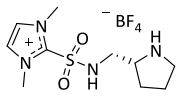
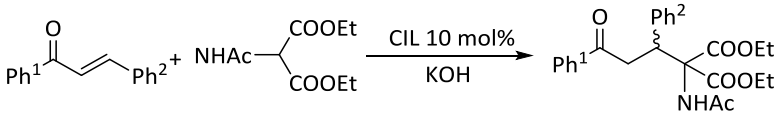
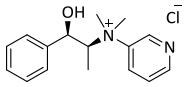
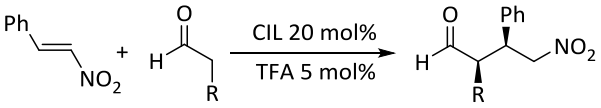
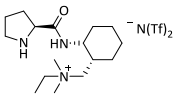
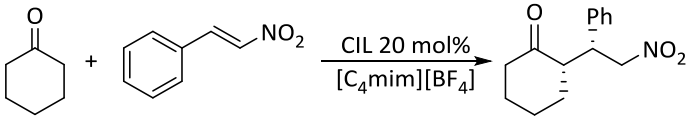
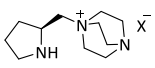
The asymmetric Michael addition is a very powerful C-C-bond forming reaction and has been subject of intense research, especially in terms of environmental friendly procedures such as metal-free organocatalysis.[59] It has been shown that chiral pyrrolidine-, imidazolidine- and proline-based structures are very promising organocatalysts for the Michael addition since they can promote an enamine-type transition state.

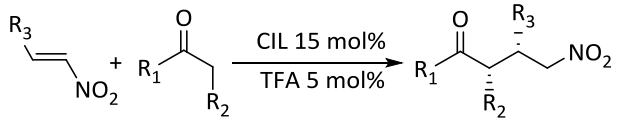
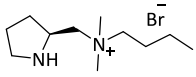
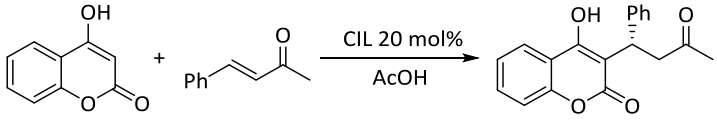
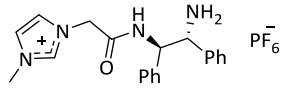
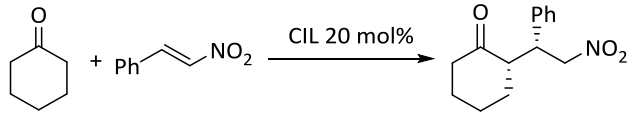
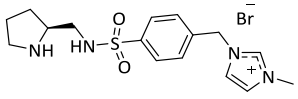
In recent years many examples of asymmetric Michael addition using CIL as single chirality source were published that typically rely on ionic liquid-tagged chiral proline or pyrrolidine units which have been shown to be favorable structures. The following table presents an overview on recent research and depicts the most successful examples (Table 2).

Table 2: Chiral ionic liquids in asymmetric Michael addition

entry	Reaction				ref.
	CIL	yield (%)	ee (%)	dr	
1					Luo[60] 2006
		99	98	99:1	
		100	99	99:1	
		86	87	98:2	
		100	94	96:4	
		40	82	96:4	

2					Luo[61] 2007
		96	94	97:3	
3					Wu[62] 2007
		up to 99	up to 97	4:1:3	
4					Headley[63] 2007
		58	82		
5					Headley[64] 2008
		95	93	99:1	
6					Li[65] 2x 2008
		96	99	97:3	
		97	99	99:1	
7					Qian[66] 2008
		98	86	20:80	

8					Miao[67] 2008
		95	99	99:1	
9					Maltsev[68] 2009
		93	96	98:2	
10					Headley[69] 2009
		97	99	99:1	
11					Vo Than[70] 2010, Truong[71] 2012
		55/98	70/80		
12					Kodama[72] 2010
		99	98	99:1	
13					Xu[73] 2010
		100	97	99:1	

14					Wang[74] 2011
		85	99	99:1	
15					Kucherenko[75] 2012
		97	78		
16					Li[76] 2013
		93	92	99:1	

Based on the reported results of organocatalytic Michael addition[48] the group around Luo designed a set of CILs starting from L-proline with an imidazolium moiety and different hydrophobic and hydrophilic counter anions like bromides, tetrafluoroborates or hexafluorophosphates (Table 2, entry 1).[60] They carefully designed these novel CILs so that the pyrrolidine moiety that is responsible for the catalytic activity was not modified, and thus available for the enamine-transition state. With this concept they could demonstrate that CILs could be used as very efficient catalysts resulting in high yields (up to 100 %) and excellent enantio- and diastereoselectivities. Furthermore they could show that the substrate range for Michael donors and acceptors was very broad and that the results could be optimized by the use of the counter ions Br^- and PF_6^-. The high diastereoselectivity and enantioselectivity was proposed to be based on the concept of an acyclic synclinal transition state, as published by Seebach and Golinski, indicating that the ionic liquid moiety can effectively block the *Si* face of the enamine double bond and thus results in the selective reaction at the *Re* side (Figure 28).[77] The same group later published the synthesis of functionalized CILs for Michael additions of racemic 4-substituted cyclohexanones, thereby representing the first example of intermolecular desymmetrization *via* organocatalytic Michael addition with chiral ionic liquids (Table 2, entry 2).[61]

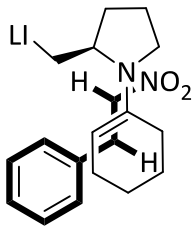


Figure 28: Transition state for asymmetric Michael addition

Although Luo *et al.* aimed to recycle and reuse the CIL in their experiments, it was the group around Wu who could successfully apply the IL in consecutive runs (Table 2, entry 3).[62] This was managed by precipitation of the catalyst by adding diethyl ether and drying of the catalyst phase.

Headley and co-workers presented a study regarding the influence of solvents for the use of functionalized CILs in Michael addition (Table 2, entry 4). They could demonstrate that the use of polar solvents such as MeOH and *i*-PrOH in combination with organocatalytically active ionic liquids results in higher yields.[63] In 2008 the same group reported further IL-based organocatalysts suitable for Michael addition that gave good yields and enantioselectivities.[64, 78]

In order to improve recyclability Li *et al.* reported in 2008 the immobilization of proline-derived CILs on solid support (Table 2, entry 6). Silica-supported CILs could be successfully applied in the Michael addition of diethyl malonate and cinnamic aldehyde, and the immobilized ionic liquid phases could be recycled for at least 5 times without any loss in catalytic activity and stereoselectivity.[65b] The same group also reported the immobilization on polymer support, e.g. Merrifield resin with a loading of 2.5 mmol active IL/g support.[65a] In comparison to the unbound form, the polymer could be reused 2-3 times more often.

Further investigations by Qian and co-workers on proline-derived CILs focused on the influence of different solvents in the stereoselective organocatalytic Michael addition (Table 2, entry 7).[66] They could demonstrate a switch from polar-protic MeOH to DMSO results in the inversion of enantioselectivity. The authors proposed this effect might be caused by coordination of DMSO to the iminium intermediate, thereby blocking the attack from one side.

II 1.2.3 Chiral Ionic Liquids in Asymmetric Diels Alder Reactions

One of the rare examples for the use of CILs as organocatalysts in asymmetric reactions other than aldol reaction and Michael addition was published by Zheng and co-workers in 2010.[79] The authors used a CIL in asymmetric aza-Diels Alder reaction and reported the first successful application of L-proline-based CIL as organocatalyst in this kind of reaction (Figure 29). Using an amount of 30 mol% organocatalyst they could obtain good yields (up to 93%) and excellent enantio- (>99%) and diasteroselectivities (>99:1). Because of the high amounts of catalyst required, the recycling of active was further investigated. The authors were able to recycle the active catalytic system over six runs without any loss in performance. The product was extracted using an organic solvent and the catalyst was reused after drying.

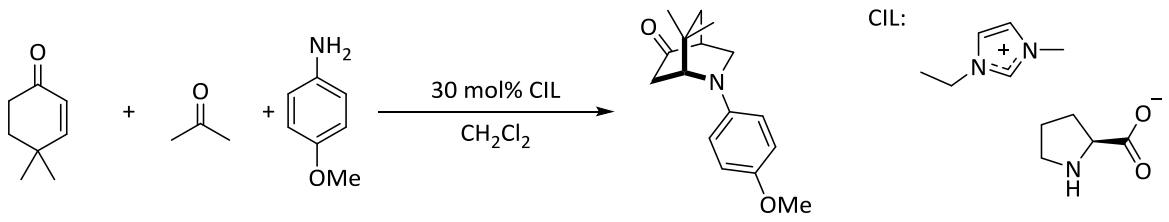


Figure 29: Chiral ionic liquids as organocatalysts in aza-Diels Alder reaction

II 1.3 Chiral Ionic Liquids as Ligands in Transition Metal Catalysis

Apart from the use as mere chiral solvent or organocatalyst, ILs can be used as support materials for chiral ligands. The general approaches involve a known structural motive approved for its good chiral induction that is grafted to an ionic liquid moiety that results in tailor-made CILs for various asymmetric transformations. In many cases, this strategy results in improved reaction rates and selectivities obtained with the supported ligand and provides the benefit of catalyst recycling.

II 1.3.1 Chiral Ionic Liquids based on Bis(oxazoline) Ligands

In 2007 Doherty *et al.* presented the first truly successful use of a CIL as single source of chirality in asymmetric copper(II)-catalyzed Diels Alder reaction. In the reaction of *N*-acryloyl- and *N*-crotonoyloxazolidinons with cyclopentadiene and 1,3-cyclohexadiene the CIL acts as ligand and not reaction media (Figure 30).[80] The ionic liquid was based on a chiral bis(oxazoline) moiety linked to an imidazolium cation with hydrophilic or hydrophobic anions. This ionic liquid-tagged chiral ligand was applied in catalytic amounts of 10 mol% and dissolved in conventional solvents or in an IL ([C_2mim][NTf_2]). Higher rates could be achieved in the IL reaction media giving excellent yields (up to 100%) and high diasteroselectivities (95% ee). Furthermore they could successfully recycle and reuse the imidazolium-tagged catalyst in 10 consecutive runs without any loss in catalyst performance, thereby emphasizing the potential of ionic liquid-tagged chiral ligands immobilized in a non-chiral ionic media.

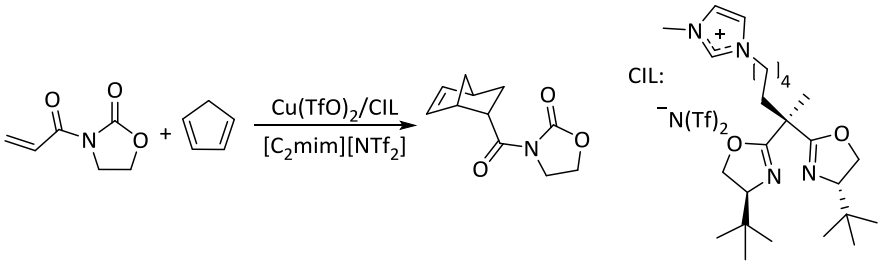


Figure 30: Chiral ionic liquids as ligand in Diels Alder reaction

As shown in chapter II 1.2 the majority of CILs find application as organocatalysts in asymmetric aldol reactions. One of the few examples for different kind of application was published by Doherty *et al.* in 2008 who used a CIL as ligand in copper-catalyzed Mukaiyama aldol reaction (Figure 31).[81] Again, bisoxazolidine structures that are known for their excellent performance when used as ligands in many asymmetric transition metal catalyzed transformations were converted to the corresponding imidazolium-tagged CILs. The authors also investigated the use of achiral IL as reaction media and were able to observe high conversions of up to 100% and enantioselectivities of up to 90% ee in both, conventional solvent and IL. Furthermore the group was able to recycle and reuse the catalytic system over 8 runs after immobilizing the CIL catalyst on a silica phase, unfortunately with some loss in conversion (29% conversion and 91% ee after the 8th run).

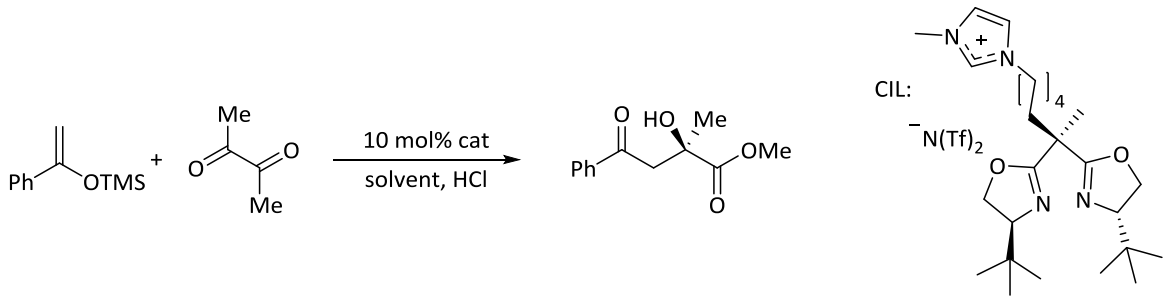


Figure 31: Chiral ionic liquids in asymmetric Mukayama aldol reaction

II 1.3.2 Chiral Ionic Liquids based on Bisphosphine Ligands in Asymmetric Enantioselective Hydrogenations

The application of CILs as ligands for hydrogenation has been shown by Lee *et al.* for the first time in 2003.[82] They used an IL backbone for the immobilization of a chiral 1,4-bisphosphine ligand in asymmetric rhodium catalyzed hydrogenation of *N*-acetylphenylethanamine in an achiral ionic liquid (Figure 32). With this grafted ligand the authors demonstrated that the stability of the complex could be increased, that catalyst leaching into the product could be circumvented and that the ligand system is highly active yielding the product with excellent conversion of up to 100% and excellent enantioselectivities of up to 97% ee.

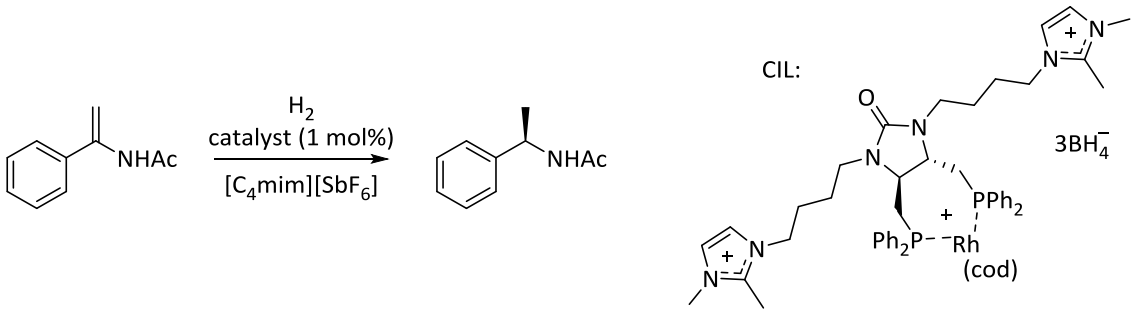


Figure 32: Immobilization of ligand on chiral ionic liquid backbone

II 1.3.3 Chiral Ionic Liquids based on Amino Alcohol and Diol Ligands

The first asymmetric alkylation of carbonyl groups with CILs was published by Gadenne *et al.* in 2004 using camphor, borneol or isoborneol based CILs with an imidazolium moiety.[83] These CILs were used as ligands in the Ti(IV)-catalyzed alkylation of benzaldehyde with diethylzinc in dichloromethane. The application of ionic liquid-tagged chiral ligands instead of the conventional ligands opened not only the possibility for recycling but enabled homogenous conditions when dichloromethane was used as co-solvent. As a result, enantioselectivity increased to 40% by introduction of the ionic liquid-supported

ligand, whereas no enantioselectivity was observed for the non-ionic camphorsulfonamide (Figure 33). Gadenne *et al.* could demonstrate that the *endo*/*exo* stereochemistry of the hydroxyl group in the borneol and isoborneol is of special importance. Enantioselectivity was significantly higher for the isoborneol diastereomer, and this form was used after separation *via* column chromatography. Furthermore, the CIL ligand could be recycled and reused for 4 runs without any loss in selectivity and with complete conversion of benzaldehyde.

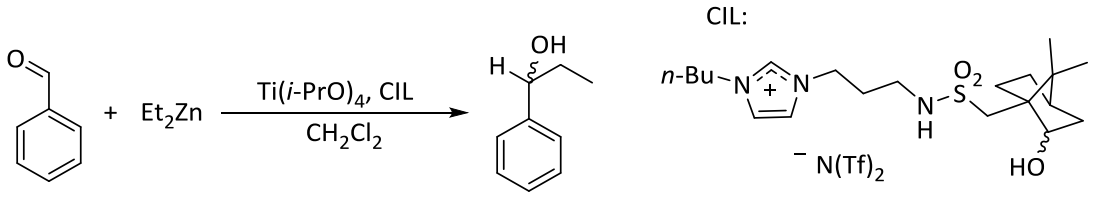


Figure 33: CIL in asymmetric alkylation reaction

Since 2,2'-binaphthol (BINOL) ligands have proved to be excellent chiral ligands in transition metal catalysis, the same group further developed novel BINOL-based CILs (Figure 34).[84] With this novel type of CIL, improved enantioselectivities of up to 82% ee were obtained and could be maintained for over five repetitive runs. While similar selectivities were observed with unfunctionalized BINOL ligands without ionic moiety, recycling of them was not possible.

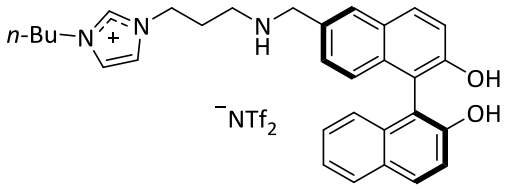


Figure 34: BINOL based chiral ionic liquids

Jurčik and co-workers presented a novel approach towards the application of CIL in alkylation reactions based on chiral C-2-symmetric bidendate ligands (Figure 35). A set of novel chiral imidazolium derivatives bearing two hydroxyl-containing substituents that can be easily deprotonated to form a carbene precursor was designed. When applied in the asymmetric alkylation of aromatic aldehydes with diethylzinc no further addition of transition metal was required and different alcohols were isolated with up to 67% yield and 67% ee.[85]

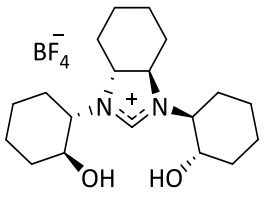


Figure 35: Example of chiral ionic liquid bearing two hydroxy-containing substituents

Recently our group reported the synthesis of a set of novel coordinating CILs derived from the chiral pool featuring an amino alcohol sub-structure (Figure 36).[86] The CILs were carefully designed to act as chiral ligand *via* their amino alcohol structure while an additional pyridinium moiety was installed to form an ionic liquid. When tested as chiral ligands in the enantioselective alkylation of benzaldehyde with diethylzinc, excellent yields and high enantioselectivities of up to 91% ee were observed. Recycling of the chiral ligand was possible; however, losses in enantioselectivity were observed.

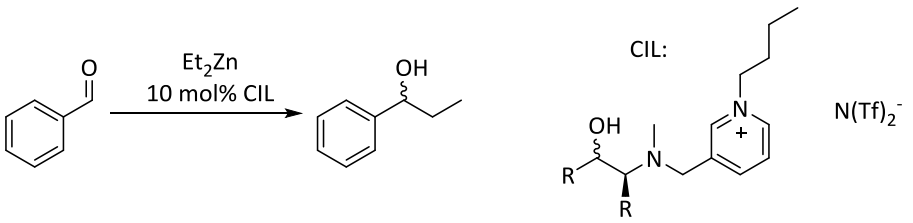


Figure 36: Chiral ionic liquids as ligands in asymmetric alkylation reaction

II 1.4 Chiral Ionic Liquids as Auxiliaries or Additives

II 1.4.1 Chiral Ionic Liquids in Asymmetric Enantioselective Hydrogenations

In 2007 Schulz *et al.* reported an elegant example for enantioselective hydrogenation featuring CILs without additional chiral metal complex. In this outstanding contribution chirality transfer was achieved solely *via* ion-pairing effects in the anion-chiral ionic liquid.[24] The CIL *N*-methylimidazolium L-camphorsulfonate was reacted in a Michael-type addition with methyl vinyl ketone to give the ionic liquid *N*-(3`-oxobutyl)-N-methylimidazolium L-camphorsulfonate with a prochiral cation. Hydrogenation of the cation under heterogeneous conditions using Ru/C in EtOH gave the corresponding hydroxybutyl derivative in excellent yield of up to 99% and high enantioselectivity of up to 80% ee (Figure 37).

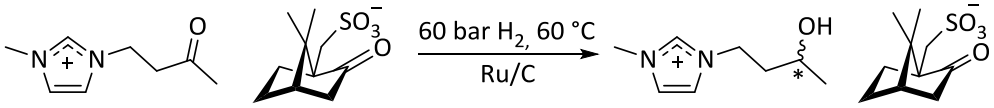


Figure 37: Enantioselective hydrogenation *via* chiral ionic liquids by Schulz *et al.*[24]

The fact that the chiral information was transmitted solely due to the ion-pairing effect was confirmed by the strong dependence of achieved enantioselectivity on concentration of the CIL and by the absence of enantioselectivity when the non-ionic substrate acetophenone was used instead of the prochiral cation. In the following years Wasserscheid *et al.* published further investigations on this effect,[87] broadening the substrate scope,[88] the reaction conditions[89] and knowledge on ion aggregation and degree of dissociation depending on concentration and solvent.[90]

In 2007 Schmitkamp and co-workers used chiral atropoisomeric binaphtyl and biphenyl ligands that are common ligands in metal catalyzed asymmetric hydrogenations in combination with CILs as reaction media.[91] Due to the rapid rotation of the phenylrings around the single bond, these ligands are present in racemic form without permanent chirality, thus the only source of chirality could be induced by the chiral reaction media. When L-proline-based CILs were used as additive in the homogeneous Rh-

catalyzed hydrogenation of 2-acetamidoacrylate and dimethyl itaconate, enantioselectivities of up to 69% were observed. In a following publication, the authors could demonstrate that chiral induction was based on chiral poisoning of the catalyst by the CIL, meaning that the CIL could effectively block one enantiomer of the catalyst. This was verified by the fact that the same results, for yield and enantioselectivity were obtained, when either the racemic ligand or the enantiomerically pure ligand was used.[92]

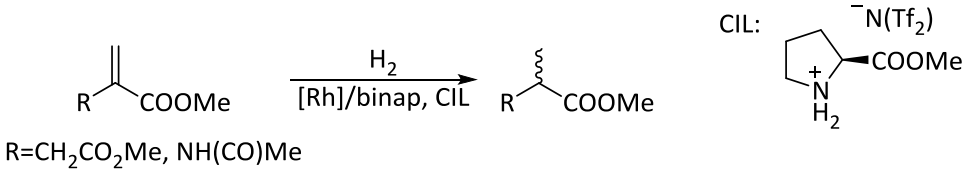


Figure 38: CIL in asymmetric hydrogenation reaction

In 2013 Ferlin *et al.* presented the enantioselective hydrogenation of several α,β-unsaturated ketones using $PdCl_2$ and several CILs, containing a proline-based anion and a tetrabutylammonium cation, as additives.[93] The group could isolate the product in quantitative yield and moderate enantioselectivities of up to 47% ee, unfortunately no adaptation of CIL:$PdCl_2$ ratio, solvent or other reaction conditions could further improve the reaction outcome.

II 2 Chiral Ionic Liquids in Separations

In the last fifteen years considerable effort has been put into the design and application of chiral ionic liquids in diverse areas. Based on their ionic structure and special properties, chiral ionic liquids are of particular interest for separation sciences. It has been shown that they provide separation characteristics that have not been observed with conventional substrates. Consequently, chiral ionic liquids offer novel separation methodologies and solutions to difficult separation problems.

Although many examples for the successful application of chiral ionic liquids in separations are known, their use is mostly focused on the analytical scale. So far, chiral ionic liquids have been successfully used as shift reagents in NMR spectroscopy, as stationary phases in chromatography or as additives in capillary electrophoreses. Only few examples exist for the separation of racemic compounds on preparative scale, indicating that the potential in this important area still has to be explored (Figure 39).

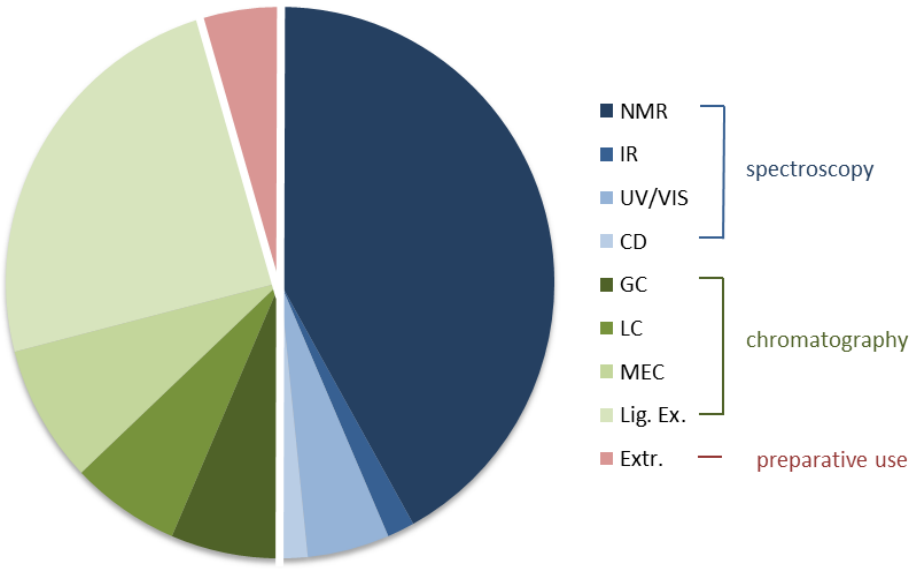


Figure 39: Applications of chiral ionic liquids in separation sciences

II 2.1 Chiral Recognition Properties in NMR Spectroscopy

Chiral ionic liquids have been recognized for years to affect the outcome of an asymmetric reaction or a separation process, although the prediction of any chiral ionic liquids' performance is difficult. In 2002 Wasserscheid *et al.* presented a new evaluation method for the chiral recognition properties of chiral ionic liquids that allowed a quantitative comparison for the strength of interactions between chiral ionic liquids and a racemic substrate (Figure 40).[94] The authors performed ^{19}F-NMR spectroscopy of a mixture of racemic Mosher's acid sodium salt and the chiral ionic liquid in a common NMR solvent. Depending on the chiral ionic liquid applied in the experiment, a splitting of the ^{19}F-signal of the CF_3-group was observed, thus giving evidence for the environment and the presence of a diasteromeric pair of the chiral cation and the two enantiomers of Mosher's acid (Figure 41). The formation of the diastereomeric salts can be further enhanced by the addition of 18-crown-6 ether to trap the potassium cation or by the application of Mosher's acid silver salt in combination with halide-based chiral ionic liquids. Since 2002, this method has found a very broad application range and is often used for the evaluation and quantification of the chiral recognition properties of novel chiral ionic liquids.

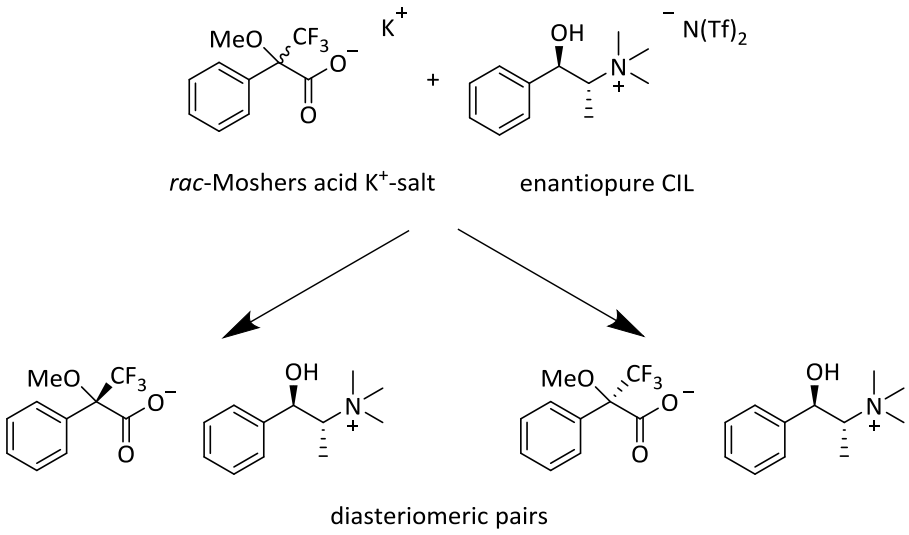
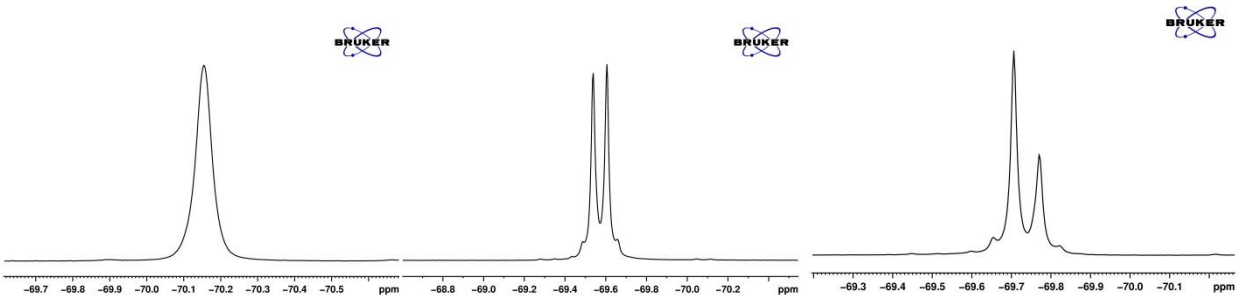


Figure 40: Formation of diastereomeric ion pairs between chiral ionic liquid and racemic Mosher's acid potassium salt



rac-Mosher's acid K^+ salt

rac-Mosher's acid K^+ salt in presence of chiral ionic liquid

enantioenriched-Mosher's acid K^+ salt in presence of chiral ionic liquid

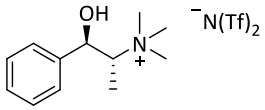
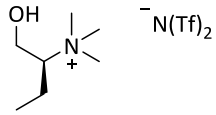
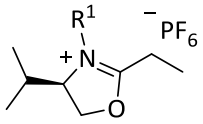
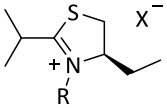
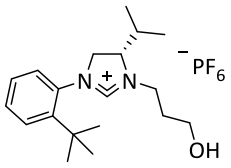
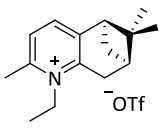
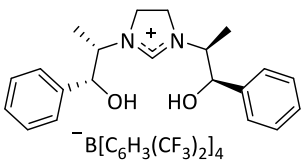
Figure 41: Splitting of the ^{19}F-signal of Mosher's acid K salt in the presence of a chiral ionic liquid

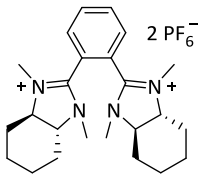
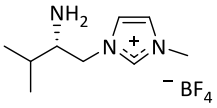
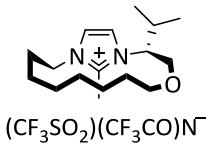
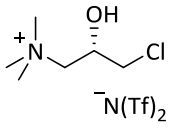
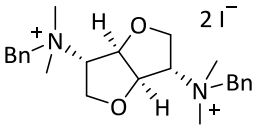
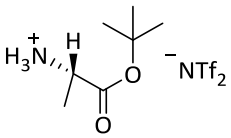
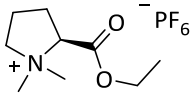
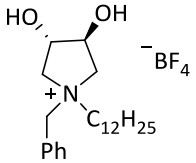
The group of Wasserscheid reported a splitting of the ^{19}F-NMR signal of 11 Hz using an ephedrine-based chiral ionic liquid in CD_2Cl_2 as solvent.[94] The strongest interactions were observed when the ionic liquid was used in a large excess of 8 equivalents. Interestingly, a strong influence of the water content was observed indicating the importance of solvent composition (Table 3, entry 1).

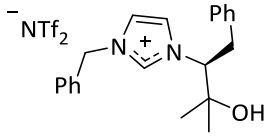
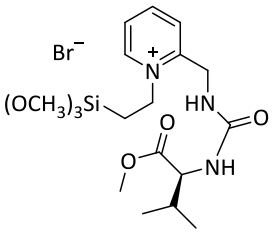
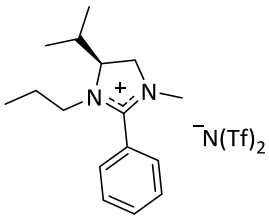
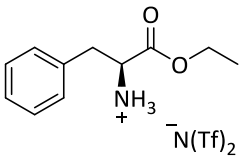
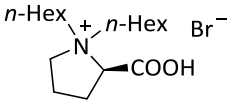
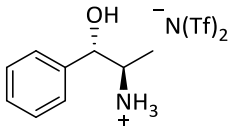
Remarkable results were obtained by Clavier *et al.* using imidazolium salts derived from L-valine achieving a splitting of 63 Hz of the ^{19}F-NMR signal (Table 3, entry 5).[95] By changing the counterion to the bulkier potassium ion the tightness of the ion pair could be decreased, leading to an increased diasteromeric interaction. In addition the group around Clavier could demonstrate the importance of the aromatic system in the CIL leading to a π-π stacking with the racemic substrate and enhanced recognition properties.

So far, the highest Δppm value was obtained by Jurčík *et al.* who specifically designed imidazolidinium salts bearing two hydroxy-containing substituents as chiral shift reagents (Table 3, entry 7).[85] Starting from chiral pool-derived amino alcohols, the incorporation of a bidentate hydroxy-structure amplified the splitting of the NMR signal and indicated the importance of the hydrogen bonding abilities. A shift difference of up to 151 Hz was observed in ^{19}F-NMR for an ephedrine-derived bidendate chiral ionic liquid which is still the largest value ever reported in literature. The authors also found a strong dependence on the anion: Whereas good Δppm values were also obtained with the weekly coordinating bis(trifluoromethane)sulfonimide the change to tetrafluoroborate resulted in the disappearance of the splitting and no measureable interactions.

Table 3: Chiral recognition properties of different ionic liquids in ^{19}F-NMR spectroscopy

entry	chiral ionic liquid	NMR shift (ΔHz)	conditions	ref.
1		11		
2		n.d.[a]	CD_2Cl_2+water, 8.2 eq. CIL, Mosher acid/ Na^+ salt	Wasserscheid[94] 2002
3	 R^1= methyl, pentyl	n.d.[a]		
4	 R= *n*-C_4H_9, *n*-$C_{12}H_{25}$ X= PF_6^-, BF_4^-, NTf_2^-	11	C_6D_6+water, 5 eq. IL, Mosher acid/ Ag^+ salt	Levillain[96] 2003
5		63	CD_2Cl_2, 3.3 eq. CIL, Mosher acid/ K^+ salt	Clavier[95] 2004
6		4	CD_2Cl_2, 10 eq. CIL, Mosher acid/ $N(Bu)_4^+$ salt	Drahonovsky[97] 2005
7		151	acetone-d_6, 1 eq. CIL, Mosher acid/ K^+ salt	Jurčíik[98] 2006

8		53	acetone-d_6, 1 eq. CIL, Mosher acid/ K^+ salt	Jurčíik[85] 2006
9		35	C_6D_6+water, 3.7 eq. IL, Mosher acid/ Ag^+ salt	Luo[23] 2006
10		7	$CDCl_3$, 3 eq. CIL, Mosher acid/ K^+ salt	Ishida[99] 2006
11		25	CD_2Cl_2+ water, 3.7 eq. CIL, Mosher acid/ Na^+ salt	Tran[100] 2006
12		15	CD_3CN, 1 eq. CIL, Mosher acid/ Ag^+ salt	Kumar[101] 2008
13		n.d.[a]	DMSO, Mosher acid/ Na^+ salt	Bwambok[102] 2008
14		n.d.[a]	Mosher acid/ Ag^+ salt	Gao[103] 2008
15		8	$CDCl_3$, 3 eq. CIL, Mosher acid/ K^+ salt	Bonnani[104] 2009

16		13	CD_3CN, 3 eq. CIL, Mosher acid/ K^+ salt	Altava[105] 2009
17		15	$CDCl_3$, 3 eq. CIL, Mosher acid/ K^+ salt	Li[106] 2009
18		15	$CDCl_3$, 2 eq. CIL, Mosher acid/ K^+ salt	Winkel[107] 2009
19		11	CD_2Cl_2 + 30% DMSO, Mosher acid/ Na^+ salt	Bwambok[108] 2010
20		11	$CDCl_3$, 20 eq. CIL, Mosher acid/ K^+ salt	Yu[109] 2010
21		13	$CDCl_3$, 5 eq. CIL, Mosher acid/ K^+ salt	De Rooy[110] 2011

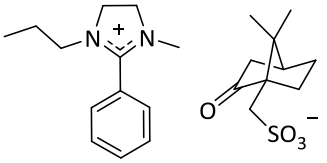
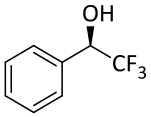
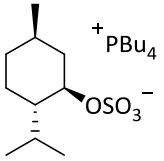
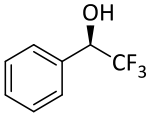
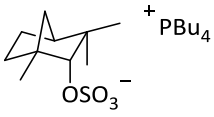
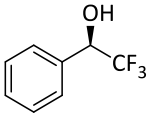
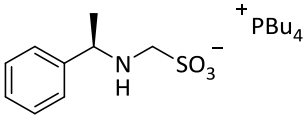
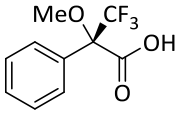
[a] no exact ΔHz values reported

In comparison with ionic liquids bearing chiral cations fewer examples exist in literature that have a chiral anion, and only few examples evaluating their chiral recognition properties *via* ^{19}F-NMR are reported. Typically 2,2,2-trifluoro-1-phenyethanol is chosen as racemic substrate (Table 4).

The group of Winkel investigated the recognition properties of different ionic liquids with chiral sulfonate-based anions such as the common camphorsulfonate and observed a splitting of up to 7 Hz (Table 4, entry 1 and entry 2).[111] In principle the authors found better results in [d_8]-toluene as solvent compared to $CDCl_3$, which might be explained by enhanced hydrogen bonding due to the decreased

polarity of the solvent. In order to improve the interaction between the chiral ionic liquid and the racemic substrate they also developed chiral ionic liquids with basic sulfonate and sulfate anions, and comparable Δppm values were obtained with 2,2,2-trifluoro-1-phenylethanol. Larger Δppm values of up to 41 Hz could be observed with racemic Mosher acid in [d_8]-toluene (Table 4, entry 4).

Table 4: Chiral recognition properties of different ionic liquids with chiral anion in ^{19}F-NMR spectroscopy

entry	chiral ionic liquid	NMR shift (ΔHz)	conditions	substrate	ref.
1		7	[d_8]-toluene		Winkel[107] 2009
2		4	[d_8]-toluene		
3		7	[d_8]-toluene		Winkel[111] 2010
4		41	[d_8]-toluene		

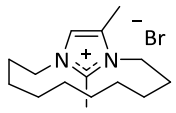
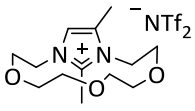
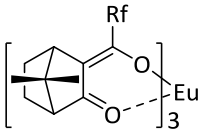
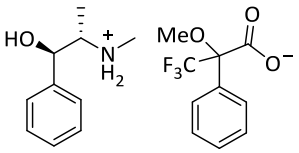
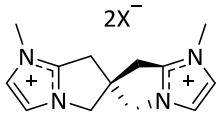
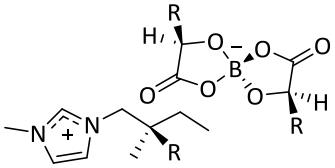
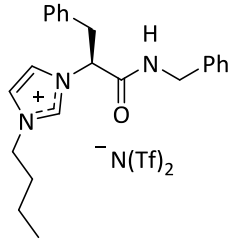
A more detailed look on cation-anion interactions was published by Schulz *et al.*, who investigated the diastereometic interactions and the aggregation behaviour of ephedrine-based chiral ionic liquids (Table 5, entry 3).[112] In order to rationalize the concentration range for efficient chirality transfer diffusion coefficients and signal split of the diastereomeric ionic liquid (1*R*,2*S*)-ephedrinium (*RS*)-methoxy(trifluoromethyl)phenylacetate were determined. Diffusion-ordered NMR spectroscopy (DOSY-NMR) was measured depending on the concentration in dichloromethane and gave aggregation numbers of cations and anions. In parallel, a significant peak splitting of the CF_3 group in ^{19}F-NMR was only observed at a concentration > 0.04 mol/L, which corresponds to the concentration range were aggregates are formed.

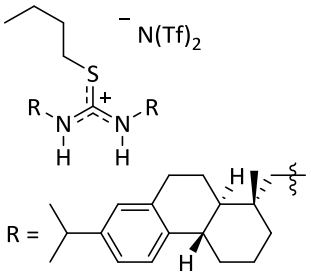
In 2013, Foreitner *et al.* published an elegant paper on enantiodiscrimination of racemic oxoanions with chiral thiouronium ionic liquids (Table 5, entry 7).[113] A series of chiral thiouronium salts was synthesized from commercially available chiral amines (*S*)-methylbenzylamine and (+)-dehydroabietylamine. A detailed study on the chiral recognition properties revealed a strong hydrogen bonding and a rigid conformation between oxoanions, *e.g.* mandelates, but also between sulfonates and phosphonates. The influence of the anion of the chiral ionic liquid was further investigated, and best enantiodiscrimination was observed in case of anions with poor hydrogen-bond acceptor abilities such as bis(trifluoromethane)sulfonimide. A 1:1 ratio between chiral thiouronium salt and oxoanion guest was identified as ideal ratio, and chiral discrimination was superior to the uncharged chiral thiourea precursor. The importance of hydrogen-bonding between the thiouronium unit and the carboxylate moiety of the guest molecule was further visualized in DFT studies and X-ray crystal structures.

The chiral discrimination of racemic carboxylate salts has been also studied by Gonzalez *et al.*, who used amino acid-derived chiral ionic liquids (Table 5, entry 6).[114] Room-temperature liquid imidazolium-based chiral ionic liquids were obtained from chiral α-amino acids in 3 steps and applied as chiral shift reagent for racemic triethylammonium mandelate in ^{1}H-NMR. The largest splitting was observed with chiral ionic liquids obtained from L-phenylalanine functionalized with a benzyl amide group, and the aromatic amide moiety was found to be crucial for chiral recognition. The NMR studies were further extended to include the triethylammonium salts of racemic ibuprofen, *p*-methoxymandelic acid and Cbz-protected phenylalanine and always showed a non-equivalence of the α-methyl signal or the Cbz-methyl signal of the guest in ^{1}H-NMR.

Yu *et al*. reported chiral ionic liquids with either chiral cation, chiral anion or both (Table 5, entry 5).[115] Based on a chiral boronate anion that was easily obtained from enantiopure α-hydroxy acids the intramolecular recognition with the racemic (*R*,*S*)-1-methyl-3-(2-methylbutyl)imidazolium cation was investigated. Differences in the NMR shifts of the cation enantiomers were observed that were dependent on the solvent dielectric constant, concentration and structural modifications of the ionic liquid. The strongest chiral recognition was observed with chiral anions bearing large substitutes as 50 mM solution in $CDCl_3$. Further the intermolecular chiral recognition was investigated with a racemic quinine derivative and a chiral ionic liquid composed of a chiral anion and the achiral 1-ethyl-3-methylimidazolium cation.

Table 5: Chiral recognition properties of different chiral ionic liquids in ^{1}H-NMR spectroscopy

entry	chiral ionic liquid	NMR shift ΔHz	conditions	analyte	ref.
1		7	$CDCl_3$, 1 eq. CIL	Ag-camphersulfonate	Ishida[116] 2002
2		19	$CDCl_3$, 10 eq. CIL, 10 eq. Et_3NCl	 Rf = C_3F_7, CF_3	Ishida[117] 2004
3		24	CD_2Cl_2 as $6.4x10^{-1}$ mol/l	-	Schulz[112] 2009
4		n.d.[a]	20% DMSO [d_6]-$CDCl_3$ 18-crown-6	Mosher acid-/ K^+ salt	Patil Mahesh[118] 2006
5	 R = Phenylmethyl	11	$CDCl_3$ 0.1mol/l	-	Yu[115] 2008
6		13	$CDCl_3$, 4 eq. CIL	triethylammonium mandelate	Gonzalez[114] 2012

7		33	$CDCl_3$, 1 eq. CIL	tetrabutylammonium mandelate	Foreiter[113] 2013

[a] no exact ΔHz values reported

II 2.2 Enantiodiscrimination with chiral ionic liquids in IR spectroscopy

In 2006, the group of Tran presented a novel technique for the determination of the enantiomeric composition of atenolol that relies on near infrared spectroscopy in the presence of enantiopure chiral ionic liquids.[100] A chiral ionic liquid based on the bis(trifluoromethane)sulfonimide anion and commercially available (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium chloride (Figure 42, left) was used. Solutions of different enantiomeric compositions of atenolol in the chiral ionic liquid were prepared and absorption spectra were measured. The recognition properties of the chiral ionic liquid lead to a characteristic change in the NIR region spectra and could be used to determine the enantiomer composition of the pharmaceutical substrates *via* multivariate data analysis.

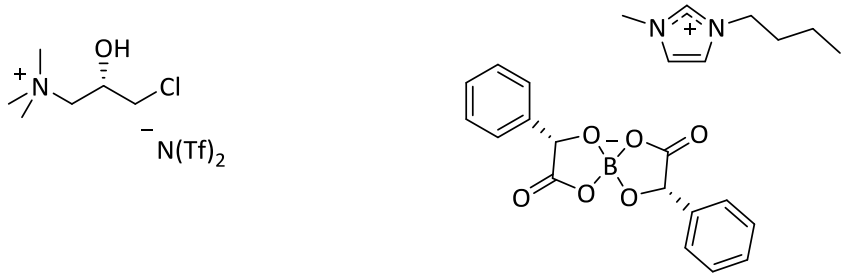


Figure 42: Chiral ionic liquids used in IR spectroscopy (left), fluorescence spectroscopy (left) and UV-VIS spectroscopy (right)

II 2.3 Enantiodiscrimination with Chiral Ionic Liquids in Fluorescence/UV-VIS Spectroscopy

The same chiral ionic liquid (*S*)-[(3-chloro-2-hydroxypropyl)triethylammonium] bis(trifluoromethane)sulfonimide was applied as chiral selector in fluorescence spectroscopy (Figure 42, left).[119] Fluorescence spectra of the pharmaceutically actives propanolol, warfarin and naproxen were recorded in the presence of chiral ionic liquids. Depending on the concentration of the drugs in the chiral ionic liquids significant changes in the fluorescence spectra of the enantiomers were observed, thus indicating that the chiral ionic liquid can differentiate between the enantiomers. Multivariate method of analysis was used to develop calibration models that allowed the subsequent determination of the enantiomeric purity of unknown samples.

In 2012, Absalam *et al.* presented the application of ionic liquid composed of a chiral boronate anion as chiral selector in UV-VIS assisted spectroscopy.[120] The chiral ionic liquid 1-butyl-3-methylimidazolium (T-4)-bis[(αS)α-(hydroxy-O) benzeneacetato-κO] borate could be easily synthesized from enantiopure mandelic acid and was applied for chiral recognition of the common beta adrenergic blocking agent propranolol (Figure 42, right). The addition of enantiopure ionic liquid to both enantiomers resulted in significant changes of absorbance at 259 nm, indicating stronger interactions of the chiral ionic liquid with (*S*)-propranolol hydrochloride. After optimization of conditions, *e.g.* concentration and temperature the ionic liquid was applied for determination of the enantiomeric excess of samples with different composition.

II 2.4 Enantiodiscrimination with Chiral Ionic Liquids in Circularly Polarized Luminescence

In 2012, the group of Kroupa reported a chiroptical luminescence technique for the evaluation of chiral discrimination ability of ionic liquids.[121] Five amino acid-derived chiral ionic liquids were chosen based on alanine, proline and leucine, and the amino acid was located either in the cation or anion of the ionic liquid. A racemic mixture of a luminescent lanthanoid europium complex Λ- vs. Δ-$Eu(dpa)_3^{3-}$ (dpa = 2,6-pyridinedicarboxylate) was dissolved in the enantiopure chiral ionic liquids. Chiral discrimination of the amino acid-derived chiral ionic liquids was measured by their ability to perturb the equilibrium population of Λ- vs. Δ -$Eu(dpa)_3^{3-}$ from racemic to non-racemic. The authors observed g_{em} values with opposite signs for L- *vs* D- amino acid ionic liquids (AAILs), thus indicating that the preference of the discrimination is dictated by the handedness of the chiral cation. While discrimination was observed with chiral ionic liquids composed of alanine or proline, leucine-derived ionic liquids failed to induce any enthalpic chiral discrimination.

II 2.5 Chiral Ionic Liquids in Chromatography

II 2.5.1 Chiral Ionic Liquids as Stationary Phases in Gas Chromatography

The thermal stability, ability to form multiple solvation interactions, and low volatility of ionic liquids make them ideal candidates for use as stationary phases in gas chromatography.[122] Remarkable separation behaviour has been found for some ionic liquids, since they display a high affinity toward dipolar solutes similar to polar stationary phases but also retain nonpolar solutes (*e.g.*, alkanes and alkenes) in a manner that is comparable to stationary phases with low polarity.[123] This unique selectivity has been described as a result of a "dual-nature" retention mechanism. Additionally, many IL stationary phases also have the advantage of high temperatures stability, whereas most conventional polar stationary phases cannot be used at temperatures greater than 280 °C.[124] This is a particular challenge for the resolution of enantiomers since there are hardly any commercially available chiral stationary phases which are stable over 280 °C. Additionally, the synthetic origin of many chiral ionic liquids provides another major advantage that is not possible with the commonly used cyclodextrin phases: The rather simple synthesis of chiral ionic liquids in both enantiomeric forms allows easily switching the handedness of a chiral stationary column when the reverse elution order is needed.

In 2004 Armstrong *et al.* presented the first application of chiral ionic liquids as stationary phase in gas chromatography using an ephedrine-based chiral ionic liquid (Figure 43).[125] After coating a fused-silica capillary tube with the chiral ionic liquid, they managed to separate racemic alcohols, sulfoxides, epoxids and acylated amines into their enantiomers. However, when further investigating the long term stability of the stationary phase the separation performance of the stationary phase was decreasing and a water-induced racemization process of the chiral ionic liquid was held responsible.

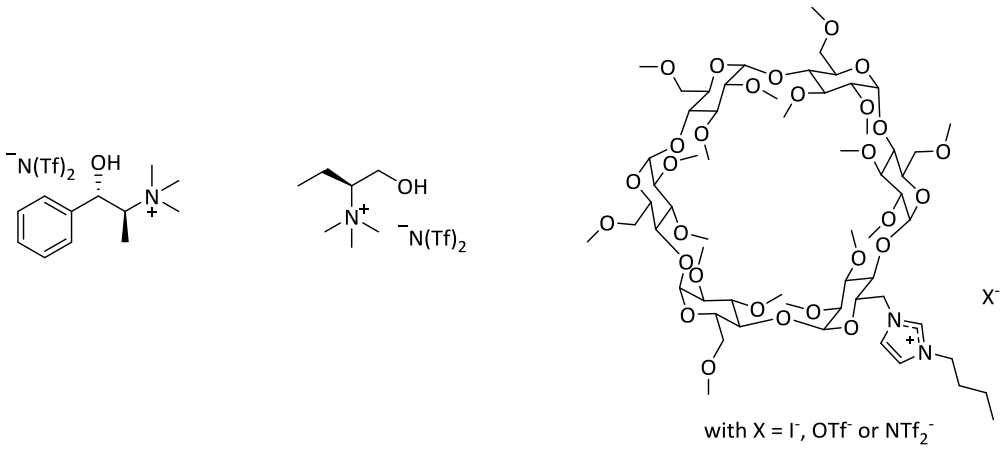


Figure 43: Different chiral ionic liquids applied as chiral selector in gas chromatography

Zhao *et al.* compared the separation characteristics of fused-silica capillary columns that were either directly coated with a chiral amino alcohol-derived ionic liquid or further modified with single-walled carbon nanotubes before the coating process (Figure 43).[126] Twelve racemic substrates including amino acids, terpenes, alcohols, amines and camphor were separated and it was seen that the single-walled carbon nanotubes improve the enantioseparation on the chiral ionic liquid stationary phase. This effect was attributed to the enhanced surface wettability of the inner wall of the capillary column, since the single-walled carbon nanotubes formed a layer with a skeletal network structure in the capillary tube.

The same chiral ionic liquid (*R*)-*N*,*N*,*N*-trimethyl-2-aminobutanol bis(trifluoromethane)sulfonimide was applied as stationary phase for gas chromatography by Yuan *et al*. An untreated fused-silica capillary column was coated with a 0.45 wt% acetone solution of chiral ionic liquid; evaporation of the solvent and conditioning gave access to an ionic liquid-coated chiral stationary phase that was applied for the separation of nine racemic compounds including racemic citronellal.[127]

Although not strictly a chiral ionic liquid technology, chiral separation using ionic liquids as stationary phases has also been achieved *via* dissolution of cyclodextrins in room temperature ionic liquids. A first approach was published by Berthod *et al*. in 2001 when two cyclodextrin/ionic liquid columns were compared with two commercial available cyclodextrin columns containing the similar chiral selector.[128] The ionic liquids $[C_4mim][Cl]$ and $[C_4mim][PF_6]$ were used for dissolution and coating. In summary Berthod *et al*. observed lower retention factors for the ionic liquid containing phases but higher peak efficiencies. Unfortunately, a third of all tested analytes that were separated on the commercially available columns where not separated on the ionic liquid-based columns. This was probably due to the imidazolium cation used which is blocking the cyclodextrin cavity through complexation and is therefore inhibiting chiral recognition. However, despite the fact that many of the substrates could not be separated on the ionic liquid-containing columns, the observations made could contribute to the better understanding of ionic liquids interactions.

In 2010 Huang *et al*. came up with a modified strategy to improve this behavior.[129] In comparison to the work of 2001 they used functionalized ionic liquids matrices for the dissolution of the chiral selector to hinder the interaction of the imidazolium core with the cyclodextrin cavity. Typically di-cationic ionic liquids based on imidazolium or phosphonium head groups were used in combination with a triflate (OTf^-) or bis(trifluoromethane)sulfonimide (NTf_2^-) anion. Furthermore, the cyclodextrin units were modified to incorporate a permanent cationic groups thus leading to stronger solute-solvent interactions and to an enhanced solubility of the chiral selector in the ionic liquid. With this novel technology Armstrong *et al*. could improve the efficiency of the column, the enantioseparation, as well as the peak shape in comparison to commercial available cyclodextrin phases. Furthermore they were able to separate all test substances that are usually examined on commercial columns, thus providing a new and very promising method for chiral separation.

II 2.5.2 Liquid Chromatography with Chiral Ionic Liquids

Chiral ionic liquids can play different roles to support or improve separations in liquid chromatography: Apart from the use as stationary phases, they can be added as chiral mobile-phase additives and dynamically coat the stationary phase.

The first application of chiral ionic liquids in liquid chromatography was published in 2006 by the group of Yuan.[127] A chiral ionic liquid based on (*R*)-2-aminobutanol was used as additive to the mobile phase consisting of H_2O and CH_3CN (10 mmol/l CIL) in combination with a commercially available C18 ODS column. Eight different analytes, *e.g.* the pharmaceutically active propranolol could be separated thus showing the potential of this chiral ionic liquid in enantioselective separation.

In 2010 Zhou *et al.* presented novel stationary phases for liquid chromatography based on silica bonded cyclodextrins that were further functionalized with 1,2-dimethylimidazolium or 1-amino-1,2,3-triazolium cations and variable anions.[130] A series of racemates including α-nitroalcohols, α-hydroxylamines, alcohols as well as two racemic drugs was chosen. With this novel chiral stationary phases and acetonitrile-based polar mobile phases they were able to separate those analytes with good to excellent resolution factors and attributed these results to the presence of both cationic and anionic moieties on the chiral selector.

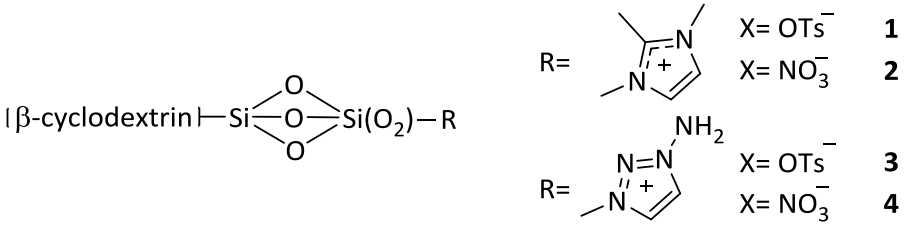


Figure 44: Ionic liquid-modified silica bonded cyclodextrines as stationary phases in liquid chromatography

When investigating the effect of the cationic moiety the authors claimed that the imidazolium cation, with its lower pK_a value (triazole pK_a 11.8 vs. imidazole pK_a 7.9) was able to form tighter ion pairs. This seems to be beneficial for chiral recognition since both the cation and anion moieties interact with the analyte. Additionally, they investigated the effect of the anion and found the nitrate anion was the better choice since it is a weaker base and consequently more ready to participate in ion exchange. For increasing the recognition abilities of the chromatography system the authors varied the composition of the mobile phase and found that increasing the acidity or basicity can lead to stronger interactions between selector and analytes and therefore enhanced resolution.

In 2009, Liu *et al*. applied amino acid-based chiral ionic liquids for the separation of racemic amino acids based on the ligand-exchange principles.[131] Pure L-proline, L-proline dissolved in [C_4mim][Br] and four 1-alkyl-3-methylimidazolium L-prolinate ionic liquids with different alkyl chain length were used as chiral mobile phase additive, and good baseline separation was obtained for racemic phenylalanine with all four amino acid-derived ionic liquids. Interestingly the chiral recognition and hence the resolution was significantly increased by lengthening of the alkyl chain in imidazolium head group from

C_2 to C_8, indicating the importance of the achiral cation which is substantially involved in the complex formation. The strong interaction of a long-chain imidazolium cation with the hydrophobic C18 column resulted in the formation of a stable complex which was able to separate enantiomers even at low concentrations of amino acid-derived chiral ionic liquid (Figure 45). It should be noted that also the use of L-proline as chiral ligand lead to base line separation; however the observed separation factor was significantly lower than that of all amino acid-derived chiral ionic liquids.

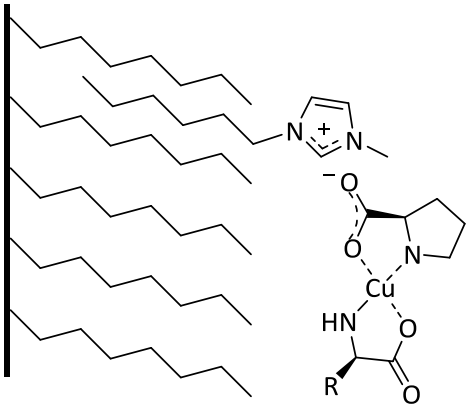


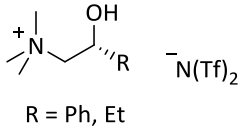
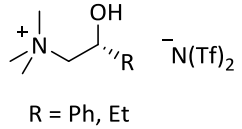
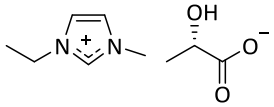
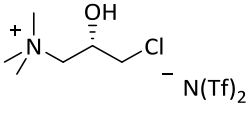
Figure 45: Ligand-exchange chromatography with amino acid-derived chiral ionic liquids

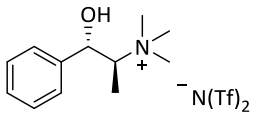
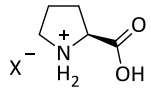
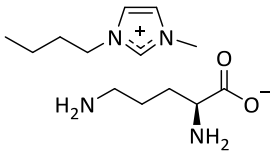
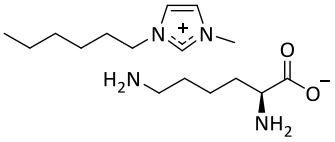
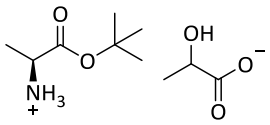
In 2011, Bi *et al.* used chiral ionic liquid-assisted ligand exchange chromatography to separate racemic ofloxacin, a fluorinated quinolone with antibacterial activity.[132] Different amino acid derived chiral ionic liquids as well as achiral ionic liquids in combination with natural L-amino acids were used in combination with $CuSO_4.5H_2O$ as mobile phase additive in HPLC. In the case of achiral cations as additives the separation of ofloxacin enantiomers could be improved when ionic liquids with short alkyl chains where used. This is due to the competition of the imidazolium cations with the copper complexes for the adsorption onto the alkyl silica surface, which is in favour of copper when short alkyl chains are used. When chiral AAILs where used as additives the authors observed a different trend than previously reported by Liu *et al.*: Enantioseparation decreased with increasing chain length of the 1-alkyl-3-methylimidazolium cation, and weaker electrostatic interactions with Cu^{2+} as well as a steric hindrance of larger cations was held responsible for this decrease. Among different chiral ionic liquids based on L-alanine, L-valine, L-phenylalanine and L-leucine, [C_4mim][L-leucinate] was found to be the most successful, so that the developed strategy could be applied for the determination of ofloxacin enantiomer distribution in various medicines.

II 2.5.3 Chiral Ionic Liquids in Capillary Electrophoresis and Micellar Electrokinetic Chromatography

Based on the work of François *et al*. on capillary electrophoresis (CE) with achiral ionic liquids as additives for capillary electrophoresis, this group evaluated the effect of chiral ionic liquids as additives in CE for the enantioseparation of different profens in 2007 (Table 6, entry 1).[133] Two chiral ionic liquids ethyl- and phenylcholine bis(trifluoromethane)sulfonimide were chosen as background electrolytes; however, no enantioselectivity was observed for the two anti-inflammatory 2-arylpropionic acids as racemic model compounds. The authors then switched to study the influence of different chiral ionic liquids in the presence of cyclodextrins (CD) that are commonly used chiral selectors. Variation of the electroosmotic flow, the total salt concentration and the structure of the chiral ionic liquids in the separation of three model profens (naproxen, carprofen and suprofen) did not help to establish a general trend concerning the nature of the chiral ionic liquid. However, in nine cases a simultaneous increase of selectivity and resolution was observed indicating a synergistic effect of the two selectors. In the last years different CILs where used in capillary electrophoresis, a short overview is given in Table 6.

Table 6: Application of chiral ionic liquids ion capillary electrophoreses

entry	chiral ionic liquid	co-electrolyte/ additive	analyte	ref.
1	 R = Ph, Et	β-cyclodextrine	2-arylpropionic acids	François[133] 2007
2	 R = Ph, Et	carboxymethyl-βcyclodextrine	benzopyran derivative	Rousseau[134] 2010
3		β-cyclodextrine	different drugs	Zuo[135] 2013
4		cholic acid, 1-*S*-octyl-β-D thioglucopyranoside	profens	Tran[136] 2008

5		-	rabazol, omeprazol	Ma[137] 2010
6	 with X = CF_3COO^-, NO_3^-, BF_4^-, SO_4^{2-}	Cu(II)	dansylated amino acids	Mu[138] 2012
7		Zn(II)	dansylated amino acids	Mu[139] 2012
8		Zn(II)	dansylated amino acids	Zhang[140] 2013
9		-	1,1-binaphthyl-2,2-dihydrogen phosphate	Stavrou[141] 2013

Rousseau and co-workers published similar results in 2010, where the same CILs (ethyl- and phenylcholine) were used as additives to the background electrolytes cyclodextrins (2,3-di-O-methyl-6-O-sulfo)-β-CD) (Table 6, entry 2).[134] With this system racemic mixtures of two pharmaceutical intermediates were successfully separated, describing the same effects as previously observed by François *et al.*: Adding chiral ionic liquid to the CD system led to a significantly higher enantiomeric resolution, again indicating a synergistic effect with the cyclodextrin. This was related to the decrease of the electroosmotic flow when the ionic liquid cation was adsorpted on the capillary wall. To exclude a simple salt effect the same experiment was repeated with achiral ionic liquids as additive, and no improvement of the chiral resolution was observed.

Chiral ionic liquids in combination with cyclodextrins were also applied by Zuo *et al*. in 2013 to separate enantiomers of several pharmaceuticals including the actives zopiclone, repaglidine and chlorphenamine.[135] The anion-chiral ionic liquid [C_2mim][(*S*)-lactate] was chosen, and the influence of ionic liquid concentration, chain length and pH dependence the system on the resolution were investigated (Table 6, entry 3). The evaluation of optimum conditions allowed the considerably improved enantioseparation of twelve racemic compounds compared to conventional cyclodextrines as sole background electrolytes. Finally, this method could be applied for high precision measurements of the enantiomeric purity of eszopiclone in commercial tablets.

Synergistic effects of ionic liquids with cyclodextrine as background electrolyte in CE were also reported by Zeng *et al*., who used 1-ethyl-3-methylimidazolium tetrafluoroborate in a glass microchip electrophoresis device.[142] The group was able to show a tremendous improvement and broadening of the separation window for two enantiomeric dipeptides with the achiral ionic liquid as additive in comparison to the commonly used boric acid buffer. The enantioseparation of three β-blockers *via* CE in the presence of an achiral ionic liquid was also achieved by the group around Jin.[143] Glycidyltrimethylammonium chloride in combination with cyclodextrine was used as background electrolyte. A remarkably low detection limit ranging from 0.1 to 0.65 mM was observed with this ionic liquid-cyclodextrine approach system, which is much lower than with conventional methods.

In 2008 Tran *et al*. demonstrated that the CIL (*S*)-[-3-(chloro-2-hydroxypropyl)trimethylammonium][NTf_2] is able to improve separation and enantioseparation in CE and can be used as co-electrolyte or chiral selector for several racemic profens including naproxen, ibuprofen and flurbiprofen (Table 6, entry 4).[136] When the chiral ionic liquid was used as background electrolyte and as single source of chirality no separation of the substrates could be achieved. However, when the chiral anionic surfactant cholic acid was added to the aqueous solution, baseline separation of seven pharmaceuticals including ibuprofene was observed. In the absence of chiral ionic liquid with cholic acid as sole additive in the mobile phase, the resolution was worse and no separation of the ibuprofen enantiomers could be achieved. In some cases the separation could be further improved by the addition of a third chiral and neutral component (1-S-octyl-β-D-thioglucopyranoside).

The ephedrine based ionic liquid *N,N*-dimethylephedrinium bis(trifluoromethane)sulfonimide that has already been successfully applied in NMR spectroscopy and gas chromatography was used as background electrolyte and chiral selector in nonaqueous capillary electrophoresis to separate enantiomers of the antiulcer drugs rabeprazole and omeprazole by Ma *et al.* (Table 6, entry 5).[137] The mechanism of enantioseparation was investigated suggesting that ion-pair interaction and hydrogen bonding are primary responsible for the separation characteristics.

Mu *et al*. could present a different approach for the use of chiral ionic liquids in CE. Amino acid-derived chiral ionic liquids were used as chiral ligands in ligand-exchange capillary electrophoresis for the separation of dansylated amino acids using Cu(II) as complexation reagent (Table 6, entry 6).[138] Based on L-proline several protic ionic liquids were obtained *via* protonation with strong acids such as HNO_3, HBF_4, CF_3COOH and H_2SO_4. After optimization of the separation conditions, [L-proline][CF_3COO]

was identified as best chiral ionic liquid and applied for the separation of nine dansylated amino acids. When the use of this protic ionic liquid was compared to the use of sole proline or proline in the presence of trifluoracetic acid the enantioseparation was inferior, indicating that the chiral ionic liquid played a special role whose exact mode of actions still has to be explored.

In the same year, this group presented the successful enantioseparation of derivatized amino acids using chiral ligand-exchange capillary electrophoresis with Zn(II) as complexation metal and L-ornithine as chiral cation (Table 6, entry 7).[139] After optimization of key parameters such as buffer pH, concentration of Zn(II) and concentration of the chiral ionic liquids Mu *et al.* were able to achieve baseline separation of 11 pairs of dansylated amino acids and could apply this strategy to investigate the inhibition efficiency of D-amino acid oxidase inhibitors. Related experiments where performed by the group around Zhang, who used different L-lysine derived ionic liquids as chiral ligands and Zn(II) complexes in ligand-exchange CE.[144] Based on imidazolium cations with variable chain length and lysinate as anion, baseline separation of seven pairs of dansylated amino acids was obtained.

In 2013 the group around Stavrou presented the use of a chiral ionic liquids in CE as single source for chiral recognition without metal complexation (Table 6, entry 9).[141] Five chiral ionic liquids based on an alanine esters with variably ester chain length and lactate or bis(trifluoromethane)sulfonimide as anion were synthesized. The chiral ionic liquids were used as additives in the background electrolyte to resolve racemic 1,1`-binaphthyl-2,2-dihydrogenphosphate. A strong influence of the ester type in the cation was observed since the enantioresolution improved with increasing bulkiness of the alkyl group. Consequently, the best resolution was obtained with alanine-*tert*-butylester as cationic moiety. Furthermore variation of ionic liquid concentration, pH value, and anion revealed that optimum conditions were present with the hydrophilic lactate anion at a pH of 8-8.5. At these conditions the baseline separation of the chiral analyte could be achieved with chiral ionic liquids as single source of enantioselectivity. Additionally it could be shown that the elution order of the two enantiomers of the analyte could be inverted when the other enantiomer of the chiral ionic liquid was used.

Achiral ionic liquids in combination with chiral polymeric surfactants and common CE buffers have been successfully applied in the separation of racemic analytes, and the ionic liquids improved the resolution.[145] Already in 2006, Rizvi and Shamshi applied two chiral ionic liquids based on leucinol and prolinol for the separation of α-bromophenylacetic acid and 2-(2-chlorophenoxy)propanoic acid in micellar electrokinetic chromatography.[146] The chiral amino alcohol precursors *N,N*-dimethylleucinol and *N*-methylprolinol were functionalized with a undecenoxycarbonyl moiety to obtain surface-active chiral ionic liquids with critical micelle concentrations (CMC) at 1.15 mM and 0.84 mM. These chiral ionic liquids as well as their polymerized derivatives were applied as pseudostationary phase in micellar electrokinetic chromatography, and a strong influence of concentration and pH value on the enantioseparation was observed. Electrostatic interactions between the acidic analytes and the cationic head groups were found to play a profound role in the separation process, baseline separation of 2-(2-chlorophenoxy)propanoic acid could be obtained with the polymerized leucine derivative at low pH values.

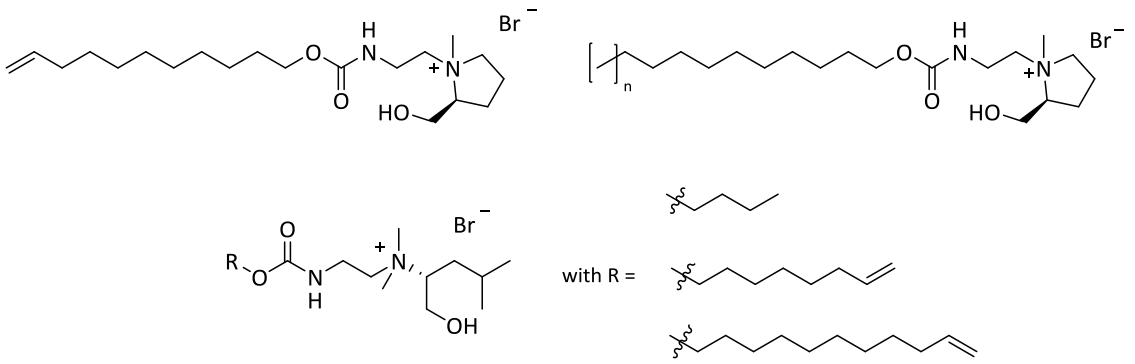


Figure 46: Prolinol- and leucinol derived chiral ionic liquids for micellar electrokinetic chromatography

The combination and synergistic effects of chiral ionic liquids with cyclodextrines is not limited to capillary electrophoresis but has been also observed in micellar electrokinetic chromatography. In 2009 Wang *et al.* reported the enantioseparation of profene drugs in micellar electrokinetic chromatography using amino acid-derived surface-active chiral ionic liquids.[147] The combined use of the chiral ionic liquid and cyclodextrine derivatives allowed enantioseparation of the racemic drugs. Detailed investigation towards the separation of fenoprofene revealed different binding constants for the two isomers due to the synergistic effect of the chiral selectors.

II 2.6 Preparative Liquid-Liquid Extractions with Chiral Ionic Liquids

Although recognition and resolution abilities of chiral ionic liquids have been investigated systematically for analytical purposes, preparative applications in separation sciences remain rare to date.

In 2010 Tang *et al*. presented the first application for preparative liquid-liquid separation of racemic amino acids *via* ligand exchange.[148] Based on proline-derived chiral ionic liquids and copper acetate as complexing agent, one enantiomer of the racemic amino acid substrate was selectively extracted and concentrated in the chiral ionic liquid phase (Figure 47). With this strategy the authors could obtain an enrichment of up to 36% ee of L-phenylalanine in the chiral ionic liquid [C_4mim][L-prolinate] using ethyl acetate as immiscible organic solvent. The effect of copper ion concentration and amino acid concentration was further investigated and a possible recycling strategy for the chiral ionic liquid was developed. Furthermore the influence of the cation was investigated and it turned out that an increase in chain length of the 1-alkyl-3-methylimidazolium cation lead to an increase of enantioselectivity from 38% ee to 51% ee, which might be explained by the reduced solvent polarity and the enhanced stability of the copper complex.

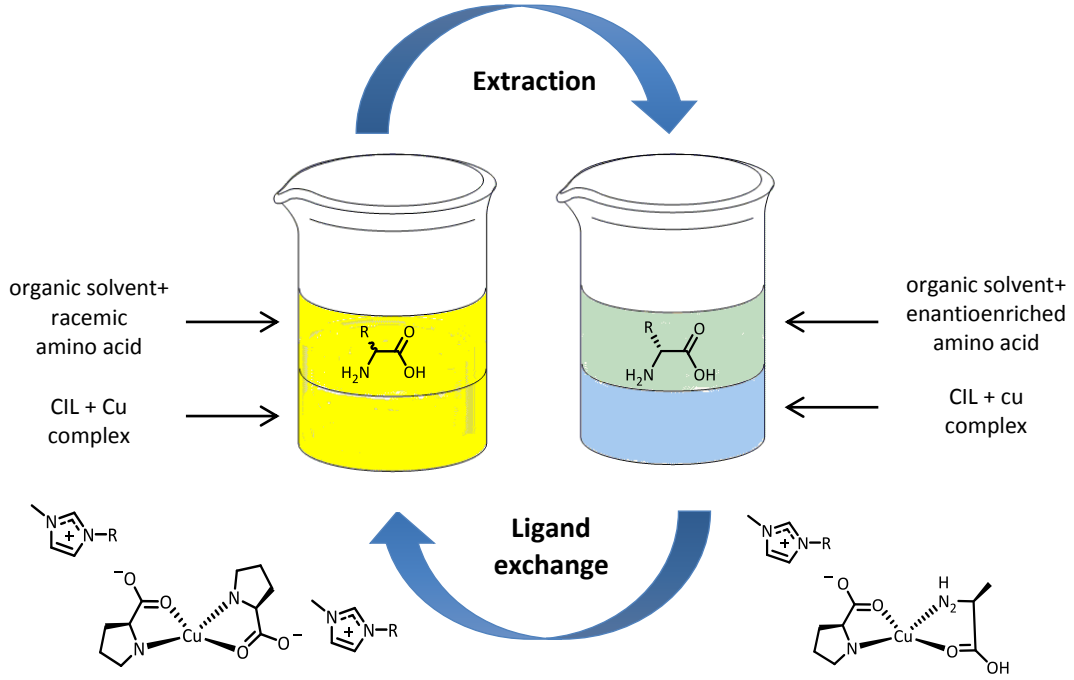


Figure 47: Liquid-liquid separation of racemic amino acids with amino acid-derived chiral ionic liquids

Zgonnik *et al*.[149] were able to apply and evolve this concept for enantioselective liquid-liquid-extraction (ELLE-process)[150] and came up with a new eco-friendly method without metal complexation but requires two different ionic liquids whose ions differ in hydrophilicity. This strategy for the enantioselective extraction of racemic amino acids from an aqueous system relies on the aggregation behaviour of ionic liquids where a hydrophilic cation combines with hydrophilic anion in the water phase and vice versa. The biphasic system in this enantioselective extraction process was obtained by mixing the chiral ionic liquid $[PBu_4]_2$[(*R*,*R*)-tartrate] and a racemic cationic substrate dissolved in the hydrophobic ionic liquid 1-octyl-3-methyl-imidazolium bis(trifluoromethane)sulfonimide ($[C_8mim][NTf_2]$). As a result of aggregation the ions combine in an enantioselective way and are concentrated in the water layer, whereas the hydrophobic liquid layer contains $[PBu_4][NTf_2]$ and the remaining enantiomer. A high dependence on temperature and incubation time was observed, the authors reported up to 30% enantiomeric enrichment of the pharmaceutically active pipecoloxylide at 50 °C (Figure 48).

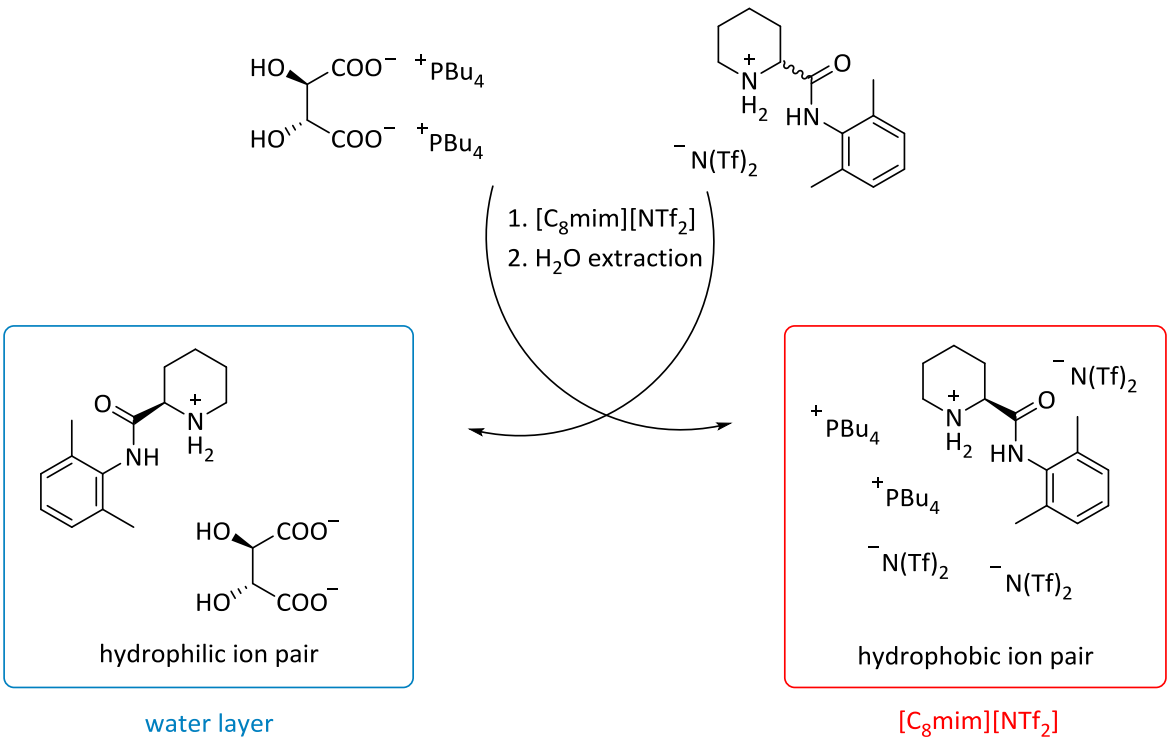


Figure 48: Enantioselective liquid-liquid-extraction with the chiral ionic liquid $[PBu_4]_2$[(*R*,*R*-tartrate]

III Results and Discussion

The task of the present work was the design and synthesis of novel chiral ionic liquids based on amino alcohols for various applications that benefit from the unique properties of ionic liquids.

The obtained chiral ionic liquids should be evaluated for their chiral recognition properties. Diastereomeric interactions with a racemic probe should be investigated *via* ^{19}F-NMR techniques in an elaborated study to get an insight into the influence of the structure of ionic head groups, core structures and concentration.

Chiral ionic liquids, mostly derived from the chiral pool should be further developed for the application in asymmetric synthesis. To demonstrate the design of highly coordinating CILs with broad applicability, two asymmetric reactions including the asymmetric alkylation of aldehydes with diethyl zinc and the asymmetric transfer hydrogenation of prochiral ketones were chosen. In addition, novel chiral ionic liquids should be designed bearing highly coordinating chiral azabis(oxazoline) structures for numerous applications in asymmetric synthesis.

Moreover investigations towards the use of ILs and selected CILs as stationary phases in gas chromatography should be performed. A coating process should be developed for achiral and chiral ionic liquids, and the separation performance of various IL-coated columns should be evaluated.

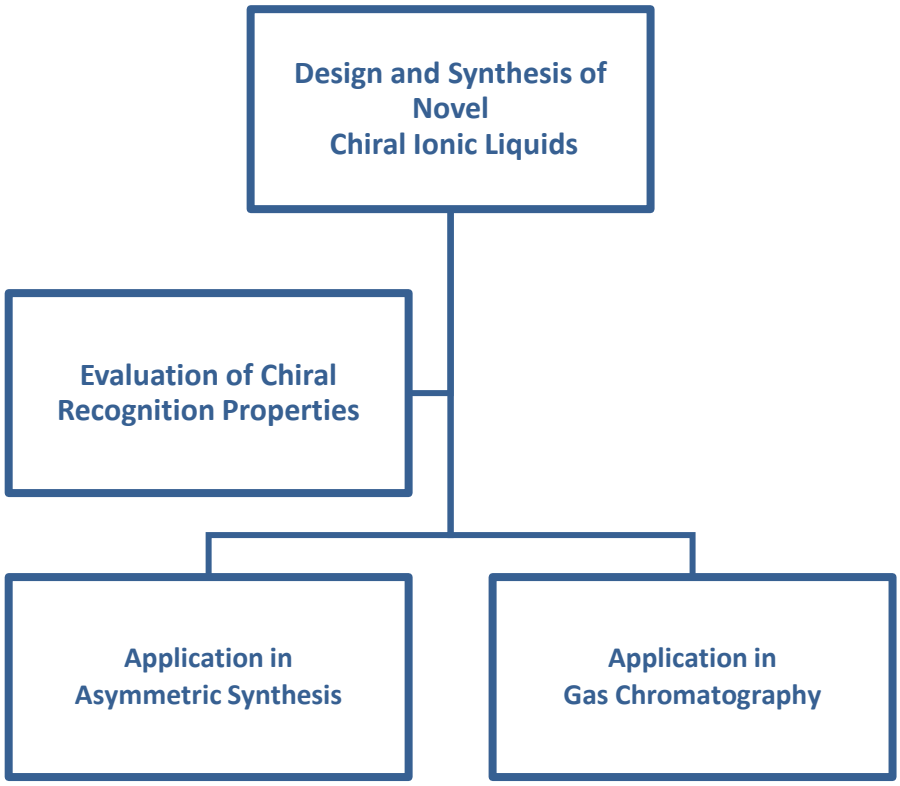


Figure 49

III 1 Chiral Ionic Liquids in Chiral Recognition

In order to obtain better understanding of diastereomeric interactions between chiral ionic liquids and a racemic substrate, a set of novel chiral ionic liquids derived from the chiral pool was synthesized. The modular design of this type of chiral ionic liquids allowed a simple connection of a chiral amino alcohol core to various cationic head groups; hence the influence of different ionic head groups and core structures can be investigated in regard to their chiral recognition properties.

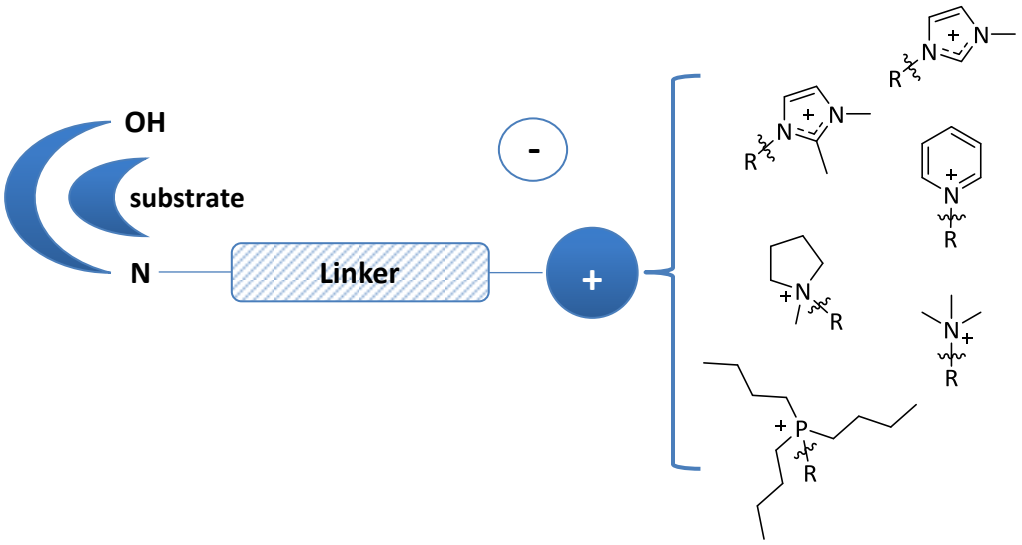


Figure 50: Design of chiral ionic liquids for chiral recognition studies

Mosher's acid is well known to be a useful chiral derivatizing agent for alcohols and amines, whose enantiomeric composition can be determined *via* ^{1}H- or ^{19}F-NMR after reaction with the racemic acid.[151] This strategy was adapted for the evaluation of diasteromeric interactions with chiral ionic liquids and is a suitable method to gain an insight into their recognition properties. Furthermore it opens the possibility to evaluate chiral recognition strength prior to application of CILs in various fields.

III 1.1 Design and Synthesis of Chiral Ionic Liquids

Initially, an enantiopure CIL, whose synthesis has been previously developed in our lab, was prepared from commercially available chiral amino alcohol (1*R*, 2*S*)-ephedrine **1**.[152] (1*R*,2*S*)-Ephedrine was converted to the corresponding carboxamide building block **2** using chloroacetyl chloride under anhydrous conditions in the presence of triethylamine. The product was further reacted with *N*-methylimidazole at 50 °C for 24 hours to introduce the cationic head group. The obtained chiral imidazolium chloride **3** was afterwards converted to an hydrophobic CIL **4** by conventional anion metathesis using bis(trifluoromethane)sulfonimide lithium salt (Figure 51).

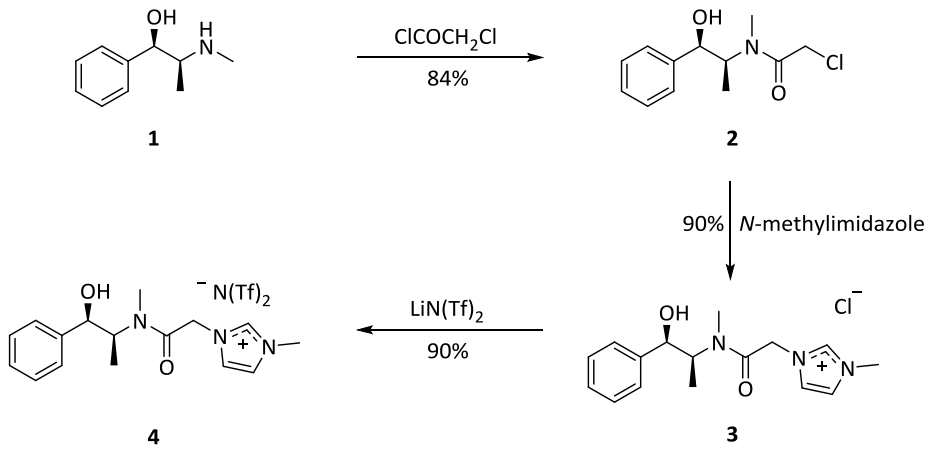


Figure 51: Synthesis of CIL for chiral recognition studies

Reaction of the chiral amino alcohol with one equivalent of chloroacetyl chloride occurred preferably at the amine to form the carboxamide **2**. Single crystals of this intermediate could be grown from ethanol, and X-ray analysis confirmed structure and absolute configuration of (1*R*,2*S*) (Figure 52).

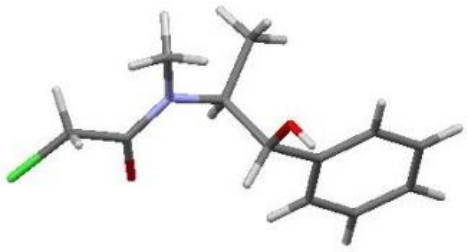


Figure 52: Single crystal analysis of product 2

Due to the hindered rotation of the amide N-C bond, rotamers could be observed in NMR spectra for all ephedrine derived CILs and their amide precursors.

Based on the synthetic route developed for the (1*R*,2*S*)-ephedrine-based CIL **4** shown in Figure 51, the range of amino alcohol-derived chiral ionic liquids was expanded. Starting from commercially available (1*R*,2*S*)-ephedrine, L-proline and L-phenylalanine as core structures CILs with different ionic head groups containing protic, aliphatic and aromatic moieties were synthesized as demonstrated in Figure 53.

For *N*-methylimidazolium and *N*-dimethylimidazolium containing CILs, the amide precursors were reacted with the quarternizing agent under solvent-free conditions. In all other cases a solvent was chosen that allowed the crystallization directly from the reaction mixture and hence the isolation of the salt in high purity. In case of pyrrolidinium and phosphonium head groups, the chloride salt could be isolated from *i*-PrOH, whereas EtOH was chosen as co-solvent in case of trimethylamine. After anion metathesis all CILs were liquid at room temperature and were isolated as viscous oil.

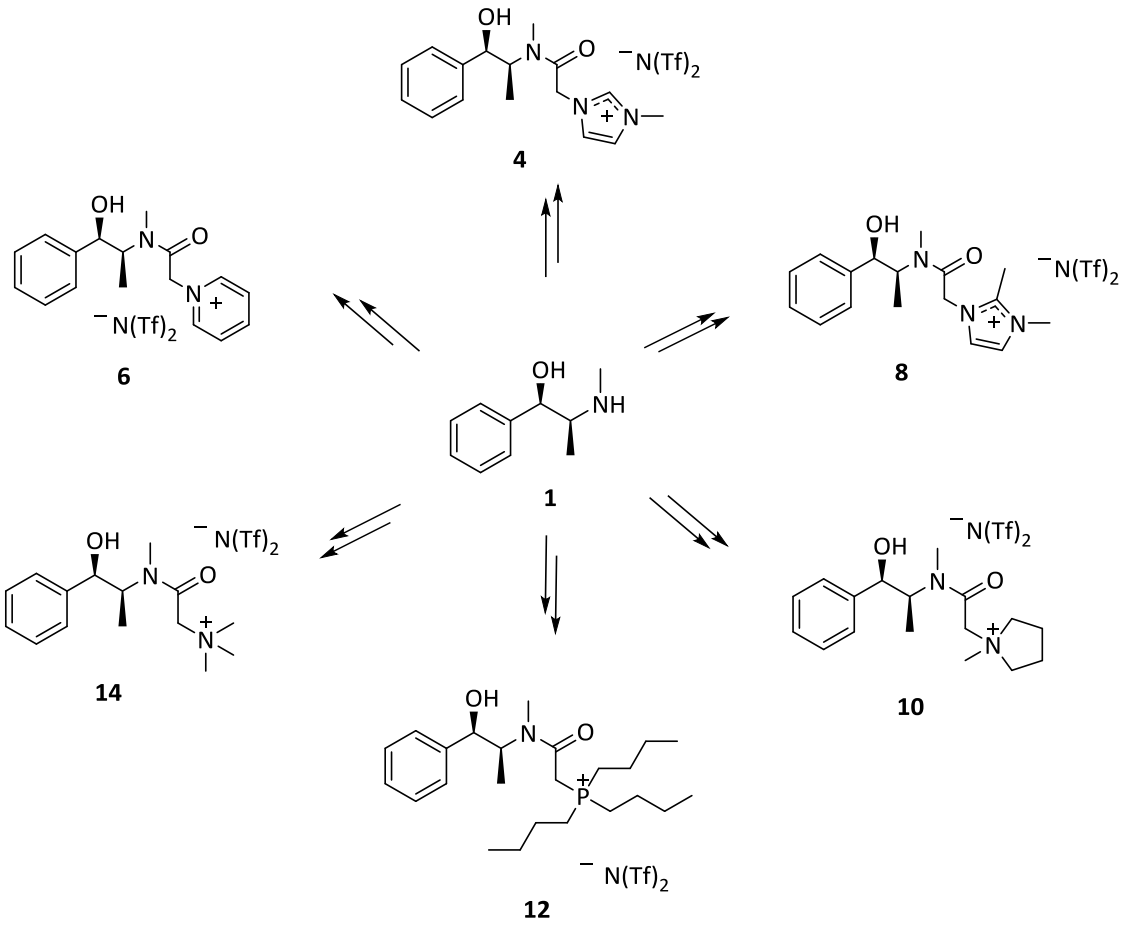


Figure 53: Chiral ionic liquids derived from (1*R*,2*S*)-ephedrine

In some cases, losses due to the high hydrophilicity of the chloride-based CIL were observed. Still, all ionic liquids could be isolated in excellent purities and yields varying from 35% to 62% over 3 steps as shown in Table 7.

Table 7: Overall yields for (1*R*,2*S*)-ephedrine-based chiral ionic liquids

CIL	head group	overall yield [%]
4	imidazolium	68
6	pyridinium	72
8	dimethylimidazolium	35
10	pyrrolidinium	57
12	phosphonium	53
14	trimethylammonium	62

In contrast to ephedrine, the starting materials for L-prolinol and L-phenylalaninol-derived chiral ionic liquids **15** and **37** had to be synthesized from the corresponding amino acids. Therefore L-proline and L-phenylalaninol were reduced using $LiAlH_4$ in THF according to literature procedure.[153] The resulting amino alcohol was then converted to the corresponding carboxylamid and further reacted to hydrophobic CIL according to the procedures for (1*R*,2*S*)-ephedrine. In case of L-prolinol trimethylammonium, phosphonium and *N*-pyrrolidinium CIL could not be precipitated from any solvent as the chloride form was already a room temperature ionic liquid.

All L-proline derived CILs could be isolated in excellent purity but yields were slightly lower due to lower conversions for the synthesis of amide-precursor and an additional reaction step (Figure 54).

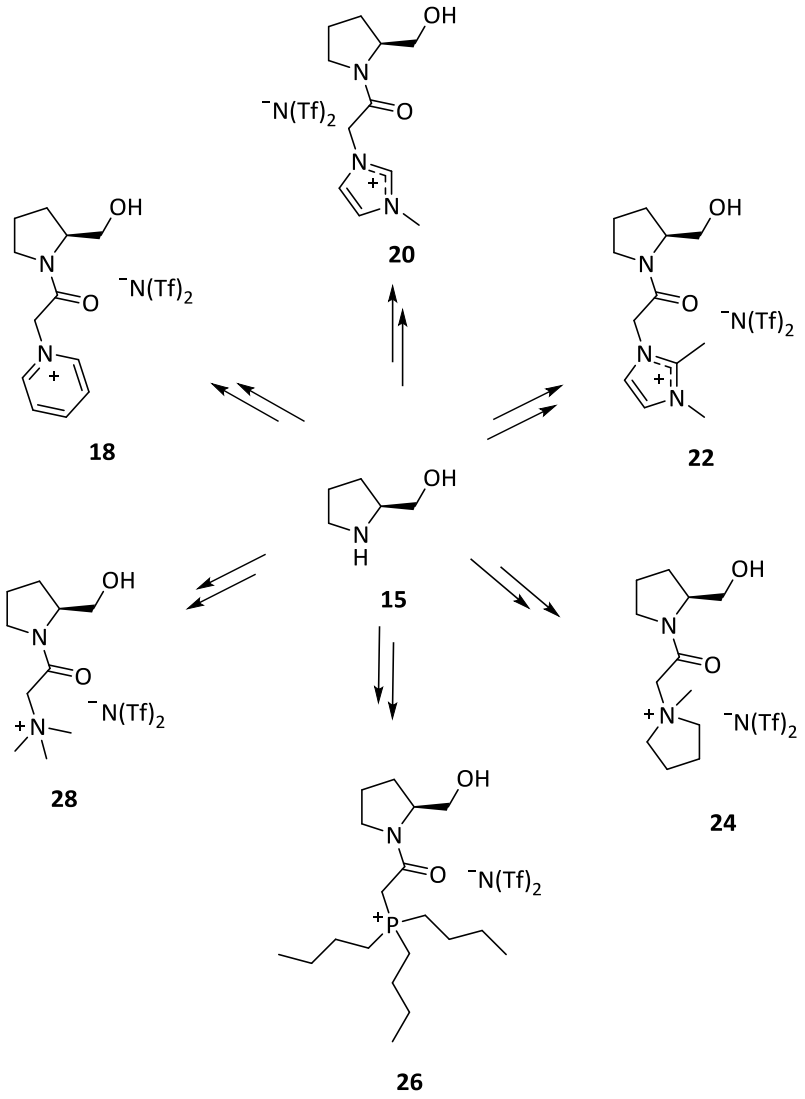


Figure 54: Chiral ionic liquids derived from L-prolinol

Table 8: Overall yields for L-proline-based chiral ionic liquids

CIL	head group	overall yield [%]
18	pyridinium	22
20	imidazolium	29
22	dimethylimidazolium	30
24	pyrrolidinium	16
26	phosphonium	15
28	trimethylammonium	31

In addition to the aromatic, aliphatic and phosphonium containing CILs, a set of protic ionic liquids was synthesized to further study the influence of protic head groups.

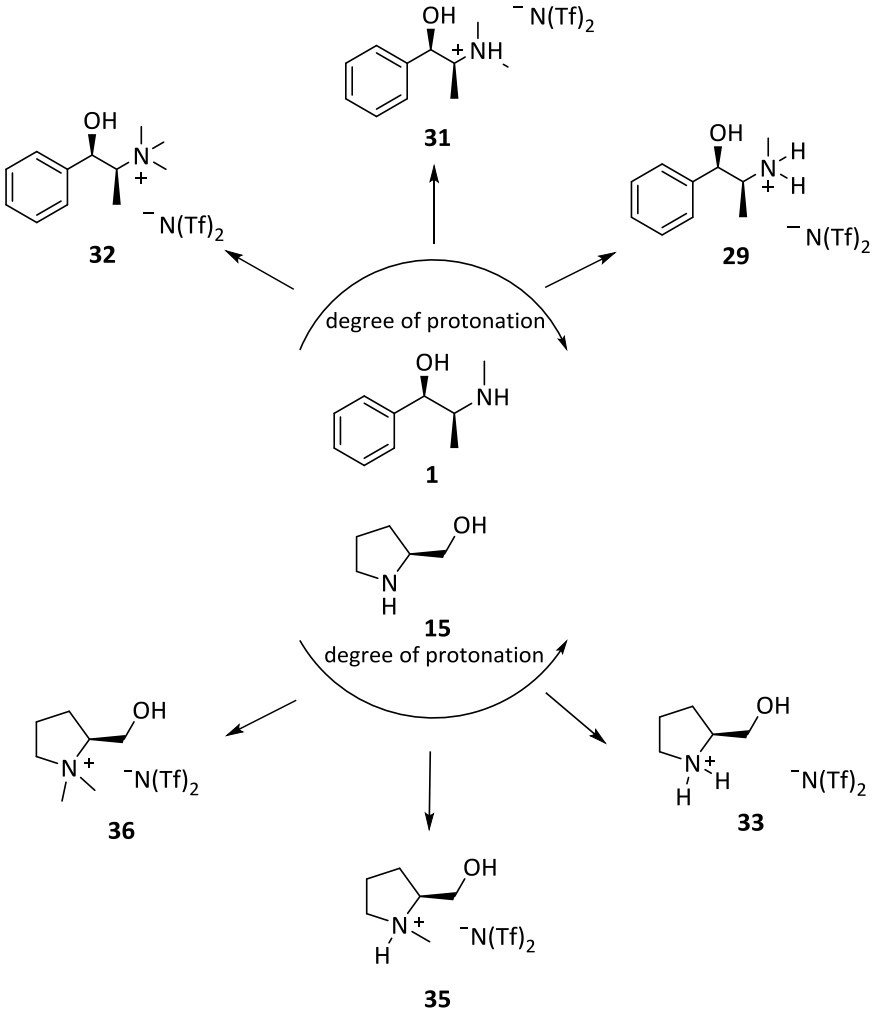


Figure 55: Chiral ionic liquids with variable protonation degree

Therefore ephedrine and proline precursors were protonated with tri(fluoromethane)sulfonimide in case of CIL **29** and **33**. For CIL **31** and **35** the precursor was first methylated according to classical Leukart-Wallach protocol and protonated afterwards with bis(trifluoromethane)sulfonimide.[86] The reductive amination towards the *N*,*N*-dimethylated component of the CIL precursor was performed by refluxing the starting material in the presence of formic acid and paraformaldehyde. For the completely methylated species CIL **32** and **36**, the precursors were methylated after reductive amination using dimethylsulfate and consecutively anion exchange was performed with bis(trifluoromethane)sulfonimide lithium salt. All protic derivatives could be isolated in good yields, as summarized in Table 9.

Table 9: Yields over 2 steps for protic and methylated chiral ionic liquids

CIL	core structure	yield
29	ephedrine	98
31	ephedrine	78
32	ephedrine	60
33	proline	99
35	proline	99
36	proline	86

The synthesis for L-phenylalanine-derived CILs was performed according to the procedure for L-proline derived CILs, which started with the reduction of the acid functionality of commercially available L-phenylalanine and consecutive amidation with chloroacetyl chloride, followed by quarternization with different agents and anion metathesis.

As with the synthesis of ephedrine derivatives, L-phenylalanine-derived chiral ILs could be obtained in good yields over 4 steps and excellent purities. Again, the synthesis in *i*-PrOH or EtOH had the advantage of obtaining the chloride salts in excellent purity, as they crystallized upon cooling from the reaction mixture (Table 10).

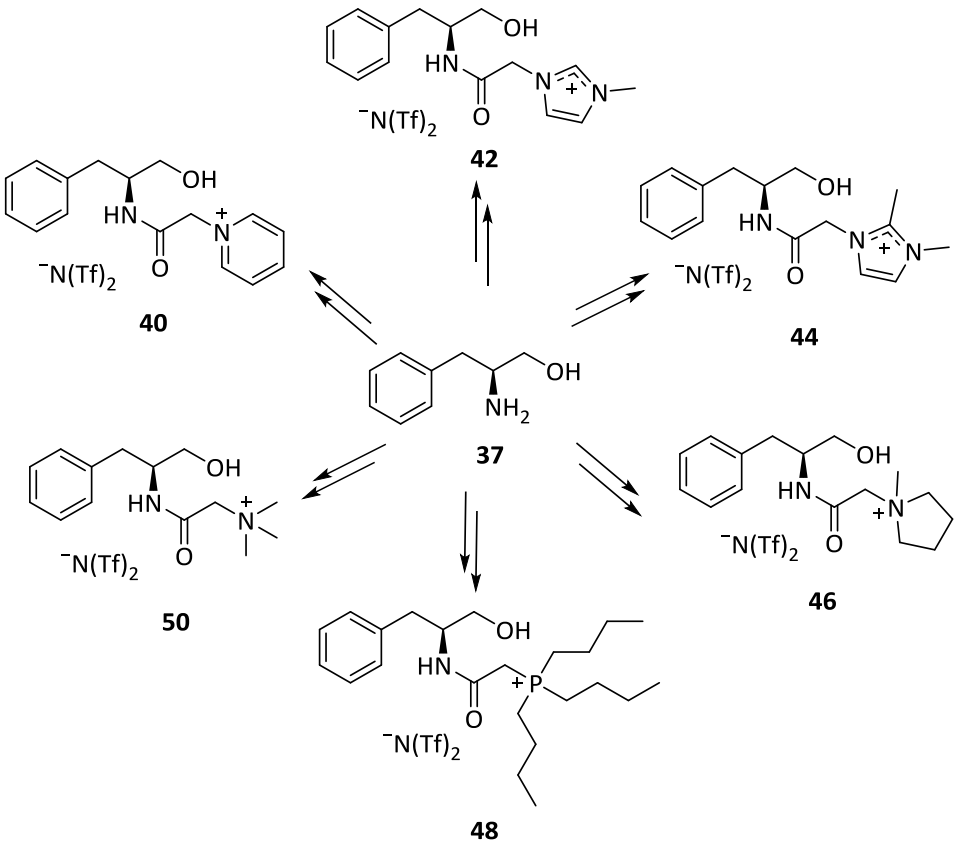


Figure 56: Chiral ionic liquids derived from L-phenylalaninol

Table 10: Overall yields for L-phenylalanine-based chiral ionic liquids

CIL	head group	overall yield [%]
40	pyridinium	44
42	imidazolium	32
44	dimethylimidazolium	27
46	pyrrolidinium	23
48	phosphonium	35
50	trimethylammonium	31

III 1.2 Method Optimization for Chiral Recognition Experiments

For the evaluation of chiral recognition properties, the initially synthesized ephedrine-based chiral ionic liquid **4** was reacted with racemic Mosher acid potassium salt to form diastereomeric aggregates as previously reported by Wasserscheid *et al.*[94] (Figure 40).

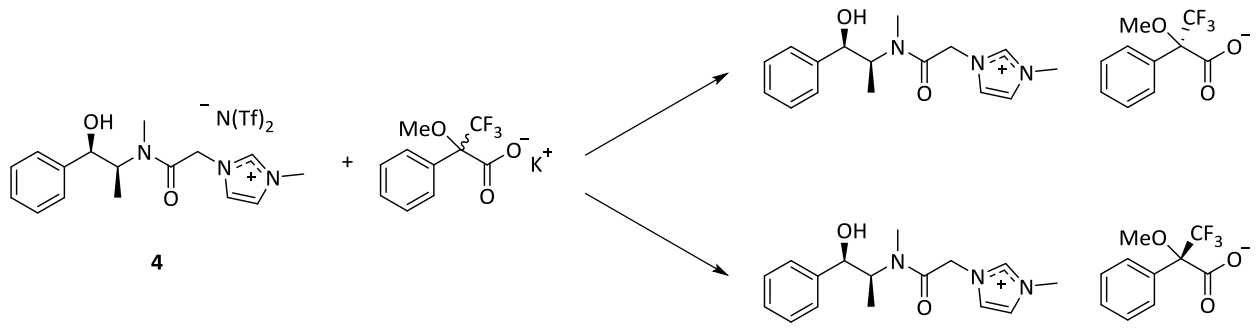


Figure 57: Formation of diasteromeric ion pairs between chiral ionic liquid and racemic Mosher's acid

The obtained ion aggregates were characterized using ^{19}F-NMR, as the differentiation of the diastereomers was easily visible *via* the different shift of the CF_3 group in Mosher's acid carboxylate. The shift difference of two diasteromers is dependent on the interaction between the chiral ionic liquid cation and Mosher's acid potassium salt. Possible interactions that account for diverging surroundings of Mosher's acid carboxylate are, for example, π-π interactions, dipol-interaction, hydrogen bonding or ionic interaction. The strength of these interactions influences the shift difference of the CF_3 group; hence it is possible to correlate a stronger splitting in the ^{19}F-NMR with stronger chiral recognition properties of the CIL for Mosher's acid carboxylate (Figure 58).

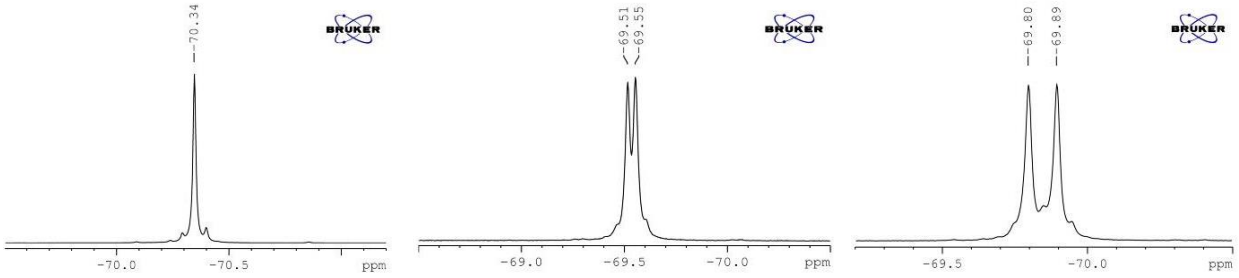


Figure 58: ^{19}F-NMR for enantiomerically pure CIL with no chiral recognition (left), low chiral recognition (middle) and high chiral recognition (right) for Mosher's acid carboxylate

Prior to the investigations towards the influence of different CIL structures, the ideal conditions and parameters were explored based on the ephedrinium-based chiral ionic liquid **4**. Initially, we selected solvents including polar protic and aprotic solvents. The *in situ* formation of diastereomeric aggregates was directly performed in an NMR tube *via* addition of the CIL dissolved in the respective solvent to Mosher's acid potassium salt. In some cases, 18-crown-6 ether was added to capture the potassium cation and to increase solubility of the formed salts. A clear solution was typically obtained after brief irradiation in an ultrasonic bath.

Table 11: Optimization of recognition studies

solvent	additives	Δδ (Hz)
d_4-MeOD	18-crown-6 ether	-[a]
d_6-acetone	18-crown-6 ether	3.9
d_6-benzene	18-crown-6 ether	-[a]
CD_2Cl_2	-	broadening
CD_2Cl_2	18-crown-6 ether	35.7

[a] no splitting of the ^{19}F-NMR signal could be observed

As can be seen from Table 11, we observed a strong influence of solvent and additive. The addition of 18-crown-6 ether was necessary to ensure the complete solvation of the chiral salt aggregate by the capture of the potassium cation and thus for shifting the equilibrium of the salt formation towards the desired CIL/Mosher's acid carboxylate aggregate. Solvation without the addition of 18-crown-6 ether was only possible in methylene chloride but lead to a smaller splitting of the signal and hence to a lower chiral recognition behavior. Best results were found for aprotic medium polar solvent dichloromethane. With protic methanol, no splitting of the signal could be observed, while only a low splitting of signal could be detected when aprotic, polar acetone was used. Hence it can be concluded that the use of an aprotic solvent is favorable, indicating that hydrogen bonding ability of the solvent

competes with the formation of close diasteromeric ionic aggregates. This corresponds to literature data, since most of the recognition studies are performed in apolar methylene chloride.

Using the optimum conditions the concentration dependence was investigated by varying the molar ratio of CIL **4** to racemic salt from 1:1 to 10:1. In all cases, the concentration of Moshers's acid potassium salt was kept constant at 0.25 mmol/ml.

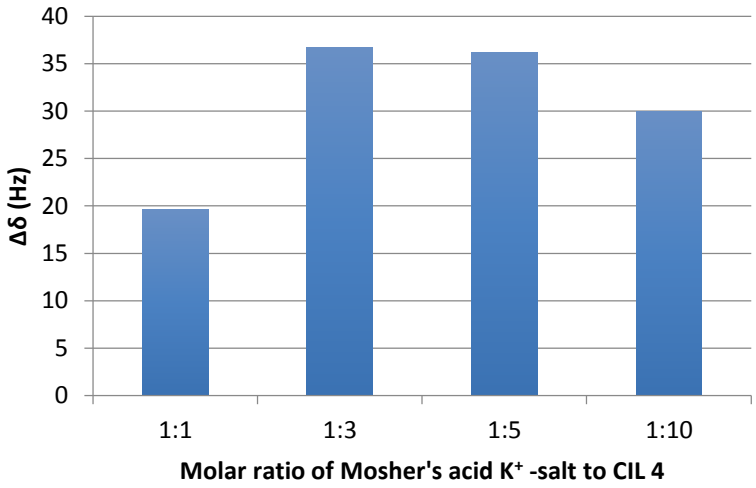


Figure 59: Influence of concentration on chiral recognition properties

As demonstrated in Figure 59 the splitting of the Mosher's acid signal reaches a maximum value with an excess of 3 to 5 equivalents of CIL **4** to Mosher's acid potassium salt. This indicates that the tightest ion aggregates and thus the highest interaction between CIL cation and Mosher's acid carboxylate are present at this concentration. An increase of CIL concentration does not further improve the chiral differentiation of the CIL. Although exceptions exist, this trend for concentration dependence was observed for most of the CILs investigated, which will be presented in the following chapter in detail.

III 1.3 Influence of Core Structures and Ionic Head Groups on Chiral Recognition

All synthesized CILs were first compared at ratios of 5 equivalents of CIL to Mosher´s acid carboxylate since this concentration was identified as best choice in prior investigations; results are summarized in Figure 60.

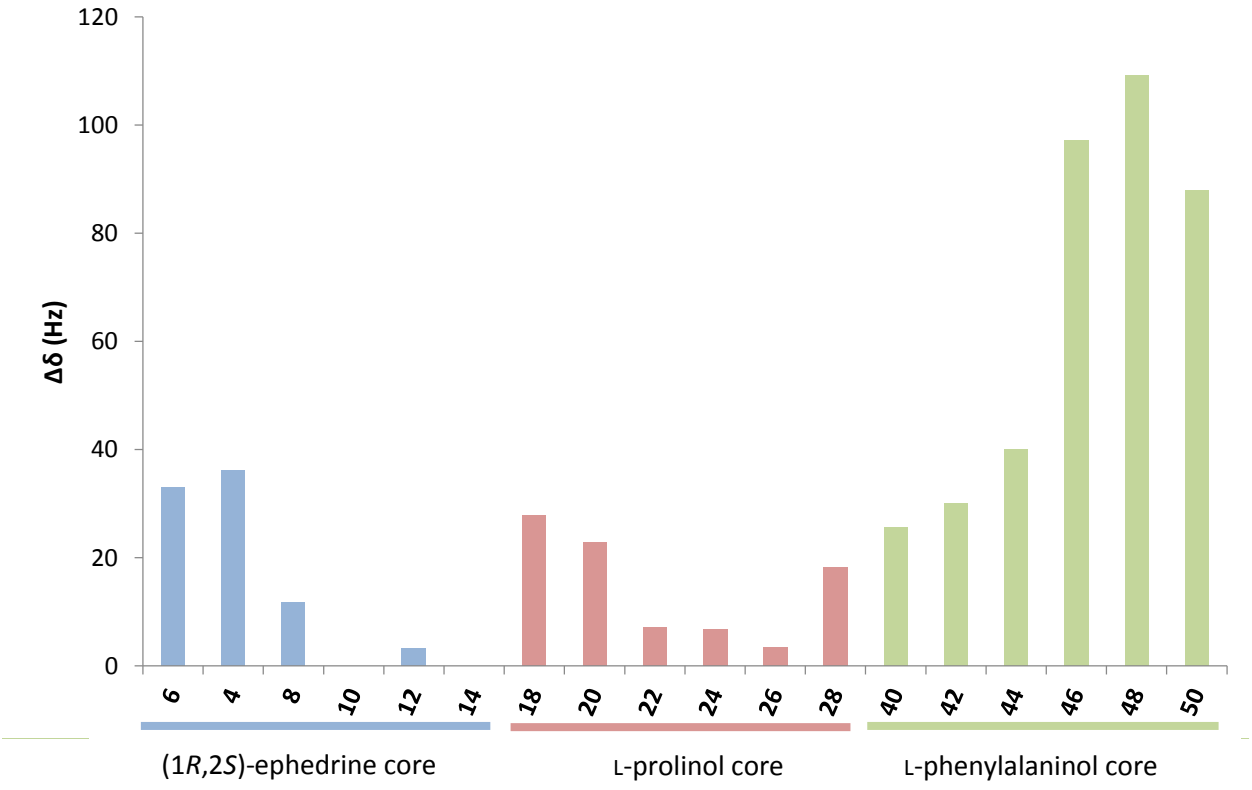


Figure 60: ^{19}F-NMR shifts of CILs/Mosher´s acid at a ratio of 5:1

When comparing ionic liquids with different chiral core groups, it becomes readily apparent by Figure 60 that the L-phenylalaninol derived chiral ionic liquids **40**-**50** show the highest splitting in ^{19}F-NMR and thus exhibit the highest diastereomeric interactions with racemic Mosher's acid potassium salt. This may be due to their aromatic system in combination with the conformational flexible amino-alcohol functionality. In contrast, considerable lower splitting values were obtained for (1*R*,2*S*)-ephedrine and L-prolinol-derived CILs. Ephedrine-derivatives show slightly better chiral recognition properties than L-prolinol-derived CILs which might be explained by the presence of the aromatic system in ephedrine.

The comparison of different ionic head groups reveals in case of (1*R*,2*S*)-ephedrine that ILs with imidazolium and pyridinium containing head groups **4** and **6** provide outstanding Δppm values and are therefore favorable structures compared to the aliphatic ammonium, pyrrolidinium and phosphonium cations. A similar trend for cationic head groups can be observed for L-prolinol-derived CILs. This

suggests that π-π interactions between cation and Mosher's acid potassium salt are advantageous for chiral recognition in those two types of chiral ionic liquids. The dimethylimidazolium-derivative **8** shows also high splitting behavior, but still lower than the imidazolium and pyridinium moiety, which might be traced back to steric reasons.

In principle, concentration dependence for different core groups revealed a complex behavior. While many CILs exhibit a maximum splitting and thus of interaction at an excess of 3 to 5 equivalents of CILs to Mosher's acid salt as previously reported for the ephedrinium derivative **4**, some exceptions exist. For example, pyridinium-based systems show a typical increase of diastereomeric interactions with increasing CIL concentration. For all CILs **6**, **18** and **40**, the highest Δppm values were obtained for a maximum of 10 eq. CIL. While this trend was also observed for trimethylammonium-based ionic liquids **14** and **28**, the trimethylammonium salt **50** based on the phenylalanine-derivative reveals a different behavior and a maximum at 5 eq. of CIL. In some cases of protic CILs the maximum splitting is even observed at equimolar mixtures of CIL and Mosher's acid salts.

These examples clearly demonstrate that a complex relationship between structure, concentration and diastereomeric interactions exists, thereby indicating that a prediction of optimum structure and conditions based on this data is difficult. Certainly further investigations and screening of concentration dependence would be necessary to gain more insight.

The results of more detailed investigations on the influence of different ratios of CIL and Mosher's acid potassium salt are given below grouped according to their core structures.

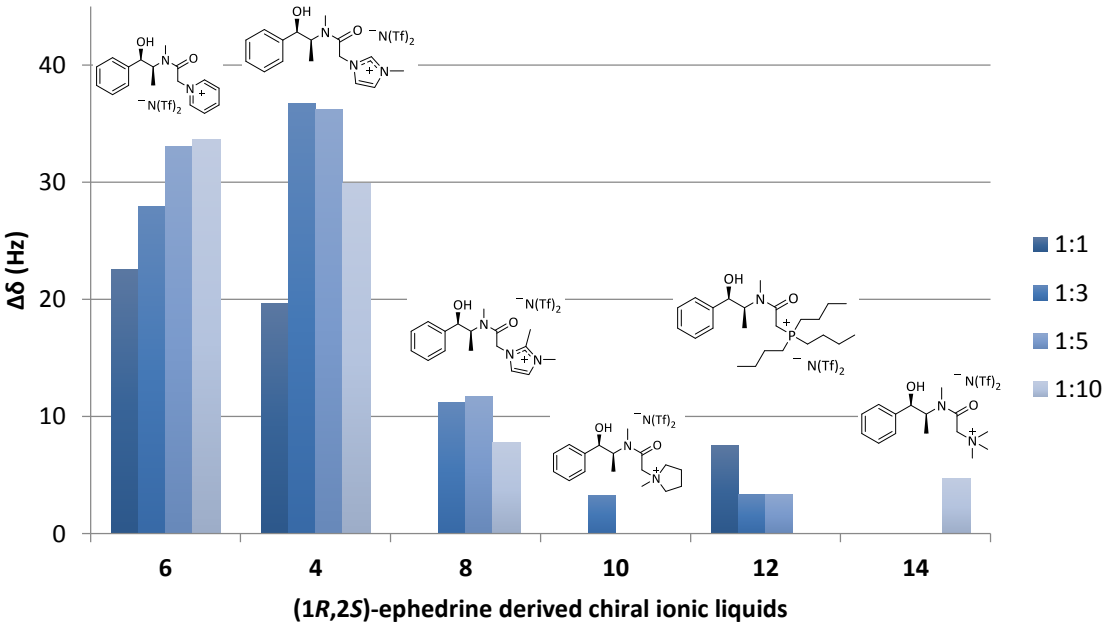


Figure 61: ^{19}F-NMR shifts for ephedrine-based chiral ionic liquids

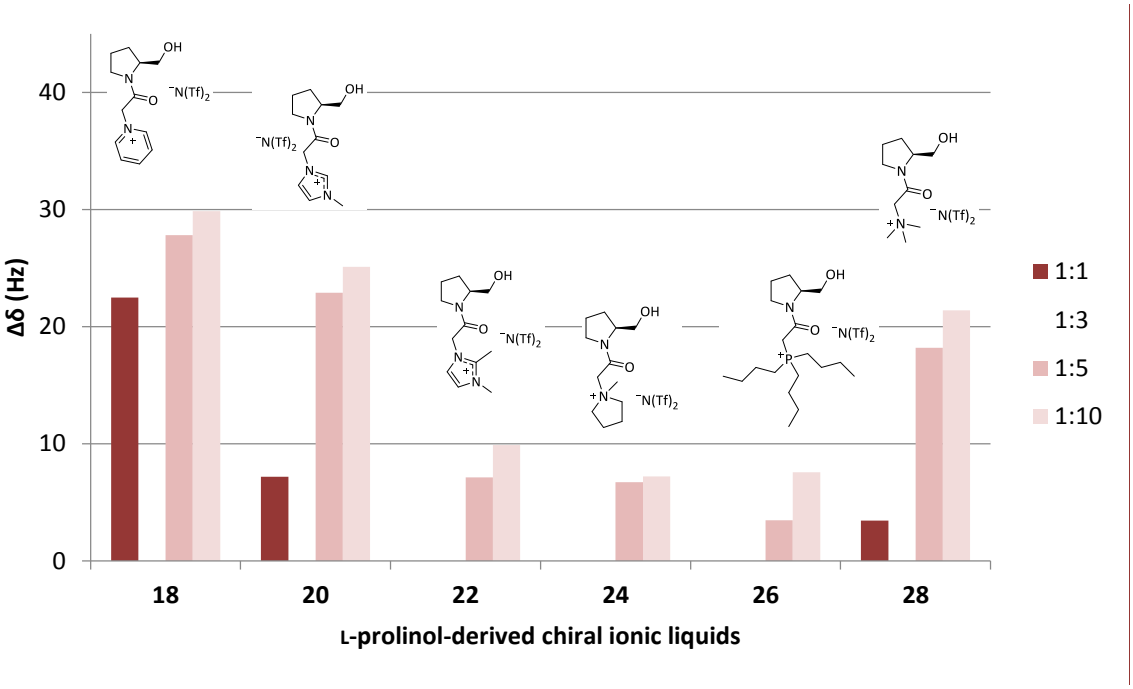


Figure 62: ^{19}F-NMR shifts for proline-based chiral ionic liquids

In case of (1*R*,2*S*)-ephedrine derived CILs the protic derivatives also exhibited good recognition behaviour - probably caused by additional H-bonding. However, this behaviour was not found for L-prolinium cations. Here, the replacement of a permanently alkylated ammonium cation with a protonated species results in a decrease of signal splitting, thereby again indicating the complexity of these diastereomeric interactions.

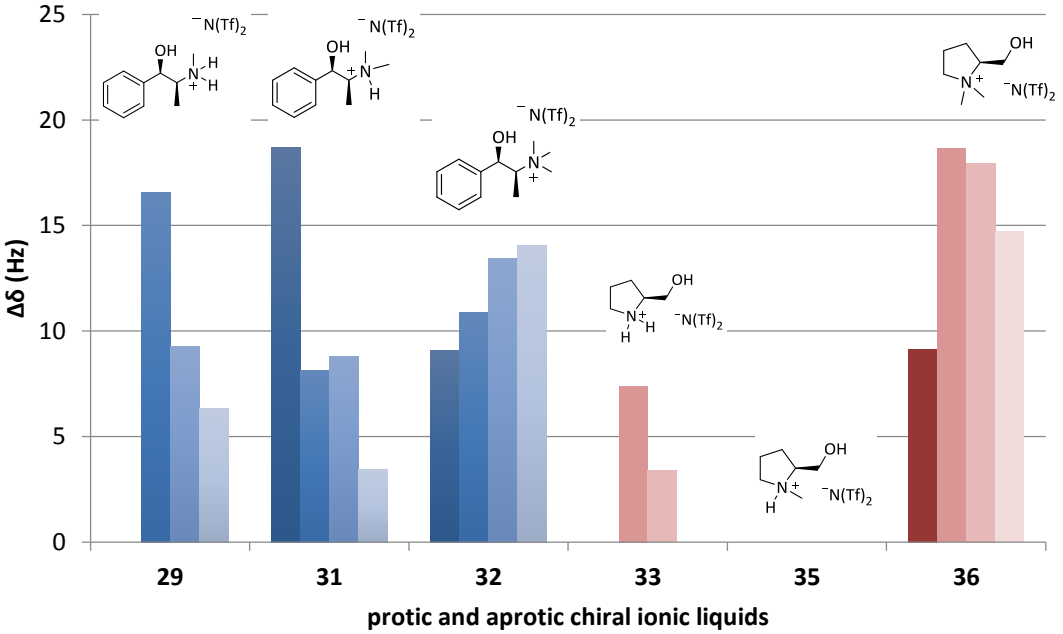


Figure 63: ^{19}F-NMR shifts for ephedrine- and proline-based CILs

On the contrary, the absence of aromatic groups is a clear advantage for L-phenylalaninol-derived CILs in regard to strength of diastereomeric interaction. The non-aromatic ammonium, pyrrolidinium and phosphonium derivatives show significantly higher $\Delta\delta$ values compared to imidazolium or pyridinium salts indicating that the presence of additional aromatic moieties competes with the π-π interactions between the chiral L-phenylalaninol core structure and Mosher's acid carboxylate.

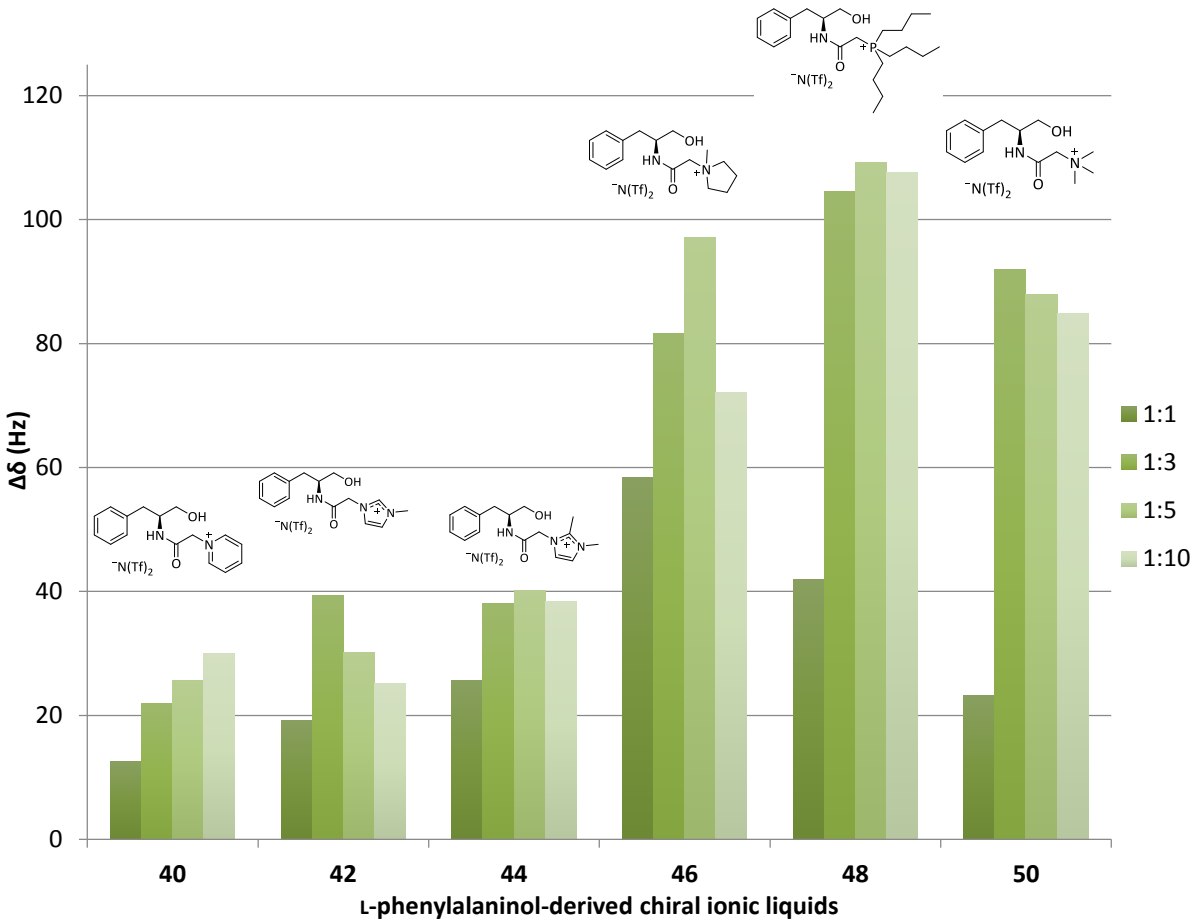


Figure 64: ^{19}F-NMR shifts for phenylalanine-based CILs

The outstanding recognition properties of L-phenylalaninol derived chiral ionic liquids towards Mosher's acid potassium salt suggest that this type of ionic liquid is of particular interest for future applications in separations or synthesis. The results obtained for the phosphonium containing CIL **48** are particularly remarkable: Despite the comparing simple structure, a maximum shift difference of 110 Hz was found. Values in this order of magnitude have been hardly reported in literature to date.

For a better understanding of the interactions that are responsible for the unique chiral recognition properties between Mosher's acid carboxylate and the phosphonium containing L-phenylalaninol core structures **48**, optimized geometries based on an MP2 and 6-311g basis set were calculated for the two diasteromeric salts (Figure 65).[vii]

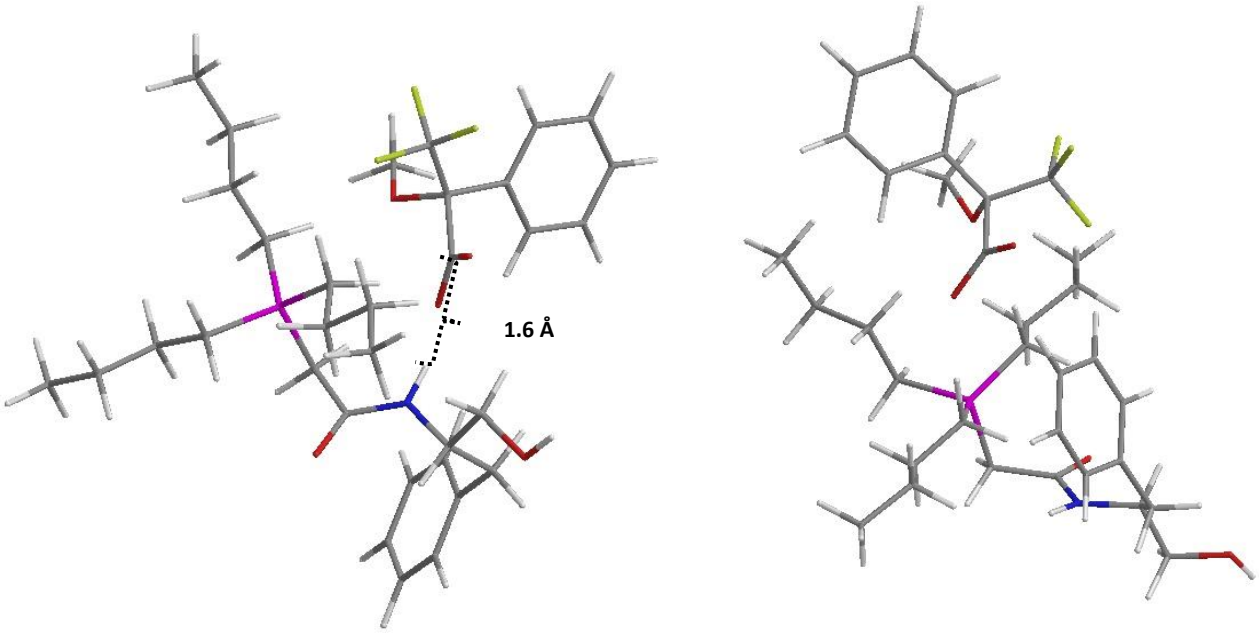


Figure 65: Theoretical calculation for geometry of diasteromeric aggregate for chiral ionic liquid 46 and (*S*)-Mosher's acid carboxylate (left) and (*R*)-Mosher's acid carboxylate (right)

As can be seen from the optimized geometry in the case of the (*S*)-Mosher's acid derived ion pair, the configuration of the carboxylate allows the formation of a very strong hydrogen bonding with a distance of 1.6 Å between the amide proton of the CIL cation and the carboxylate of Mosher's acid as hydrogen-bond acceptor (Figure 66). This strong interaction is not possible in the case of the (*R*)-Mosher's acid containing ion pair mainly due to the sterical hindrance by the alkyl chain of the phosphonium moiety.

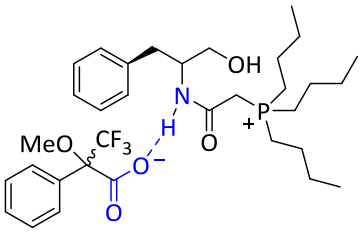


Figure 66: Hydrogen bonding in chiral ionic liquid 48 / (*S*)-Mosher's acid carboxylate aggregate

[vii] Perfomed by Dr. Christian Schröder, Institute of Computational Biological Chemistry, University of Vienna

III 2 Chiral Ionic Liquids in Asymmetric Synthesis

Due to the extremely important role of enantiopure compounds for biological applications, there is tremendous interest in research on their stereospecific synthesis. After ground-breaking contributions that were later awarded with the Nobel Prize, the field of asymmetric synthesis became very broad and numerous methods have been developed.[48, 154] Still, many of the known asymmetric reactions have drawbacks and the optimization and improvement of these methodologies is a constant matter of investigations. Chiral ionic liquids represent an innovative approach to deal with some of the drawbacks, as they can be used as sole source of chirality in asymmetric reactions and provide tunable properties for specific enantioselective reactions. The role of chiral ionic liquids in asymmetric reactions can differ as depicted in previous chapters (II 1).

Apart from the fact that CILs can be used in common ways as novel chiral ligands or organocatalysts and therefore may exhibit unknown activity, their unique structure allows to fine tune the activity of the ligand or catalyst in hand to the given reaction conditions. The adaptation of properties, especially in regard to solvation behavior is hardly possible with conventional ligands and catalysts and makes CILs particularly interesting in this field and creates the possibility of recycling.

In the following chapter, applications of novel chiral ionic liquids in the field of asymmetric synthesis are presented. Based on mostly naturally occurring chiral pool amino alcohols, highly functionalized novel CILs were specially designed to promote three different asymmetric transformations including alkylations or hydrogenations. In all cases, chiral inductors that are known for their excellent chiral induction where grafted to ionic liquid moiety thereby providing target-designed CILs with adaptable solubility.

III 2.1 Chiral Ionic Liquids in Asymmetric Alkylation

III 2.1.1 Chiral Amino Alcohols as Ligands for Dialkylzinc Addition

The enantiopure synthesis of substituted alcohols is of high importance as they are key starting substrates for many pharmaceutical compounds and precursors for many functional group transformations in organic molecules.

In 1984 Oguni and Omi where the first ones to report the use of dimethylzinc in the presence of catalytic amounts of L-leucinol to react with benzaldehyde to the corresponding enantioenriched alcohol under Lewis basic conditions.[155] Although only moderate enantioselectivities of 49% ee were reported, research in enantioselective alkylation reactions with zinc organyls was rapidly growing. It was Noyori's group which published the first highly enantioselective dimethylzinc addition in 1986 using (2*S*)-(-)-3-*exo*-dimethylaminoisoborneol ((-)-DAIB) as chiral ligand and investigated the reaction mechanism profoundly (Figure 67).[156]

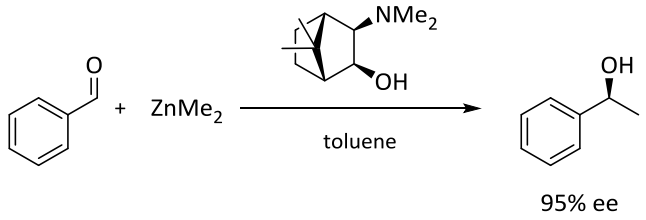
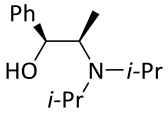
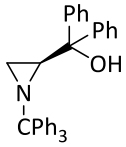
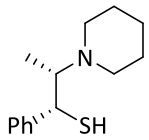
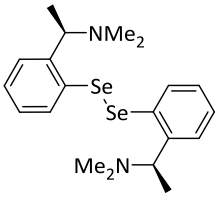
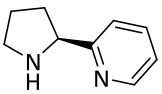
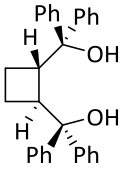
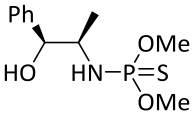


Figure 67: Asymmetric alkylation of benzaldehyde by Noyori and co-workers

Considerable effort was put into design and optimization of chiral ligands for asymmetric alkylation reaction, and chiral amino alcohols were identified as benchmark ligands. Nowadays a wide selection of chiral ligands is available and some outstanding examples for various functionalities are summarized below (Table 12).

Table 12: Examples for ligands in asymmetric alkylation

ligand	ee (%)	yield (%)	lit.	functionality
	91 (*S*)	73	Soai[157] 1994	amino alcohol
	90 (*S*)	99	Lawrence[158] 1999	aziridino alcohol

	100 (*R*)	94	Kang[159] 1996	amino thiol
	91 (*S*)	70	Wirth[160] 1995	diselenid
	93 (*S*)	100	Chelucci[161] 1991	diamine
	88 (*R*)	79	Ito[162] 1994	diol
	95 (*S*)	93	Soai[163] 1993	phosphoramide

Noyori's studies revealed that the chiral ligand controls not only the stereoselectivity of the reaction but also activates the zinc organyl. After coordination of the amino alcohol, the nucleophilicity of the alkyl groups is increased by converting the linear zinc organyl to a tetrahedral geometry. Key step in the proposed pathway is the necessity of a second dialkyl zinc molecule to activate the chiral ligand and to facilitate the alkyl transfer. In the following mechanism, the transition state of the dimeric complex favours *si* face alkylation of benzaldehyde (Figure 68), which comes from the *anti* coordination of benzaldehyde to the zinc complex, as calculated by molecular orbital and density functions.

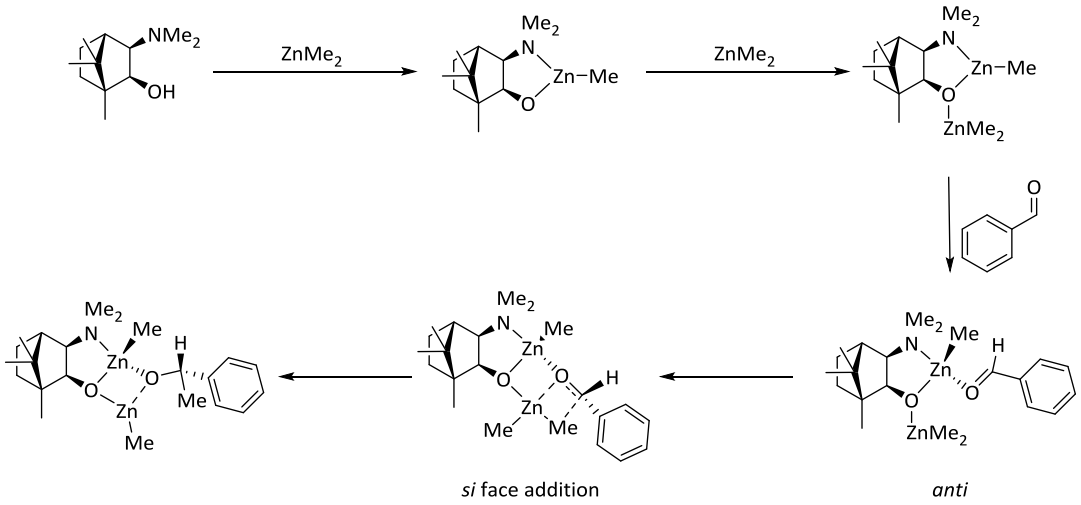


Figure 68: Mechanism of dialkyl zinc addition by Noyori *et al.*

Further investigations performed by Noyori's on the dimeric transition state showed that the asymmetric alkylation using zinc organyls exhibits a large positive non-linear effect, due to the equilibrium between the monomer and the dimer intermediate. The less stable (+)(+) or (-)(-) homodimer reacts much faster, while the (+)(-) heterodimer, which is more stable, consumes the unfavourable ligand, thereby leading to the excellent enantioselectivities observed for this reaction (Figure 69).

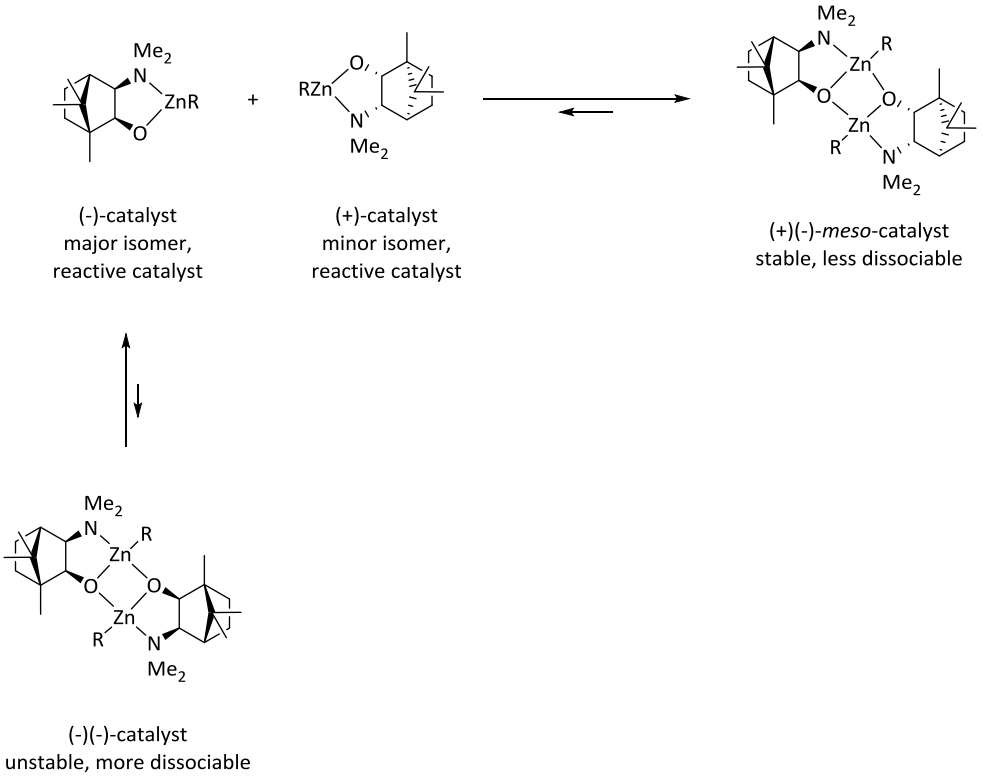


Figure 69: Non-linear effect observed for dialkylzinc addition to aldehydes

III 2.1.2 Design and Synthesis of Chiral Ionic Liquids for Asymmetric Alkylation

Inspired by the extraordinary potential of chiral of amino alcohols and the possibility to convert them into ionic liquids, a set of highly coordinating CILs with amino alcohol functionality was designed for the alkylation of benzaldehyde using diethyl zinc.[86] Therefore the chiral amino alcohol ligand was grafted to an IL precursor, yielding a chiral tridendate ligand which was selectively alkylated to obtain a coordinating CIL (Figure 70). A pyridinium cationic group was chosen for the selective alkylation, not only because of the good availability of the pyridine precursor but also because of the possibility to use this CIL under basic conditions due to the absence of acidic protons. Additionally, steric or electronic interactions of the cation might further influence the transition state.

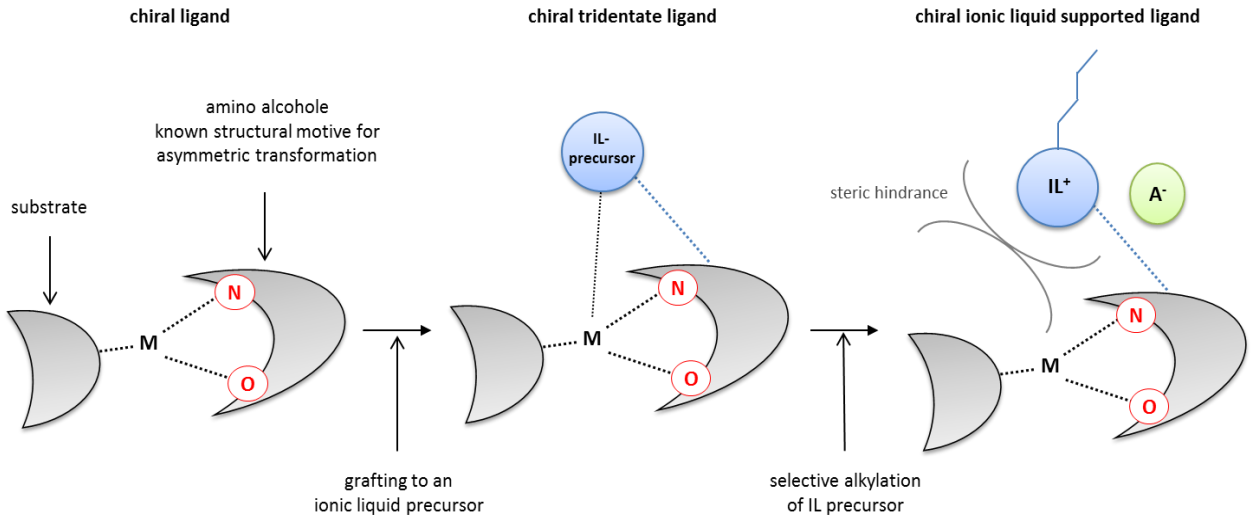


Figure 70: Strategy for chiral ligand synthesis

As outlined with the commercially available chiral amino alcohol **51**, the primary amino alcohol was first converted to the intermediate tridentate ligand by reaction with pyridine-3-carbaldehyde in anhydrous methanol in the presence of freshly activated molecular sieve followed by successive reduction using $NaBH_4$ (Figure 71). The obtained secondary amine **52** was further *N*-methylated according to the classical Leukart-Wallach protocol using formic acid and formaldehyde to yield the corresponding tertiary amine **53**. This was done due to previous work in our group that showed that secondary amines can inhibit the alkylation reaction.[152] The tridentate ligands were alkylated at the pyridinium moiety using a small excess of *n*-butyl bromide at 50 °C overnight under solvent free conditions giving product **54**. The careful selection of these alkylating conditions allowed selective monoalkylation without the formation of double alkylation or side products. This is probably due to the terminal position of the pyridine and the easier steric access, as double alkylation was only observed when an excess of highly reactive methyl iodide was used as alkylating reagent. A final ion exchange with bis(trifluoromethane)sulfonimide lithium salt gave access to hydrophobic CIL **55** with an amino alcohol substructure in four steps.

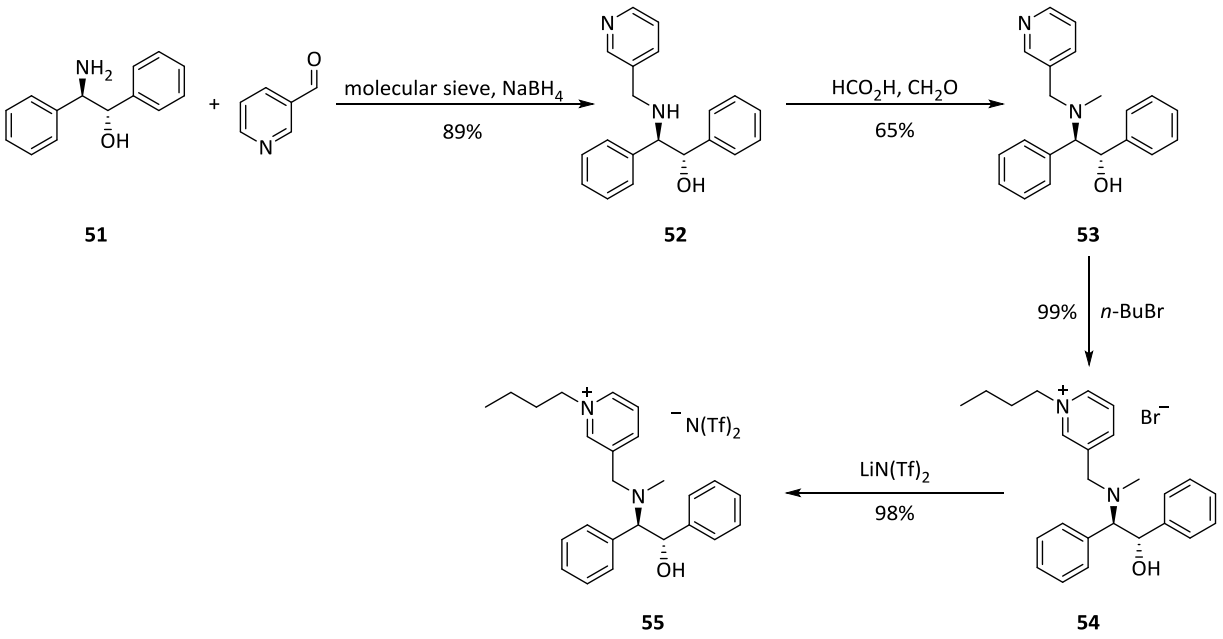


Figure 71: Synthesis of amino alcohol-derived chiral ionic liquids for alkylation reaction

After optimization of this procedure, the range of starting materials was expanded to a set of enantiopure amino alcohols from the chiral pool, including alkaloids such as ephedrine or its diastereomer, amino acid-derived amino alcohols or the camphor-derived aminoisoborneol. This gave access to a small library of novel CILs with chelate formation capabilities that are suitable as ligands for asymmetric alkylation reactions of aldehydes to the corresponding enantioenriched alcohols (Figure 72).

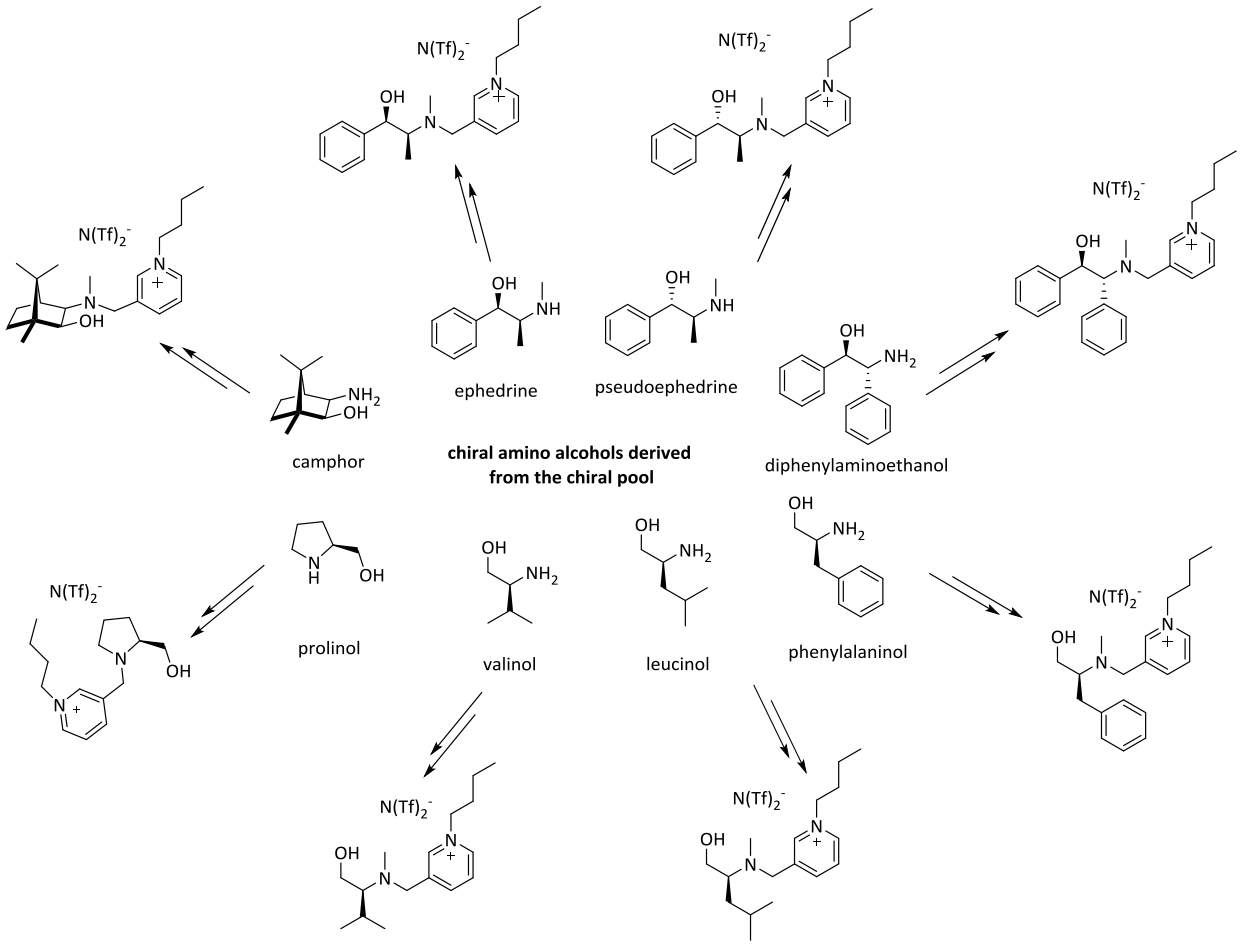
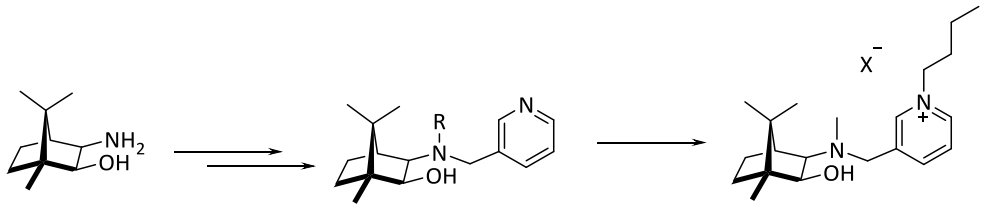


Figure 72: Synthesis of enantiopure amino alcohol-derived chiral ionic liquids

The synthesis of primary amines with pyridine-3-carboxyladehyde and the successive reduction to the desired tridendate ligands went smoothly in all cases, as already established in our laboratory and reported by Bica *et al*.[164] Despite the presence of two nitrogen atoms, alkylation with *n*-butyl bromide occurred selectively to the pyridinium bromide, and no double alkylation was observes in any case (Figure 73, Figure 74). Anion exchange gave the products in excellent purity, and yields over four reaction steps are given in Table 13.

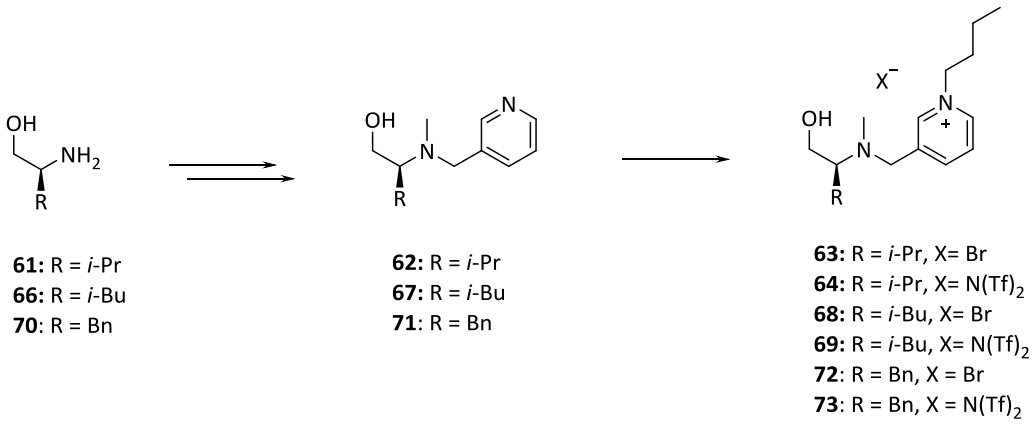


56

57: R = H
58: R = Me

59: X = Br
60: X = $N(Tf)_2$

Figure 73: Synthesis of camphor-derived CILs



61: R = *i*-Pr
66: R = *i*-Bu
70: R = Bn

62: R = *i*-Pr
67: R = *i*-Bu
71: R = Bn

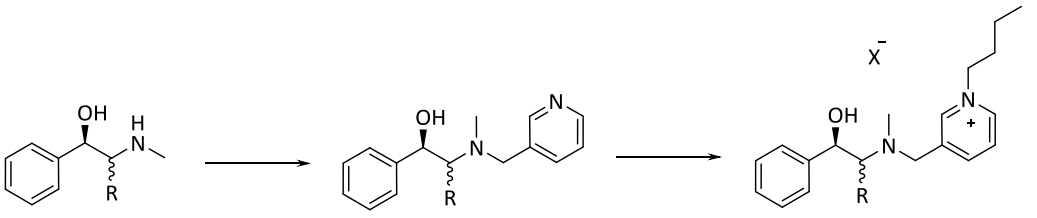
63: R = *i*-Pr, X= Br
64: R = *i*-Pr, X= $N(Tf)_2$
68: R = *i*-Bu, X= Br
69: R = *i*-Bu, X= $N(Tf)_2$
72: R = Bn, X = Br
73: R = Bn, X = $N(Tf)_2$

Figure 74 Synthesis of L-valine, L-leucin and L-phenylalanine-derived chiral ionic liquids

Table 13: Yields over last 3 steps for camphor-, L-valinol-, L-leucinol- and L-phenylalaninol-derived chiral ionic liquds

product	**60**	**64**	**69**	**73**
yield [%]	48	64	81	82

In case of secondary amino alcohols **1**, **77** and **15** as starting materials, the synthetic procedure was slightly adapted. Reductive amination of these amino alcohols with pyridine-3-carboxaldehyde occurred *via* formation of the *N*,*O*-acetals and gave direct access to the tertiary amino alcohols **74**, **78** and **81** using $NaCNBH_3$ and acetic acid for *in situ* reduction. In case of L-proline-derived CILs *in situ* reduction was performed using $NaBH_4$ in acetonitrile. Since no further methylation was necessary, the yields of the products were slightly higher than in case of primary amines as starting materials. Again, alkylation occurred selectively on the outer pyridine unit for all amino alcohols, and the ionic liquids were isolated in good overall yields after anion metathesis.



1: R = Me (1*R*,2*S*)
77: R = Me (1*S*,2*S*)

74: R = Me (1*R*,2*S*)
78: R = Me (1*S*,2*S*)

75: R = Me (1*R*,2*S*), X = Br
76: R = Me (1*R*,2*S*), X = $N(Tf)_2$
79: R = Me (1*S*,2*S*), X = Br
80: R = Me (1*S*,2*S*), X = $N(Tf)_2$

Figure 75: Synthesis of (1*R*,2*S*)-ephedrine- and (1*S*,2*S*)-pseudoephedrine-derived chiral ionic liquids

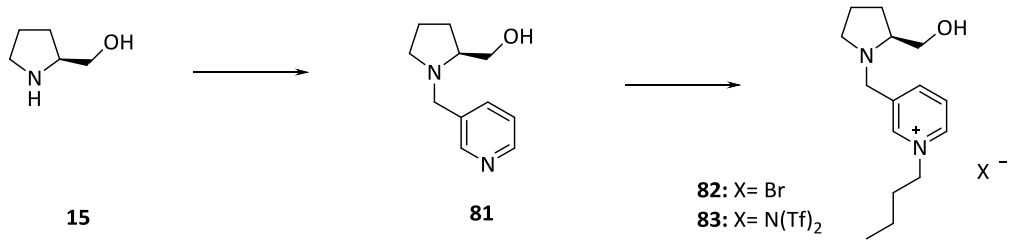


Figure 76: Synthesis of L-proline-derived chiral ionic liquids

Table 14: Yields over last 2 steps for (1*R*,2*S*)-ephedrine-, (1*S*,2*S*)-pseudoephedrine-and L-proline derived chiral ionic liquds

product	**76**	**80**	**83**
yield [%]	66	72	77

Prior to application of the synthesized CILs as ligands in asymmetric alkylation, the chiral recognition properties were investigated and evaluated *via* ^{19}F-NMR spectroscopy as already discussed in chapter III 1. Therefore the CILs were converted to diasteromeric salt aggregates using Mosher's acid carboxylate with a concentration of 5 eq. CIL, as this turned out to be the ideal concentration in previous investigations (III 1.2), and furthermore 18-crown-6 ether was added as potassium scavenger. This method might be a suitable approach to evaluate the chiral influence of CIL in this reaction, since some structural similarities between the aromatic substrate and Mosher's acid potassium salt exist.

Table 15: Evaluation of chiral recognition properties *via* ^{19}F-NMR

entry	CIL	core structure	Δδ [ppm][a]
1	**76**	ephedrine	17.5
2	**55**	diphenylaminoethanol	12.6
3	**69**	leucin	8.3
4	**64**	valine	6.3
5	**80**	pseudoephedrine	3.6
6	**73**	phenylalaninol	-[b]
7	**60**	aminoisoborneol	-[b]
8	**83**	prolinol	-[b]

[a] Chemical shift splitting of the CF_3 signal (^{19}F-NMR, 376.5 MHz) of racemic Mosher's acid potassium salt in the presence of 5 eq. chiral ionic liquid and 1 eq. 18-crown-6 ether. [b] Broadening but no measurable splitting of the CF_3 signal.

A significant splitting could be observed for ephedrine derived CIL **76** and diphenylaminoethanol-derived CIL **55**. It seems that the possibility of π-π interaction between Mosher acid and CIL is crucial in this case of interaction. Surprisingly phenylalanine and pseudoephedrine-derived CIL **73** and **80** showed only low recognition properties. The results from chiral recognition in ^{19}F-NMR can to some extent be connected to their performance in asymmetric alkylation reactions as discussed in the following chapter.

III 2.1.3 Asymmetric Alkylation of Benzaldehyde in the Presence of Chiral Ionic Liquids

To investigate the chiral induction properties of the novel CILs, the synthesized CILs were further applied as chiral ligands in sub-stoichiometric amounts of 10 mol% in asymmetric alkylation of benzaldehyde with diethylzinc.

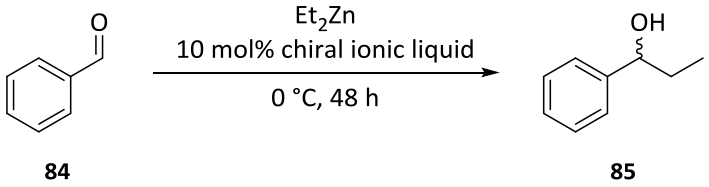


Figure 77: Asymmetric addition of diethylzinc to benzaldehyde

To evaluate optimal reaction conditions, different solvents were chosen and homogeneous and heterogeneous systems examined. The reaction was performed under homogenous conditions using the conventional solvent dichloromethane, under toluene that gave a hetereogenic mixture since the ionic liquid-supported ligand was insoluble, as well as under biphasic conditions in the system 1-butyl-2,3-dimethylimidazolium bis(trifluoromethane)sulfonimide ($[C_4m_2im]N(Tf)_2$)/*n*-hexane. This immobilization of ionic liquid-tagged chiral ligands, e.g. a bisoxazoline derivative in hydrophobic ionic liquids has already been reported by Doherty *et al.*, and the biphasic methodology proved to be extremely suitable for Diels-Alder and Mukayama aldol reactions.[80]

Table 16: Asymmetric addition of diethylzinc to benzaldehyde in the presence of coordinating chiral ionic liquids

CIL	amino alcohol core	solvent	yield [%][a,b]	ee [%][c,d]
60	camphor	CH_2Cl_2	79	91 (*R*)
		toluene	83	80 (*R*)
		$[C_4m_2im]N(Tf)_2$	85	50 (*R*)
76	ephedrine	CH_2Cl_2	81	74 (*R*)
		toluene	30	40 (*R*)
		$[C_4m_2im]N(Tf)_2$	79	70 (*R*)
80	pseudoephedrine	CH_2Cl_2	67	55 (*R*)
		toluene	69	56 (*R*)
		$[C_4m_2im]N(Tf)_2$	74	56 (*R*)
55	diphenylaminoethanol	CH_2Cl_2	92	66 (*R*)
		toluene	94	70 (*R*)
		$[C_4m_2im]N(Tf)_2$	90	59 (*R*)
73	phenylalanine	CH_2Cl_2	26	23 (*S*)
		toluene	56	24 (*S*)
		$[C_4m_2im]N(Tf)_2$	98	18 (*S*)
69	leucine	CH_2Cl_2	72	20 (*S*)
		toluene	<1	n.d.
		$[C_4m_2im]N(Tf)_2$	83	21 (*S*)
64	valine	CH_2Cl_2	78	32 (*S*)
		toluene	83	70 (S)
		$[C_4m_2im]N(Tf)_2$	59	54 (*S*)
83	proline	CH_2Cl_2	<1	n.d.
		toluene	<1	n.d.
		$[C_4m_2im]N(Tf)_2$	86	15 (*S*)

[a] Performed with 2 mmol benzaldehyde, 4.4 mmol of a 1 M solution of Et_2Zn in *n*-hexane and 0.2 mmol CIL at 0 °C for 24-48 hours. [b] Isolated yield. [c] Determined by HPLC using a DAICEL Chiralcel IB column. [d] Absolute configuration determined *via* optical rotation and comparison with literature values.

After screening of homogeneous and heterogeneous conditions, the use of the biphasic mixture *n*-hexane/$[C_4m_2im]N(Tf)_2$ was identified as best solvent system. This combination allowed not only to avoid the environmentally problematic dichloromethane but provides good prospects for ligand immobilization and potential recycling. Moreover the use of $[C_4m_2im]N(Tf)_2$ gave, in most of the cases, the best yield. In some examples it was only possible to perform the reaction exclusively in this solvent, while no conversion was observed in dichloromethane or pure *n*-hexane.

In accordance to the previously performed recognition studies in ^{19}F-NMR, the ephedrine-derived CIL gave the best results with 79% yield and 70% ee. When comparing the chiral ionic liquids derived from the diastereomers ephedrine **76** and pseudoephedrine **80** we found that ephedrine is better suited: Good yields and selectivities could be obtained with the ephedrine derivative, whereas both yield and selectivity decrease in case of the diastereomer. Aminodiphenylethanol-, pseudoephedrine- and camphor-derived CILs **55, 80** and **60** also performed reasonably well, while amino acid-derived CILs gave lower enantioselectivities. In case of valine-, leucine- and proline-derived CILs **64, 69** and **83** this might be related to the missing aromatic system, as non-aromatic CILs also failed to induce a significant splitting in previous NMR experiments (Table 15). Interestingly proline-derived CIL **83** only yielded the product under heterogeneous reaction conditions; however no enantioselectivity was observed.

The ease of work-up is another feature supporting the biphasic system 1-butyl-2,3-dimethylimidazolium bis(trifluoromethane)sulfonimide ($[C_4m_2im]N(Tf)_2$)/*n*-hexane, as a suitable recycling protocol could be developed by adapting the solubility of the IL solvent and ligand *via* the choice of the proper anion. After complete reaction the mixture was hydrolyzed using diluted hydrochloric acid to give a three-phase system. Due to the hydrophobic anion, the ionic liquid-supported chiral ligand remained immobilized in the lowest ionic liquid layer. The enantioenriched product was easily extracted in the upper *n*-hexane phase, while Zn salts remained in the aqueous middle phase. The *n*-hexane layer with the product was therefore simply decanted, yielding the product in spectroscopically pure form (Figure 78). This high purity could not be obtained in dichloromethane or toluene as solvent system, and additional chromatographic purification was necessary. After successive separation of the metal-containing aqueous phase, the remaining IL mixture was dried under vacuum and could be used for consecutive runs.

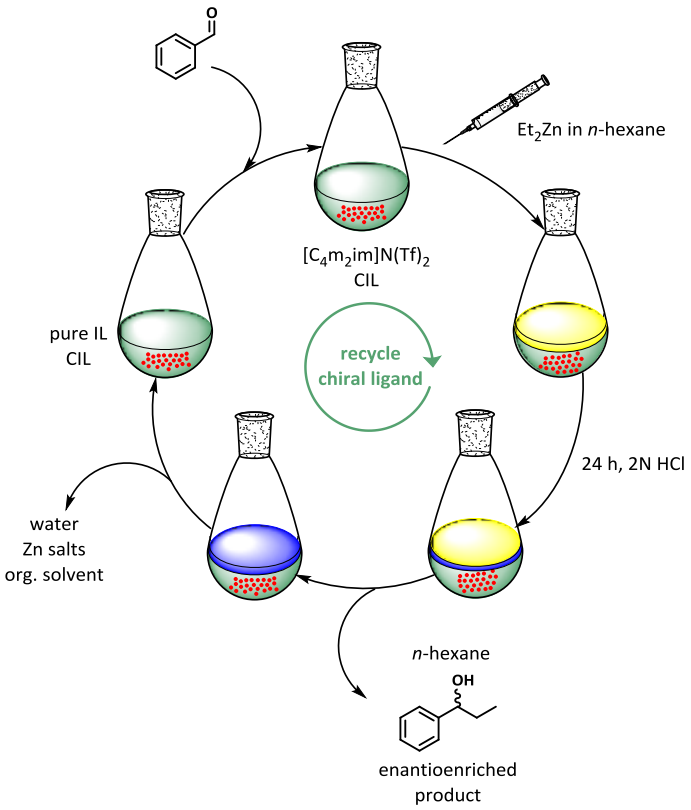


Figure 78: Recycling strategy of immobilized ligand

Based on this strategy, recycling of the immobilized ionic liquid-tagged chiral ligand was performed for the two lead candidates ephedrine- and camphor-derived CILs **76** and **60** for five 5 consecutive runs.

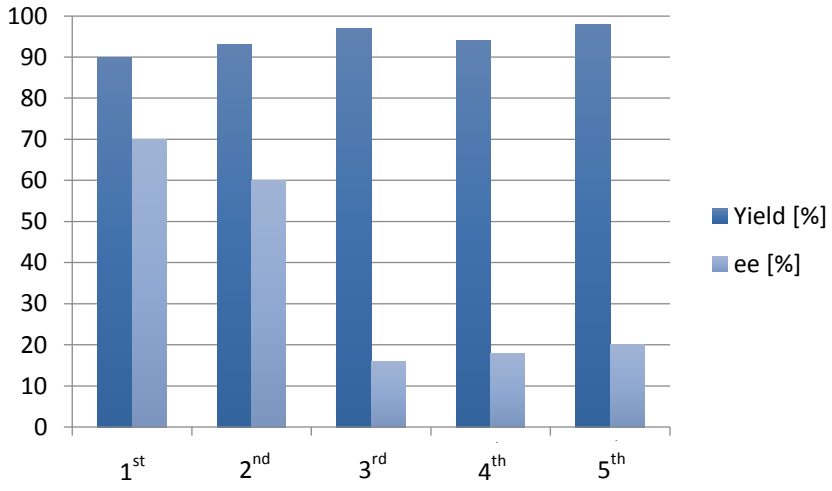


Figure 79: Recycling of ephedrine-derived chiral ionic liquid 76

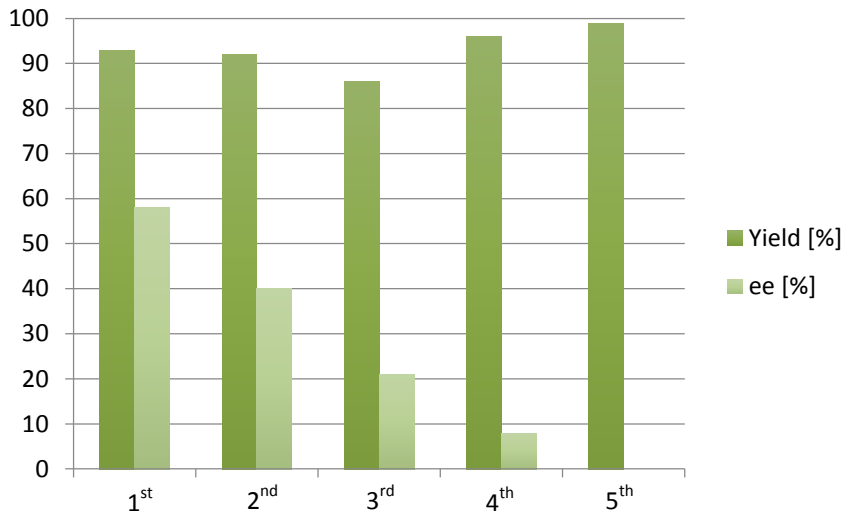


Figure 80: Recycling of camphor-derived chiral ionic liquid 60

As can be seen in Figure 79 and Figure 80, it was possible to reuse the chiral ligand in five consecutive runs. Excellent yields could be maintained and no additional purification of the product was required after simple phase separation. However, despite efforts of optimizing the recycling protocol a drop in enantioselectivity was observed for both ionic liquid-supported chiral ligands after the 2nd run. In case of camphor-derived CIL **60** enantioselectivity was even completely lost after the 4th run, while a selectivity of 20% ee was maintained with the ephedrine-derived chiral IL **76**. This behaviour was probably caused by leaching or undesired side reactions of the chiral ligand, and might be improved by future adaptation of counter anion, extraction solvent or reaction media.

Taking literature known mechanisms and observations made in our group into consideration, a tentative mechanism and equilibria for the *in situ* generated Zn complex can be proposed. As for conventional amino alcohol ligands, an equilibrium between monomer and dimer transition state exists resulting in the activation of diethylzinc. However, the exact role of the cationic head group remains unclear and requires more detailed investigations. Although the alkylated nitrogen of the pyridinium moiety is not available for coordination there is the possibility for d-π interaction of the metal and the pyridinium. Additionally, the bulky and sterically demanding *n*-butyl pyridinium unit might further influence the geometry of transition state and affect the stereochemical outcome of this reaction.

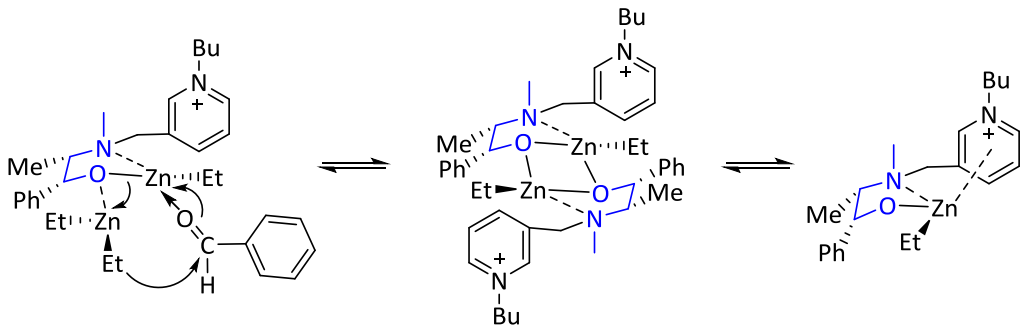


Figure 81: Equilibrium in transition state

III 2.2 Chiral Ionic Liquids in Asymmetric Transfer Hydrogenation

III 2.2.1 Amino Alcohols in Asymmetric Transfer Hydrogenation

As reported in the prior chapter, the stereoselective reduction of carbonyls and imines is among the most important transformations in asymmetric synthesis as chiral alcohols can be widely used as starting material for further synthetic transformations.[165] Consequently, a variety of options for this reaction have been investigated in search for the best results in respect of conversion, enantioselectivity, atom efficiency and sustainability of the reaction conditions.

Among all catalytic procedures that have emerged in recent years, asymmetric transfer hydrogenations (ATH) are a particularly attractive strategy, as they provide an efficient access to chiral alcohols using small and non-hazardous organic molecules as hydrogen donor.

In general, transfer hydrogenation is defined as the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst as demonstrated in Figure 82.[166]

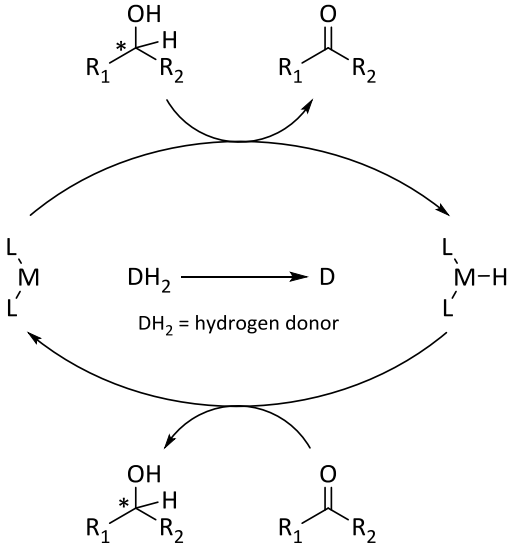


Figure 82: Transfer hydrogenation

Two reaction mechanisms have been proposed for the transfer hydrogenation of ketones, both depicted in an example using inexpensive and benign *i*-PrOH as hydrogen donor.

1) Reduction *via* direct hydrogen transfer
The hydrogen transfer occurs in a six-membered cyclic transition state in which the hydrogen donor (*i*-PrOH) and acceptor (ketone) are in very close proximity to the metal center. This mechanism is very similar to the proposed mechanism for the Meerwein-Ponndorf-Verley reduction.[167]

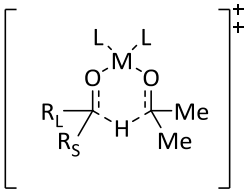


Figure 83: Transition state for reduction *via* direct hydrogen transfer

2) Reduction *via* hydridic route

This mechanism can be generally described as outlined in Figure 84: A metal hydride **B** which is formed by the elimination of acetone or carbon dioxide from **A** undergoes hydride transfer to the coordinated ketone **C**. The exact mechanism is dependent on metal catalyst and hydrogen donor.[165] Most of the metal catalysts used for transfer hydrogenation are based on mono- or polynuclear Ru(II), Rh(I) or Ir(I) complexes with phosphorus or nitrogen containing ligands.

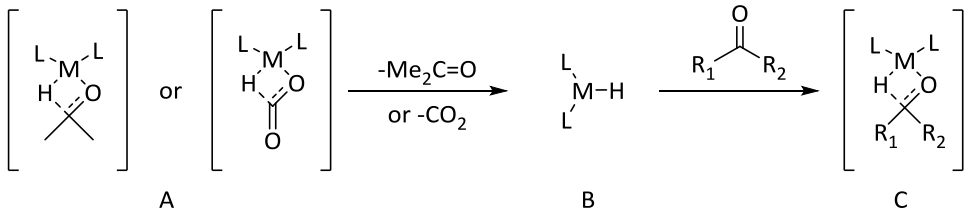
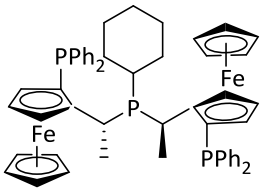
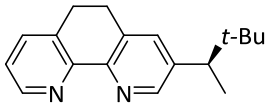
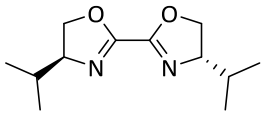
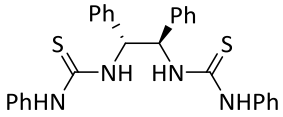
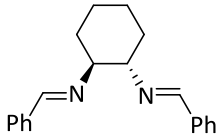
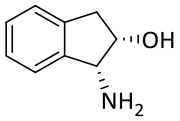


Figure 84: Mechanism for reduction *via* hydridic route

In 1995 Noyori *et al.* were the first to present an asymmetric transfer hydrogenation (ATH) of aromatic ketones using a ruthenium(II) catalyst, a chiral diamine ligand and *i*-PrOH as hydrogen source at room temperature.[168] With this methodology, a variety of aromatic ketones could be reduced with good to excellent enantioselectivities. However, the authors always faced the problem of back-reactions as the product could also function as hydrogen donor. Depending on the reaction equilibria, it was not always possible to drive the reaction to complete conversion. Nevertheless *i*-PrOH is a very convenient hydrogen source for ATH due to its favourable properties such as stability, nontoxicity, environmental friendliness and cheap price. Additionally, *i*-PrOH readily dissolves many organic compounds, whereas the produced acetone is easily removable.[167]

To circumvent the problem of reversibility, considerable effort has been put into the improvement of this reaction. It was in 1996 when Noyori's group published the use of formic acid in combination with triethylamine as hydrogen source.[169] This inexpensive reducing agent results in the irreversible formation of CO_2 and leads to conversions of 100% and excellent enantioselectivities of up to >99% ee for various aromatic ketones. The Ru(II)-catalyzed back reaction of CO_2 with molecular hydrogen to formic acid is not a problem, as no molecular hydrogen is involved in the catalytic cycle as reductions strictly proceed *via* hydride transfer.[170] After extensive investigations towards reaction conditions, chiral ligands and Ru(II) catalyst, tolylsulfonyl-substituted diamine ligands in combination with benzene substituted Ru(II) catalyst were identified as ideal reagents and can up to date be considered as the benchmark system. Since then, many bidendate diamines with various functionalities, *e.g.* BINOL-derived diphosphite[171] and amino alcohol[172] based ligands as depicted in Table 17 were developed and investigated.

Table 17: Examples of chiral ligands for asymmetric transfer hydrogenation

ligand	ee (%)[a]	yield (%)[a]	lit.	functionality
	72 (R)	99	Barbaro[173] 1997	phosphine
	63 (*S*)	89	Zassinovich[174] 1989	pyridine
	58 (*R*)	89	Müller[175] 1991	bis(oxazole)
	87 (*S*)	96	Gamez[176] 1996	diamine
	28 (*S*)	89	Krasik[177] 1994	diimine
	91 (*S*)	70	Palmer[178] 1997	amino alcohole

[a] Results for asymmetric transferhydrogenation of acetophenon to phenylethanol in the presence of 5 mol% Ru(II) catalyst.

Apart from the previously mentioned advantages, the use of water-soluble sodium formiate as hydrogen donor also provides the opportunity to run the reaction in aqueous medium. Driven by the trend to adjust organic reactions to greener conditions, the replacement of volatile organic solvents with water is a rapidly growing research area nowadays. Additional to the environmental benefits, water has been shown to influence reaction rates and selectivities in many organic transformations.[179] Consequently, considerable effort has been put into development of novel water-soluble catalysts and ligands for ATH. In 2001, Chung *et al.* first presented this concept using $[Ru(p\text{-cymene})Cl_2]_2$ and L-proline amide as water-soluble catalyst complex and reduced various ketones to the corresponding enantioenriched alcohols with excellent conversion and moderate to good enantioselectivities (46-95% ee).

The development of comparing benign and widely applicable ATH reactions also launched interest in immobilization and recycling strategies of the notoriously expensive Ru(II) catalyst and chiral ligand. In 2004 Li *et al.* were the first to report a PEG-immobilized ligand for ATH.[180] A simple extraction of the formed enantioenriched alcohol with ether allowed separation of the catalyst that could be used in 14 further consecutive runs with hardly any loss in performance.

III 2.2.2 Synthesis of Novel Amino Alcohol Derived Chiral Ionic Liquids

Inspired by the outstanding progress on Ruthenium-catalyzed asymmetric transfer hydrogenation in the past years, a novel approach featuring hydrophilic chiral ionic liquids was explored. The modular design of chiral ionic liquids with variable anions is a clear advantage, as chiral ligands with adaptable solubility can be designed for the desired reaction conditions in aqueous asymmetric transfer hydrogenations using ammonium formiate as hydrogen source.

As already shown in literature, chiral amino alcohols are favourable ligands for asymmetric transfer hydrogenations. In contrast to chiral diamines that are preferably used as ligands in this reaction, amino alcohols can often be directly obtained from the chiral pool and hence provide a cheap and attractive alternative for the often expensive chiral diamine ligands. Consequently, the concept of coordinating CILs with amino alcohol structure was further adapted and expanded to provide hydrophilic chiral ligands graphted on a cationic head group (Figure 85).

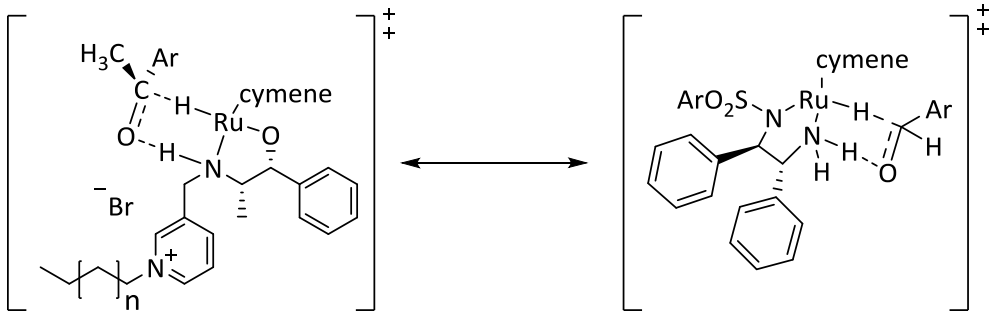


Figure 85: Novel chiral ionic liquid-supported complex *versus* conventional complex

In contrast to the application of amino alcohol-derived chiral ionic liquids in diethylzinc alkylation, the application in asymmetric transfer hydrogenations requires a secondary amine functionality to form a six-membered transition state with the carbonyl substrate. The synthetic protocol was therefore adapted to prepare a small set of chiral ionic liquids with secondary amino alcohol sub-structure.

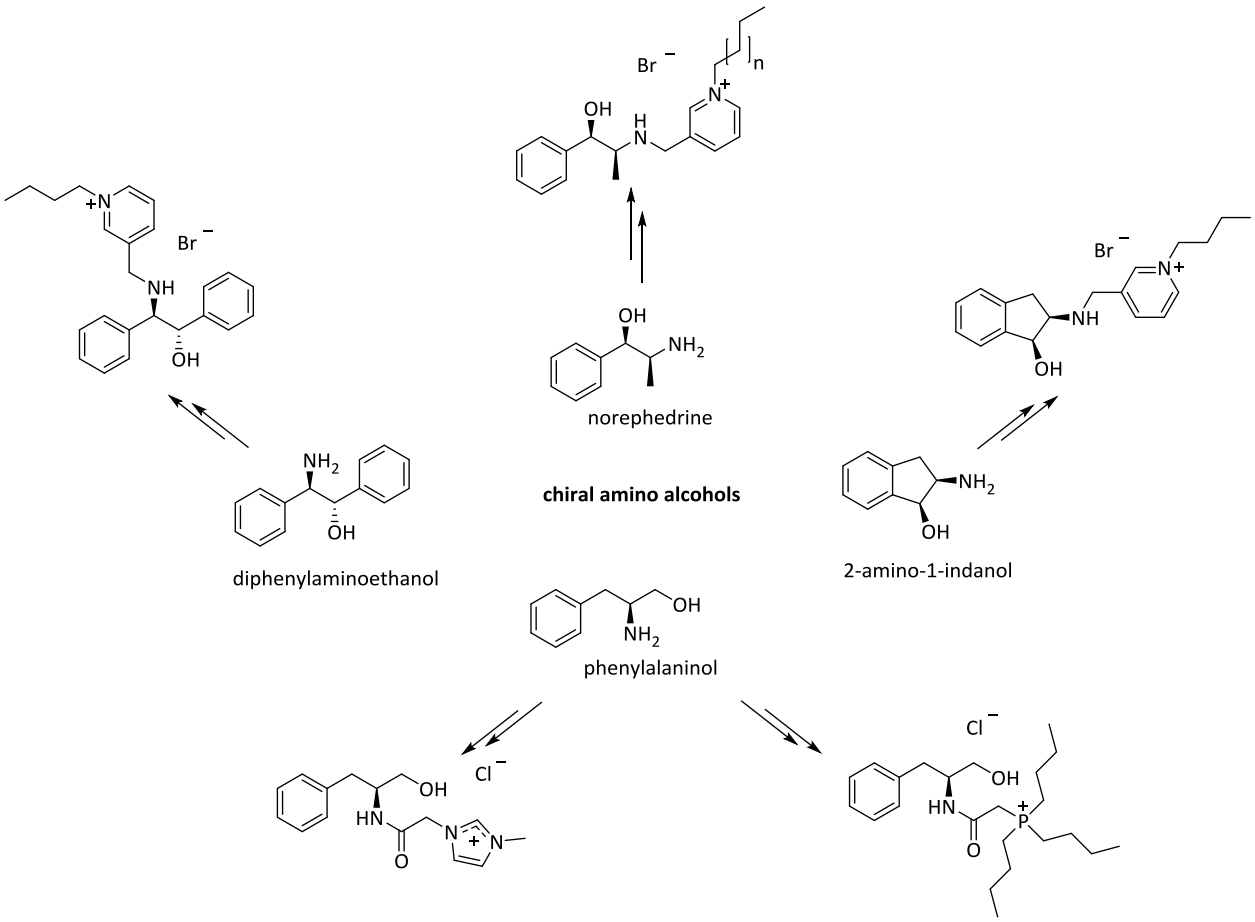


Figure 86: Synthesis of novel chiral ionic liquids for asymmtric transfer hydrogenation

Starting from commercial available chiral amino alcohols two types of coordinating chiral ionic liquids with different functionalities were explored. In contrast to ionic liquids **88**, **89**, **90**, **91** and **94**, phenylalaninol-derived systems differ and provide an electron-withdrawing amide-structure as linker to the cationic head group. This might be useful in asymmetric transfer hydrogenations, as an electron-withdrawing toslylate substituent has been identified as crucial feature in the common diamine ligand systems (Figure 86).

As previously established, primary amino alcohols norephedrine, diphenylaminoethanol and 2-amino-1-indanol were reacted with pyridine-2-carboxaldehyde in presence of activated molecular sieve and subsequently reduced with sodium borohydride to obtain the CIL precursors. The chiral *N*,*N*,*O*-tridentate ligands were further converted to the IL *via* quarternization with *n*-butyl bromide at

50 °C under solvent-free conditions. The obtained halide ionic liquids are highly hydrophilic and provide water solubility of the active ruthenium complex. Furthermore, in case of norephedrine-derived CILs different alkyl chain lengths were installed at the pyridinium moiety to investigate the influence of the self-assembly of the catalyst complex in water (Figure 87).

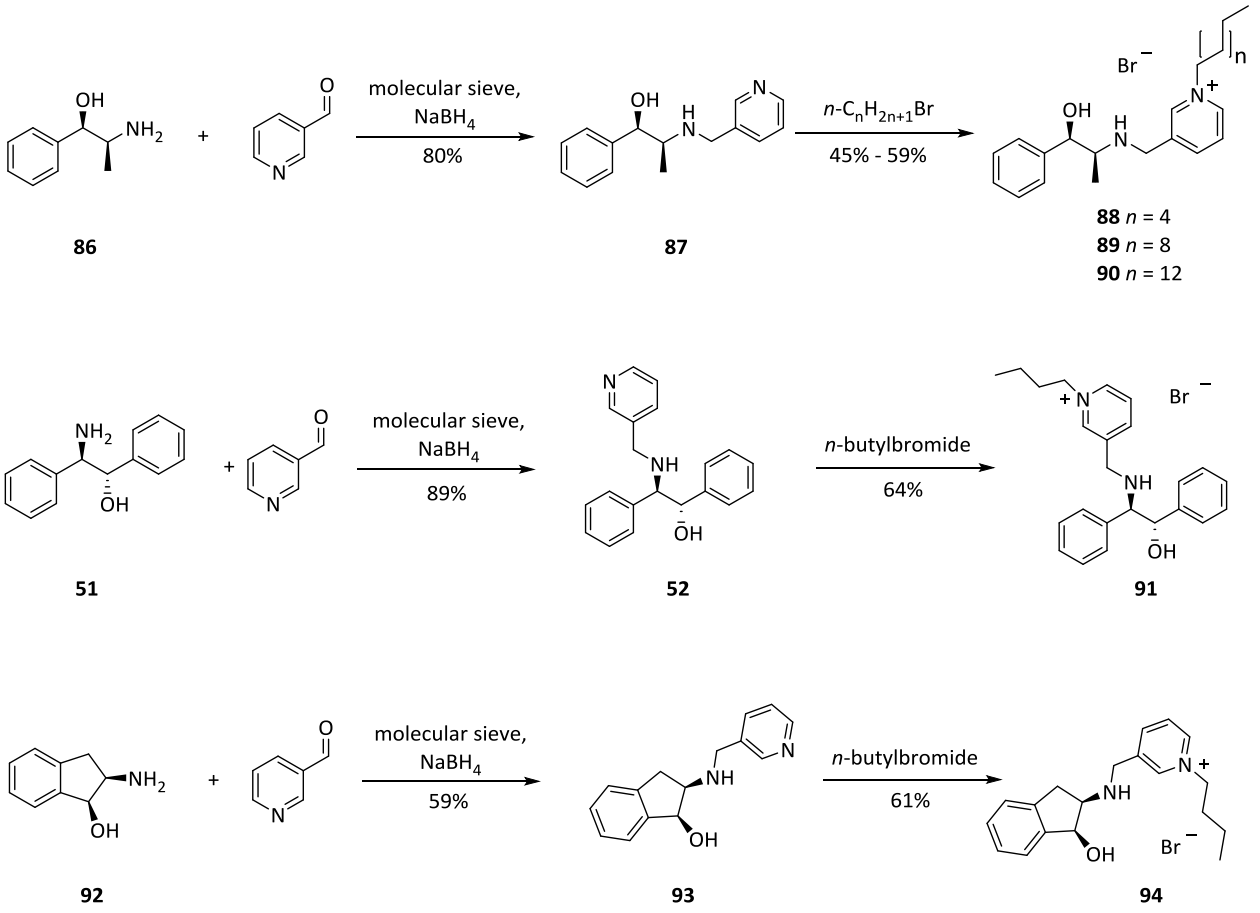


Figure 87: Synthesis of chiral ionic liquids for asymmtric transfer hydrogenation

In contrast to the alkylation of tertiary *N*,*N*,*O*-ligands such as the ephedrine-derivative **74**, the alkylation of secondary amino alcohols **87** with *n*-butyl bromide did not occur selectively on pyridine. Quaternization with 1.1 eq. *n*-butyl bromide at 50 °C gave a mixture of the mono- and dialkylated derivative; however, the pyridinium cation was still formed preferentially and a ratio of approximatively 2:1=mono:dialkylated species was observed, as calculated by ^{1}H-NMR. Even when lowering the amount of *n*-butylbromide to 1 eq. and the reaction temperature to 40 °C double alkylation was observed. The mixture of mono- and dialkylated species could be eventually separated *via* preparative HPLC and isolated yields of the desired final chiral ionic liquid are still in an acceptable range of 45-64%. Preparative HPLC was performed under reversed phase conditions using methanol and water as mobile phase on a C18 column.

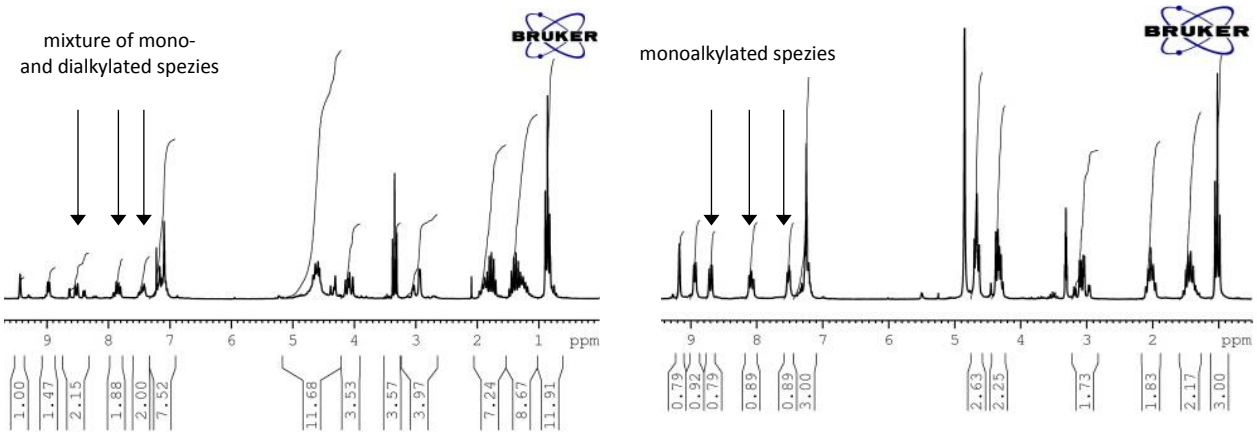


Figure 88: ^{1}H-NMR spectra after alkylation as mixture of mono- and dialkylated substrate 94 (left) and after purification *via* preparative HPLC (right)

Since ionic liquids can hardly be purified by conventional column chromatography or distillation due to their salt structure, their purification is often a very tedious work. This approach *via* reversed phase chromatography is highly useful when dealing with small amounts of functionalized ionic liquids, and the products could be obtained in very high purity.

In parallel, the second type of amide-linked chiral ionic liquids was obtained from selective reaction of L-phenylalaninol with chloroacetyl chloride and successive alkylation with *N*-methylimidazole or tributylphosphine as previously described.

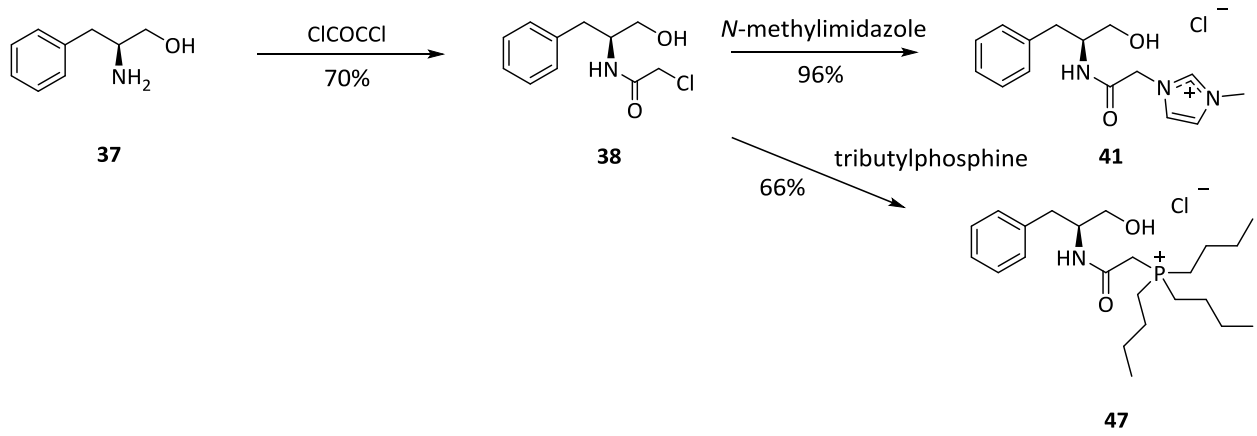


Figure 89: Synthesis of L-phenylalaninol-derived chiral ionic liquids for asymmtric transfer hydrogenation

III 2.2.3 Application of Chiral Ionic Liquids in Asymmetric Transfer Hydrogenation

In order to evaluate these novel hydrophilic CILs in asymmetric transfer hydrogenation, the reduction of acetophenone catalyzed with 5 mol% [Ru(*p*-cymene)Cl_2]$_2$ was chosen as test system. Initially, ideal reaction conditions in respect to reaction temperature and concentration of acetophenone in water were investigated.

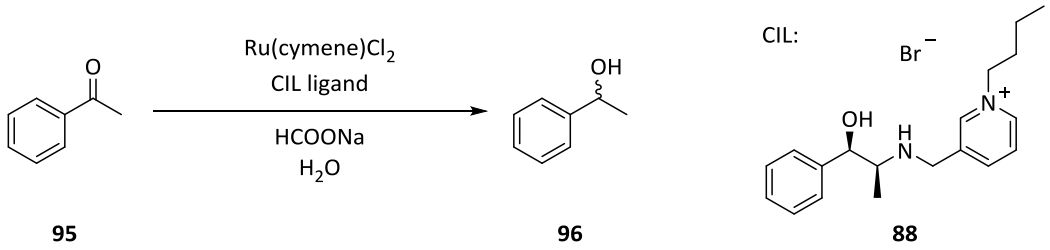


Figure 90: Benchmark reaction for asymmtric transferhydrogenation in the presence of chiral ionic liquids

Based on the air-sensitivity of the involved Ru(II) catalyst, all reactions were strictly performed under inert atmosphere *via* Schlenk techniques. Water was thoroughly degased using pump-freeze techniques prior to use, and flasks were charged with the sensitive [Ru(*p*-cymene)Cl_2]$_2$)catalyst in a glove box.

Table 18: Optimization of reaction conditions

entry[a]	T	conc. of 95 [M]	conv. [%][b]/ yield[c]	ee [%][d,e]
1[f]	40 °C	0.5	98	74 (*S*)
2	50 °C	2	97	73 (*S*)
3	50 °C	1	99 (99)	68 (*S*)
4	50 °C	0.5	98 (97)	71 (*S*)
5	50 °C	0.25	86	68 (*S*)
6	50 °C	0.1	51	46 (*S*)
7	50 °C	0.05	27	66 (*S*)
8	30 °C	0.5	85	75 (*S*)
9	40 °C	0.5	99 (97)	75 (*S*)
10	60 °C	0.5	99 (96)	63 (*S*)
11	70 °C	0.5	76	40 (*S*)

[a] Performed with 2 mmol acophenone, 10 mmol sodium formiate, 12 mol% CIL and 5 mol% Ru(II) catalyst for 48 hours. [c] Isolated yields are given in brackets. [b] Conversion determined by GC. [d] Determined by HPLC using a DAICEL Chiralcel IB column. [e] Absolute configuration determined *via* optical rotation and comparison with literature values. [f] Literature value for ephedrine ligand after 24 hours.[180]

Using CIL **88** the variation of concentration revealed that a concentration varying from 0.5 to 2 M was applicable, and complete conversion of acetophenone **95** was observed after 48 hours with good enantioselectivities of 68-75% ee. More dilute conditions resulted in a significant decrease in reaction rate and in a lower selectivity. A strong influence of the reaction temperature was observed in regard to enantioselectivity, as a higher reaction temperature gave lower enantioselectivity. Since the reaction was in most of the cases completed after 24 hours no further increase in temperature over 50 °C was necessary.

Eventually, a 0.5 M solution of acetophenone **95** in degassed water and 50 °C reaction temperature were identified as ideal conditions that were further applied to investigate the influence of different hydrophilic chiral ionic liquids.

Table 19: Variation of chiral ionic liquids for asymmetric transfer hydrogenation

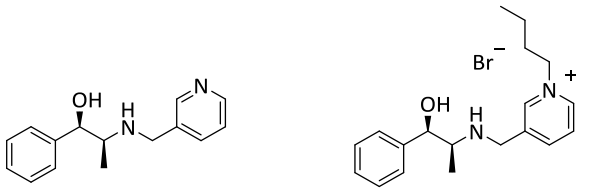
entry[a]	CIL	core structure/ ionic head group	conv. [%][b]/ yield[c]	ee [%][d,e]
1	**88**	ephedrine, *n*=4	94 (93)	71 (*S*)
2	**89**	ephedrine, *n*=8	98 (98)	72 (*S*)
3	**90**	ephedrine, *n*=12	99 (98)	71 (*S*)
4	**91**	aminodiphenylethanol	83 (80)	47 (*R*)
5	**94**	indanol	28	28 (*S*)
6	**41**	phenylalaninol/ imidazolium	<1[f]	n.d.
7	**47**	phenylalaninol/ phosphonium	<1[f]	n.d.

[a] Performed with 2 mmol acophenone, 10 mmol sodium formiate, 12 mol% CIL and 5 mol% Ru(II) catalyst for 24-48 hours. [b] Yield determined by GC. [c] Isolated yields are given in brackets. [d] Determined by HPLC using a DAICEL Chiralcel IB column. [e] Absolute configuration determined *via* optical rotation and comparison with literature values. [f] No conversion after 72 hours.

As can be seen from Table 19, best results were obtained with ephedrine-derived hydrophilic chiral ionic liquids. Aminodiphenylethanol-derived system **91** also performed quite well, whereas indanol-based chiral ionic liquid **94** gave lower conversion and selectivity. On the contrary, carboxamide-based CILs **41** and **47** gave no conversion after 48 hours, indicating that the carbonyl functionality is interfering with the formation of the active catalyst and ketone reduction. The influence of different chain lengths seems

to be limited, as ephedrine-derived CILs with different alkyl chain lenghts gave similar results. This is surprising, given the fact that dynamic light scattering (DLS) experiments as well as electron microscopy clearly indicated the presence of micelles for the *N*-dodecyclpyridinium bromide **90** that could not be observed for shorter alkyl chain lengths.

In a further experiment the reaction process for the ionic liquid-supported chiral Ru-catalysts (ligand **88**) was compared to the neutral ephedrine ligand **87**, the product prior to quaternizing alkylation. While no difference in enantioselectivity was observed for the two systems, the reaction proceeded significantly faster with the salt form of the ligand, thereby emphasizing the merit of a hydrophilic chiral ionic liquid. Good enantioselectivity was reached from the start of the reaction and stayed constant over the entire reaction time.



87 **88**

Figure 91: Ephedrine-derived ligand and ephedrine-based chiral ionic liquid

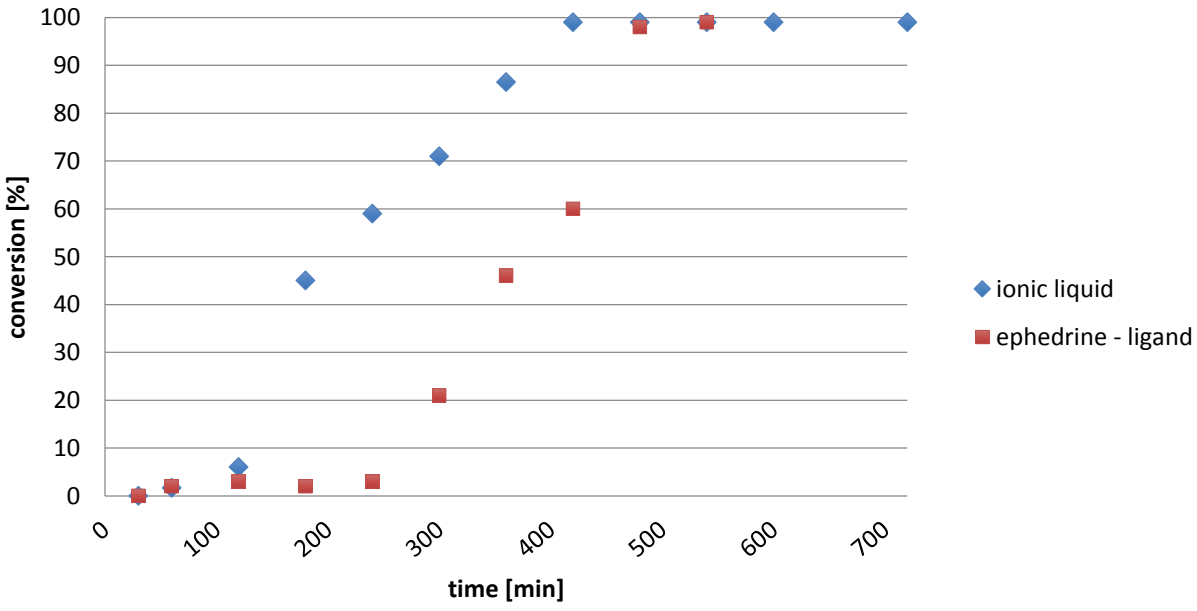
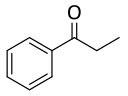
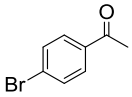
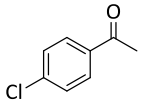
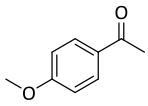
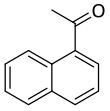


Figure 92: Reaction progress for ephedrine tridendate ligand and ephedrine-derived chiral ionic liquid

For further investigations of substrate tolerance, a set of prochiral ketones was chosen bearing both electron-withdrawing and electron-rich substituents. With the exception of propiophenone, moderate to good conversion and good selectivities of >60% ee were obtained using CIL **88**.

Table 20: Investigation of substrate scope

entry[a]	substrate	conv. [%][b]	ee [%][c,d]
1		29	65
2		54	73
3		98	67
4		64	60
5		76	85
6		86	71

[a] Performed with 2 mmol ketone, 10 mmol sodium formiate, 12 mol% ephedrine-derived CIL **88** and 5 mol% Ru(II)catalyst for 24-48 hours. [b] Conversion determined by GC. [c] Determined by HPLC using a DAICEL Chiralcel IB column. [d] Absolute configuration determined via optical rotation and comparison with literature values.

Based on the published reaction mechanism of ATH in water proposed by Wu *et al.* in 2007, following reaction mechanism seems likely for the ATH of benzaldehyde in water using hydrophilic CILs as chiral ligands and sodium formiate as hydrogen donor.[179]

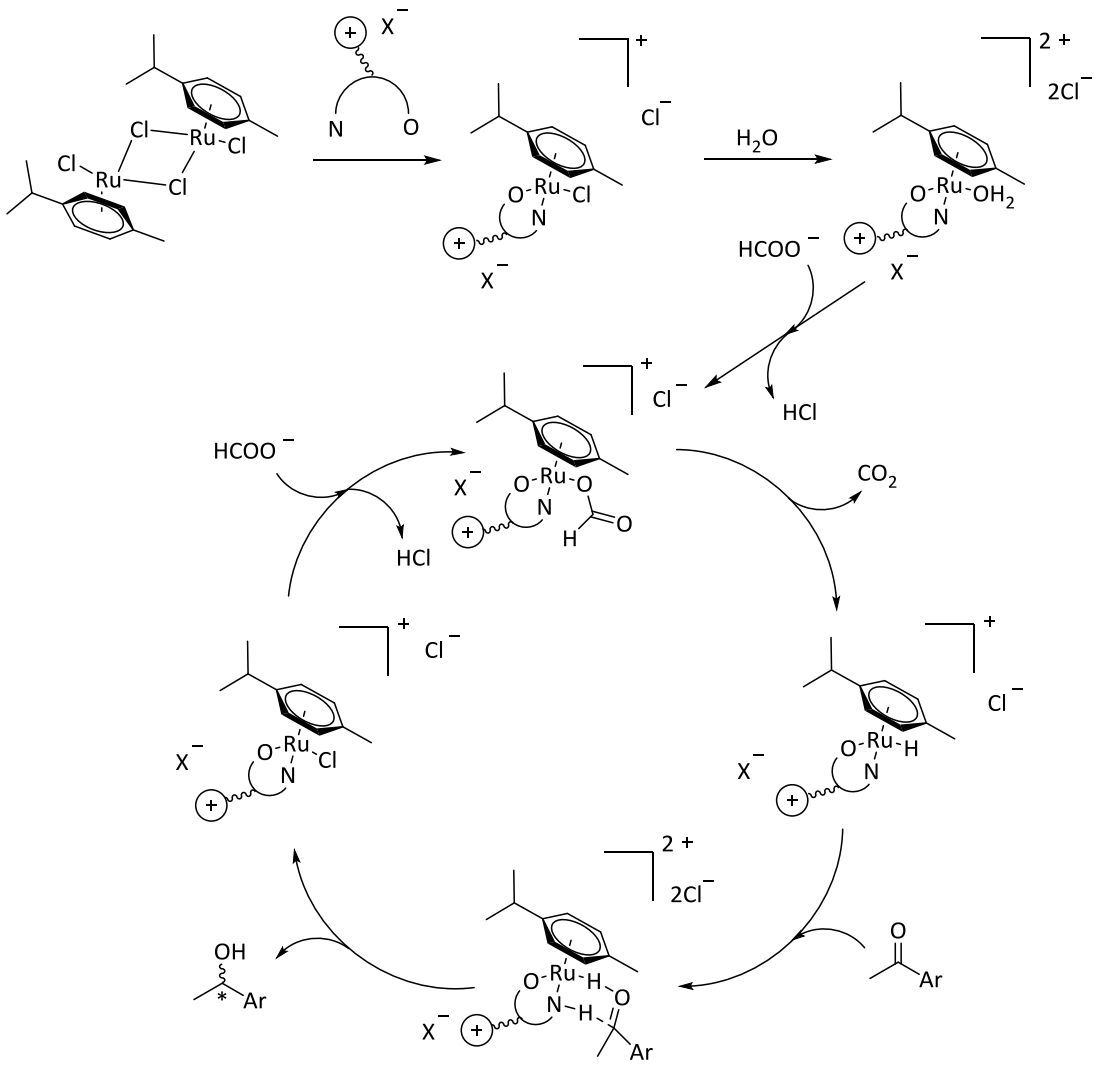


Figure 93: Proposed mechanism for asymmetric transfer hydrogenation in water with chiral ionic liquids and formic acid as hydrogen donor

After formation of the chiral ionic liquid-catalyst complex, formiate is coordinated to the Ru catalyst followed by release of carbon dioxide. The carbonyl substrate can insert into the active catalyst complex for further hydride transfer *via* a highly ordered six-membered transition state (Figure 93). After release of the enantioenriched alcohol a further molecule of formiate can coordinate to the active catalyst complex, regenerating the ionic liquid-bound catalyst which can again reduce benzaldehyde.

III 2.3 Bisoxazoline Ligands in Asymmetric Synthesis

Since their design and application in 1991 by Corey[181] and Evans,[182] bis(oxazolin) (Box) ligands have become one of the most important and useful chiral ligands in asymmetric catalysis. They can be used for various transition-metal-catalyzed reactions due to their ability to coordinate to metals like copper, palladium, cobalt and zinc and are synthesized from inexpensive amino alcohols. Consequently, Boxligands have a very broad application field and are suitable ligands for many asymmetric transformations, including Diels-Alder reactions,[181] cyclopropanations,[182-183] allylations,[184] Mukayama aldol reactions[185] or Michael additions.[186]

Consequently a variety of Box derivatives has been synthesized for divert applications. In order to improve their ability to coordinate with various metals, electron donating groups or functional groups that can further coordinate to the metal centre were installed (Figure 94).

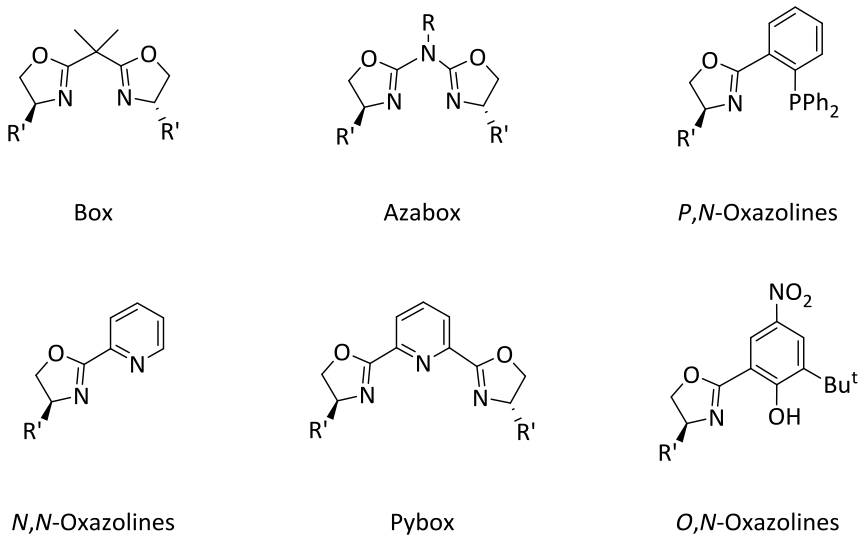


Figure 94: Examples for bisoxazoline ligands

The high chiral induction properties of Box ligands can be explained through the presence of a C_2-axis, a feature that is highly favourable for enantioselective transformations, as it reduces the number of possible transition states by the equivalence of the structures after rotation of 180° around the C_2-axis (Figure 95). Due to the high interest and immensely increasing number of publications dealing with Box ligands since 1991, the mechanism of stereocontrol has been investigated in detail and a considerable number of X-ray structures has been published.[187]

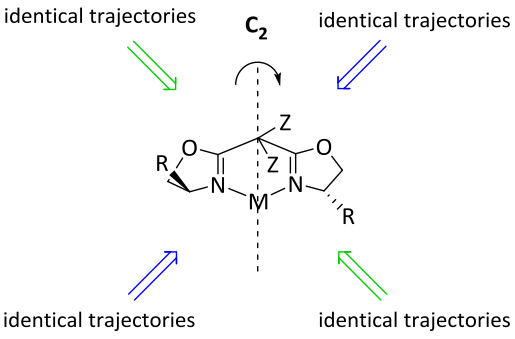


Figure 95: Demonstration of C_2-axis

The structure elucidation of a Pd(II)/Box ligand complex *via* X-ray[183, 188] has been a landmark in the investigations towards the function of Box ligands as asymmetric promoters (Figure 96).[183] In this complex, the Box ligand is strongly bent which results in a boat conformation of the six-membered palladacycle to minimize steric interaction.

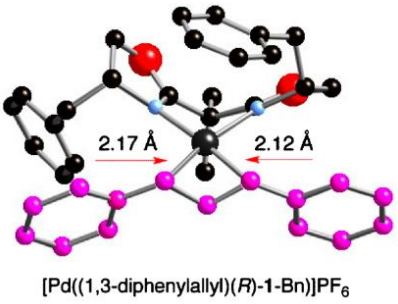


Figure 96: X-ray structure of Pd(II)-Box complex with diphenylallyl ligand

When used as catalyst in allylic substitution reactions, the extraordinary enantioselective performance of this complex can be explained by the square-planar geometry of the palladium (Figure 97). This leads to a larger Pd-carbon bond length to reduce steric strain and results in the preferential attack of the weaker bond (Figure 98).

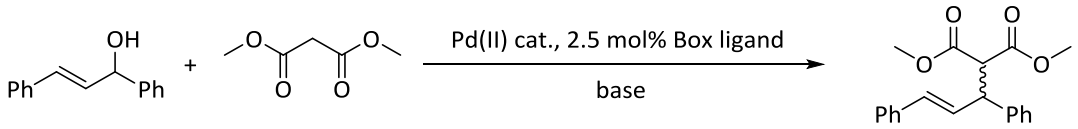


Figure 97: Example of allylic substitution reaction using Box ligands

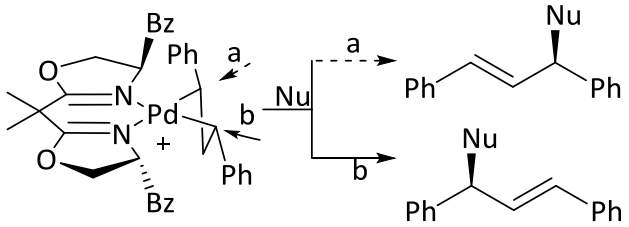


Figure 98: Favored attack in Box/Ru(II) complex

However the use of these high performance asymmetric ligands suffers from one major drawback: the high substrate-to-catalyst ratio, which is between 1-10 mol%. Although the starting material, an amino alcohol derived from naturally available amino acids is convenient, the ligands themselves are synthesized in most of the cases over a minimum of 4 reaction steps and have high molecular weights, thus their use in industrial applications is limited.[189] Therefore many attempts to recycle Box ligands have been made since 1997, based on both homogenous and heterogeneous approaches as can be seen from Figure 99.

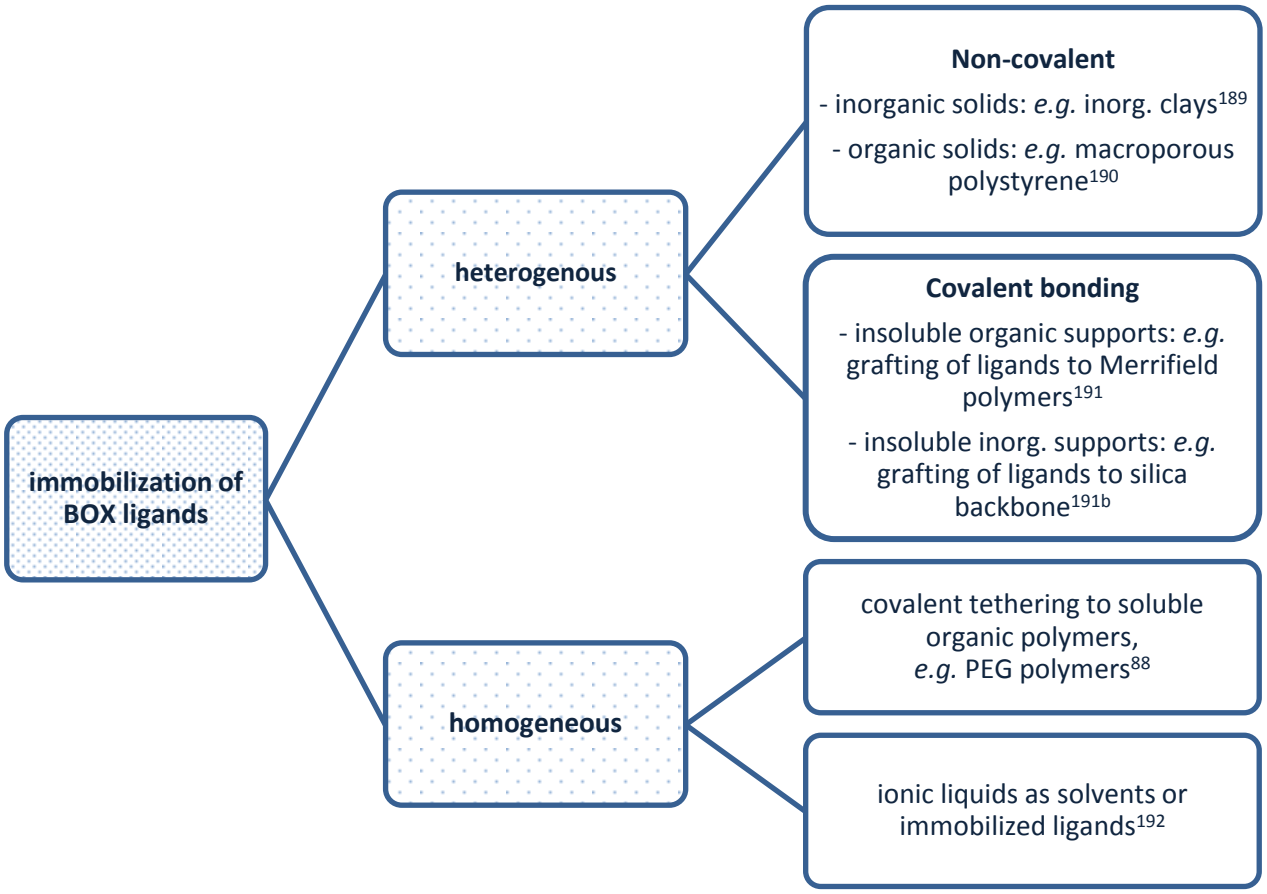


Figure 99: Immobilzation strategies for bisoxazolin ligands

Heterogeneous conditions often have been carried out using polymer-immobilization or grafting of the ligand to a silica backbone. These approaches are favourable due to the easy separation of the chiral ligand from the reaction mixtures and the simple handling.[194] Advantages of homogenous immobilization strategies are the more diverse potential applications and in many cases, increased reaction rates in comparison to heterogeneous conditions.

The use of achiral ionic liquids in immobilization strategies has already shown to be an advantageous approach for the recycling of chiral Box ligand when an IL was used as reaction media by Fraile *et al.*, and lead to an improvement of the recycling protocol since no chiral ligand leached to the product during the extraction step.[195] Also the immobilization of the chiral Box ligand by grafting it to an ionic liquid moiety was shown by Doherty *et al.*.[80] The authors used Box-derived CILs for asymmetric Diels-Alder reaction and were not only able to reuse the immobilized ligand in 10 consecutive runs with no loss in conversion and enantioselectivity, but could also show that reaction rates could be increased.

III 2.3.1 Synthesis of Aza-bisoxazoline – Chiral Ionic Liquids

Taking all these aspects into consideration, the concept of grafting an aza-bisoxazolidine (azabox) ligand to an ionic liquid moiety was further investigated to promote allylic substitution reactions using this immobilized ligand. The simple change between homogenous and heterogeneous conditions as well as the tunable physical properties *via* the choice of counter ion clearly are attractive features with the ionic forms.

Furthermore, different cationic head groups should be investigated as the ionic head group could interfere with the catalyst complex and exhibit the following interactions:[196]

- A dynamic steric effect by shielding one side of the complex and thus enhance enantioselectivity
- A ligating effect and participating *via* π-interaction of the aromatic head group
- A directing effect by interaction with the substrate

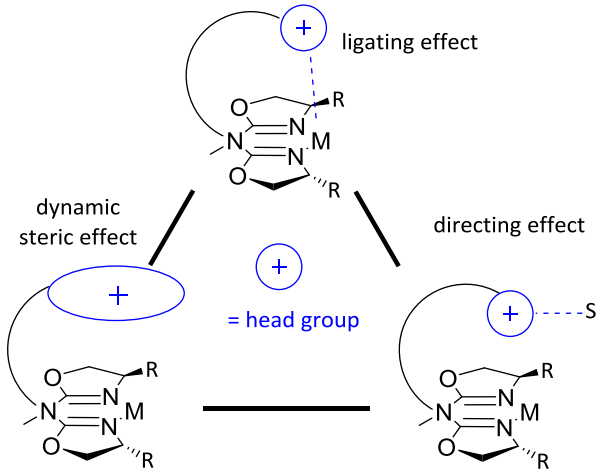


Figure 100: Possible interactions of cationic head group with catalyst complex

The Azabox-precursor for chiral ionic liquids were synthesized according to literature known procedures[193] starting from commercially available L-valine, followed by reduction and cyclization using *in situ* generated cyanogen bromide **97** and condensation of two substituted oxazolidinones on a Dean and Stark apparatus to yield the azabox ligand **98**. In a first strategy, the obtained azabox ligand should be directly quaternized at the central nitrogen unit giving **99**. The secondary amine was therefore first deprotonated using *n*-BuLi at -78 °C, followed by reaction with an excess of reactive methyl iodide and anion exchange with lithium bis(trifluoromethane)sulfonimide (Figure 101). Unfortunately CIL **99** turned out to be unstable and prone to decompositions after storage of the CIL at room temperature according to ^{1}H-NMR experiments. Consequently the CIL was not applied for further experiments and investigations towards enantioselectivity in asymmetric transformations.

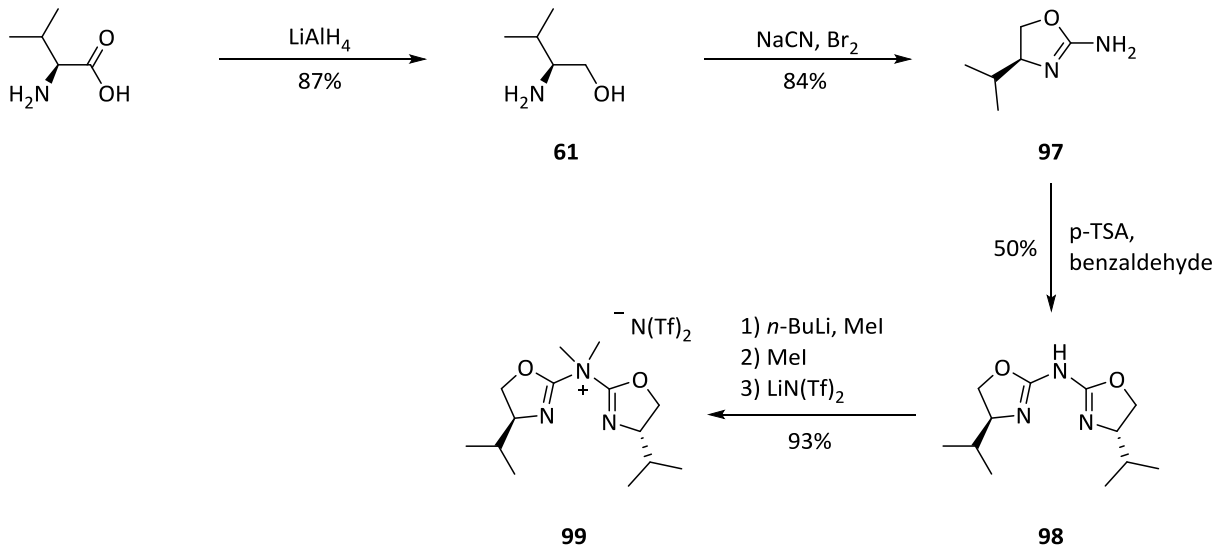


Figure 101: Synthesis of azabox-derived chiral ionic liquid

The initial plan was therefore adapted and an alkylation step was performed first with several dibromoalkanes of different chain length as alkylating unit. This allowed introducing imidazolium- or ammonium-structures as ionic liquid core without direct alkylation of the central nitrogen of the azabox system (Figure 102).

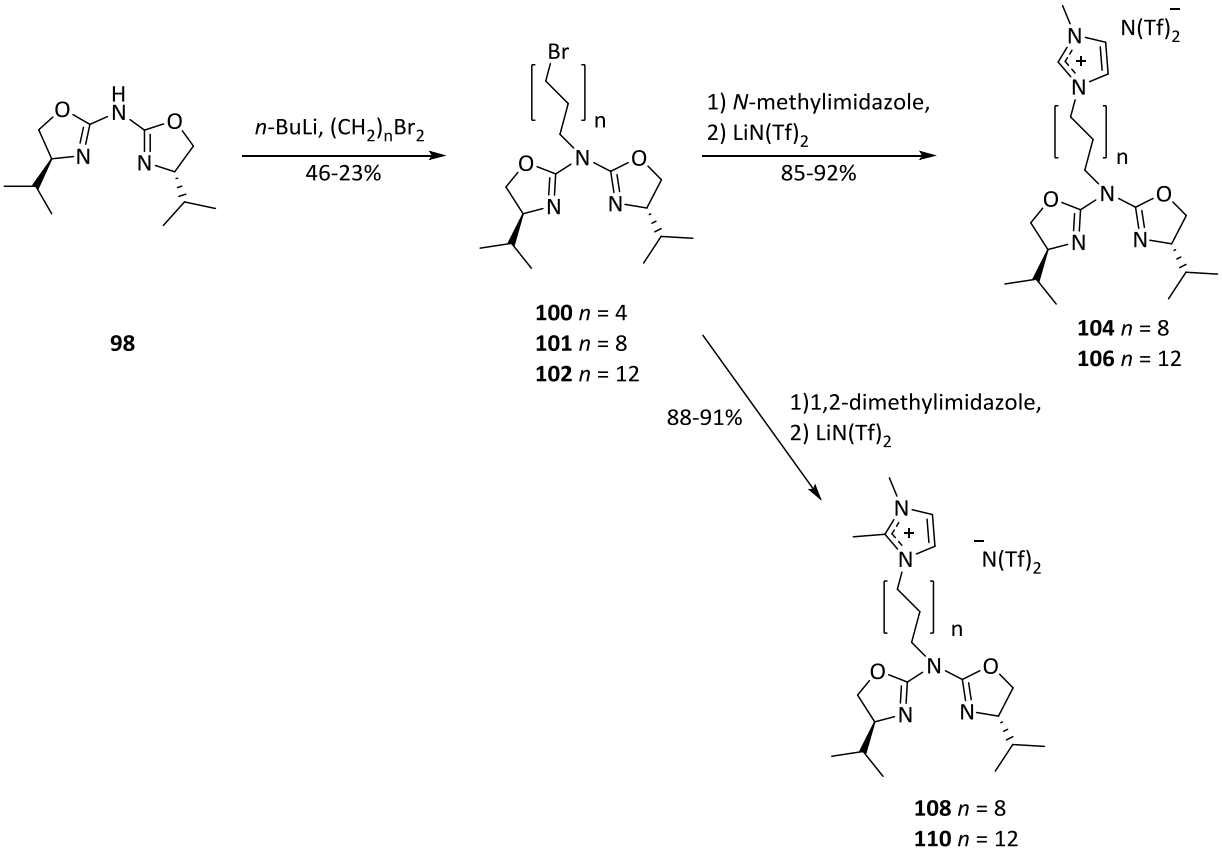
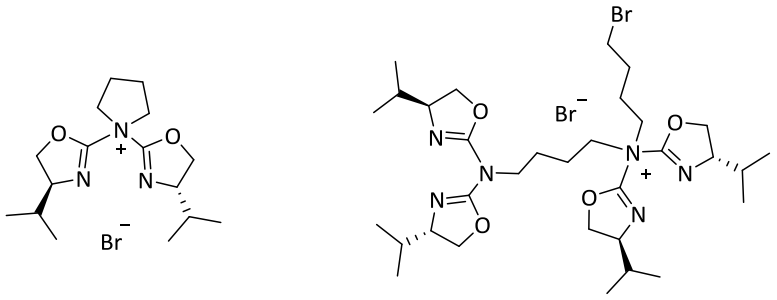


Figure 102: Synthesis of azabox-derived chiral ionic liquid

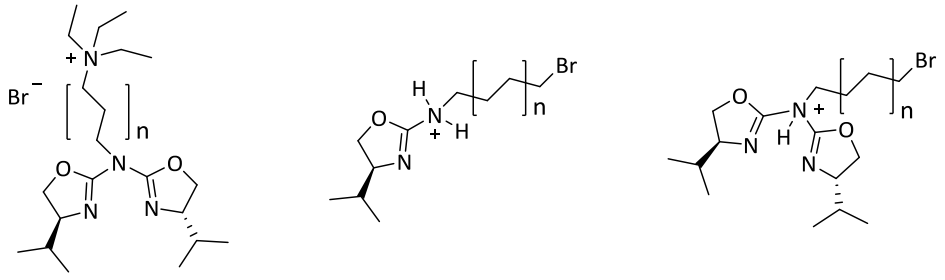
As this strategy required selective monoalkylation with the corresponding dibromoalkanes, a solution containing deprotonated azabox ligand **98** (*n*-BuLi at -78 °C) was slowly added dropwise *via* a transfer cannula to a solution of 8 eq. of dibromoalkane in anhydrous THF at 0 °C under argon atmosphere. The solution of dibromoalkane was highly diluted and deprotonated azabox ligand **98** was slowly added with a drop rate of approx. 1 drop/s to avoid double substitution of the dibromoalkane. Despite the cautious reaction conditions and investigations towards optimal reaction setting, several byproducts for the synthesis of the alkylated species **100-102** were observed and identified by TLC-MS analysis. In case of butyl chain containing precursor **100**, the product had a great tendency to self-alkylate under the reaction condition and byproducts **I** and **II** were found (Figure 103). This reaction could not be suppressed neither by lowering the reaction temperature nor by solvent optimization and the synthesis of the *n*-butyl bromide-derivatives was no longer investigated.



I **II**

Figure 103: Byproduct detected by TLC-MS during the synthesis of 98

Octane- and dodecyl-bromides **101** and **102** were less prone to byproduct formation. Still, the obtained precursors had a tendency to either decompose or react under the conditions used to purify the product by chromatography, and various byproducts **III**-**V** were identified by TLC-MS (Figure 104): For example the reaction with triethylamine used for chromatographic purification gave byproduct **III**. The purification protocol was therefore adapted and chromatographic purification of compound **101** and **102** was done by extraction with hydrochloric acid. This allowed isolating intermediates **101** and **102** as hydrochlorides that were used for the next step without storage times. After consecutive alkylation with 1-methylimidazole and 1,2-dimethylimidazole the hydrophilic bromide CILs could be transformed in hydrophobic CILs *via* ion exchange.

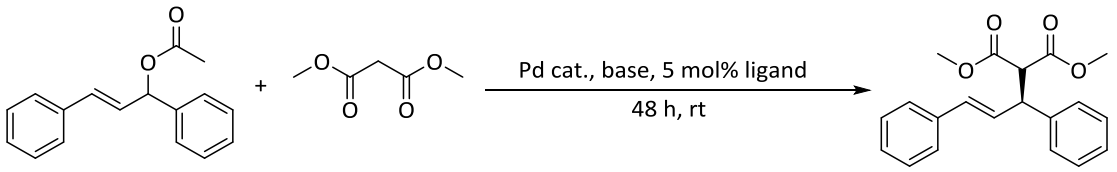


III **IV** **V**

Figure 104: Byproduct detected by TLC-MS during the synthesis of 99 and 100

III 2.3.2 Application in Asymmetric Tsuji-Trost Reaction

To explore the potential of these chiral ionic liquids in asymmetric synthesis, we investigated their application as supported ligands in asymmetric Trost-Tsuji coupling reaction. This palladium-catalyzed nucleophilic substitution of allylic compounds can be performed with azabox ligands as described by Fritschi *et al.*[197] with excellent enantioselectivities of up to 95% ee.



111 **112** **113**

Figure 105: Chiral ionic liquids in asymmetric Tsuji-Trost reaction

Initially, different reaction conditions and Pd(II) sources were screened. Optimum conditions were present at a reaction temperature of 40 °C in dichloromethane with 5 mol% chiral ligand, 2 equivalents *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate (KOAc). Despite attempts to optimize the reaction for the CIL, the immobilized chiral ligand did not perform very well in comparison to literature, and conversion rates stayed rather low even after 1 week of reaction time, especially for dodecyl- derivatives.

Additionally, enantioselectivities were very low with all CILs, and a maximum of 30% ee was observed in case of the imidazolium-tagged azabox ligand **102**.

Table 21: CILs in asymmetric Tsuji-Trost reaction

CIL	head group	catalyst	yield [%][a, b]	ee [%][c]
104	1-methylimidazole	$Pd_2(allyl)_2Cl_2$	15	30
		$Pd_2(dba)_3\,CH_3Cl$	62	<5
108	1,2-dimethylimidazole	$Pd_2(allyl)_2Cl_2$	58	12
		$Pd_2(dba)_3\,CH_3Cl$	63	5
101	bromide precursor	$Pd_2(allyl)_2Cl_2$	70	96
		$Pd_2(dba)_3\,CH_3Cl$	78	95

[a] Performed with 0.4 mmol 1.3-diphenylacetate, 1.2 mmol dimethylmalonate, 5 mol% CIL and 2 mol% Pd catalyst for 5 days. [b] Yield determined by GC. [c] Determined by HPLC using a DAICEL Chiralcel AS-H column. [d] Absolute configuration determined via optical rotation and comparison with literature values.[197]

That the poor performance of the ionic liquid-tagged ligands is due to the ionic liquid part becomes obvious when comparing their performance with the non-ionic precursor **101**. When this azabox-derivative was used as ligand, excellent enantioselectivities of 96% *ee* and rather high conversion rates were observed after 1 hour reaction time only.

The failure of chiral ionic liquids might be traced back to stability problems of these systems. As already observed during synthesis, the obtained salts were prone to side reactions and decompositions, and numerous byproducts were obtained. Although chiral ionic liquids **104**-**108** could be isolated in pure form, TGA data showed very poor thermal stability and decomposition of the product was observed after storage at room temperature in ^{1}H-NMR. Based on these investigations as well as on the tedious and rather low yielding synthesis no further attempts were made, as this type of chiral IL was clearly not able to promote the desired reaction.

III 3 Ionic Liquids in Gas Chromatography

Besides many advantageous properties of ILs, their wide liquid ranges as well as their comparing high temperature stability are among the most valuable characteristics. Furthermore they can solubilize complex polar molecules like cyclodextrins and have a high wetting ability.

These properties make them ideally suited as coating medium for chromatographic applications. The use of IL as stationary phases, where temperature stability is one of the most important features, has already been repeatedly reported in literature. Starting from 1999 the group around Armstrong and others presented IL-coated stationary phases for GC that meanwhile are commercially available and provided by Supelco®.[122, 198] These IL-based columns express a unique retention behavior in comparison to conventional stationary phases: For non-polar analytes they act as non-polar stationary phase while at the same time they express very strong retention behavior for polar substrates. This dual nature of the ILs, e.g. the imidazolium-based IL [C_4mim][PF_6] opens the possibility for novel stationary phases and allows new separation approaches.

The application of CILs is particularly interesting in this field, since commercially available chiral stationary phases for GC suffer from temperature instability as their main restriction. To date, successful examples for the use of CILs in coated stationary phases are limited.[125] Based on the previous work on chiral recognition properties as well as on their use in asymmetric synthesis, the application range of the chiral ionic liquids described so far should be extended towards analytical separations. Selected candidates should be applied to the preparation of chiral IL coated stationary phases with the overall goal of developing novel and temperature stable chiral GC columns with novel separation behavior for racemic substrates.

III 3.1 Coating Process

Prior to the application of CILs for the preparation of stationary phases, the coating process was adapted and optimized using literature known achiral IL for comparison reasons. Based on the work of Armstrong *et al.* the coating of commercially available fused capillary columns with ionic liquids was divided into five steps which are going to be discussed in detail in this chapter (Figure 106).[122]

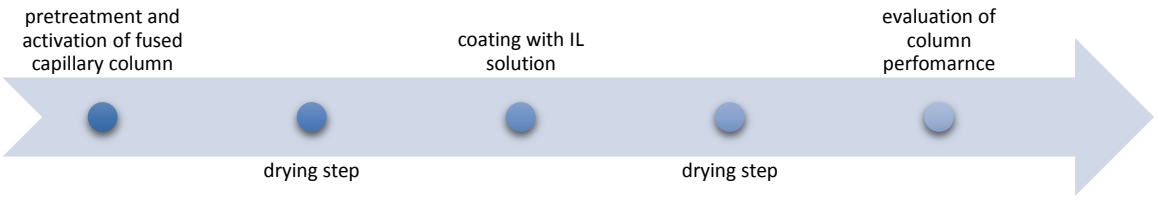


Figure 106: Coating process for stationary phases in gas chromatography

III 3.1.1 Pretreatment and Activation of Fused Capillary Columns

The pretreatment of uncoated capillary columns is essential for a consistent coating since the activation dramatically increases the inner surface of the capillary column. This makes the coating with the sometimes rather viscous IL easier and more effective. As can be seen from pictures taken on an electron microscope, the inner surface of the capillary column, which is coated with an polyimide outer coating to ensure stability, is rather smooth (Figure 108) and not suitable for a static coating. Consequently, no deposition of ionic liquid was observed without pretreatment.

There are several possibilies to activate the surface of the column, *e.g*. etching with hydrofluoric acid or deposition of inorganic salts such as sodium chloride[199] or barium carbonate.[200] Due to safety reasons etching was not performed in our lab and the deposition of inorganic salts was investigated and monitored *via* electron microscopy. The use of sodium chloride was identified as best method and the deposition of small crystalls could be observed.

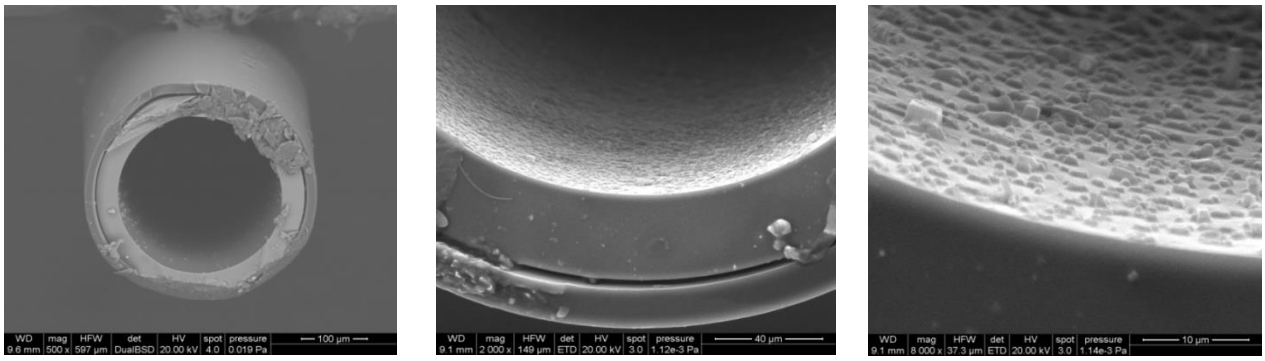


Figure 108: Electron microscopy pictures for untreated capillary columns (left and middle) and activated column (right)

Figure 107: Apparatus for coating of capillary columns

The activation was performed according to the procedure of Dhanesar *et al.*[199], using a colloidal sodium chloride solution. A saturated sodium chloride solution in methanol was added dropwise to anhydrous methylenchloride to give a fine suspension, which was stable for one day after 10 minutes of sonication. The suspension was then applied to the column as shown in Figure 107. The sodium chloride suspension was placed in a storage vessel and pumped through the column by application of nitrogen pressure. Particular attention was paid to stop pressure in time, so that pure nitrogen flushing through the column could not remove the suspension. The filled column was tightly sealed with a septum and stored at room temperature for 24 hours before vacuum was applied from the injector side to remove the solvent overnight at 5 mbar.

The removal of spare solvent was alternatively performed by further flushing and drying with nitrogen. However, this gave unsatisfying results compared to the vacuum technique that was applied in all further experiments.

III 3.1.2 Coating with ionic liquid

After successful sodium chloride deposition, the pretreated column was further flushed with an ionic liquid solution. Based on its low boiling point and good dissolution properties for ionic liquids, dichloromethane was chosen as solvent and different concentrations of IL in dichloromethane were investigated covering a range from 0.1 wt% - 4 wt%. The best results were obtained with a concentration of 4 wt% IL in methylene chloride. For IL coating, a similar set-up as for the pretreatment was used (Figure 107). Again, care had to be taken to avoid flushing the capillary column with pure nitrogen. After coating the column with IL solution, the capillary column was stored at room temperature for 24 hours, followed by a predrying step at a vacuum pump overnight (5 mbar).

Conditioning of the column was performed by attaching the column at the injector side in the GC oven with an open end while the regulation of the helium flow was fixed at 1.5 ml/min. The column was first heated at 40 °C for 60 min, then heated with a ramp of 0.5 °C/min to 150 °C which was held for 360 min. Afterwards the columns was installed in the GC by attaching the end to the detector side, followed by several blank runs until consistency of the baseline was achieved.

Although [C_4mim][Cl] is reported in literature as suitable coating IL, it was not possible to achieve reproducible results using this IL, which might be caused by the hydrophilicity of the IL (column A) (Figure 109). Therefore the counter ion was changed to the hydrophobic bis(trifluoromethane)sulfonimide anion which improved reproducibility and gave significantly better results (column B). Based on the bis(trifluoromethane)sulfonimide anion, further retention studies were performed with imidazolium ILs with longer alkyl chains to gain more insight in the retention behavior (column C). Additionally, a hydroxyl-containing IL was applied to investigate the influence of functional groups that could also act as hydrogen bond donor (column D). Furthermore two additional columns were coated with phosphonium cation bearing ILs with different chain lengths (column E and F), since this class of ILs exhibits high temperature stabilities of up to 320 °C.

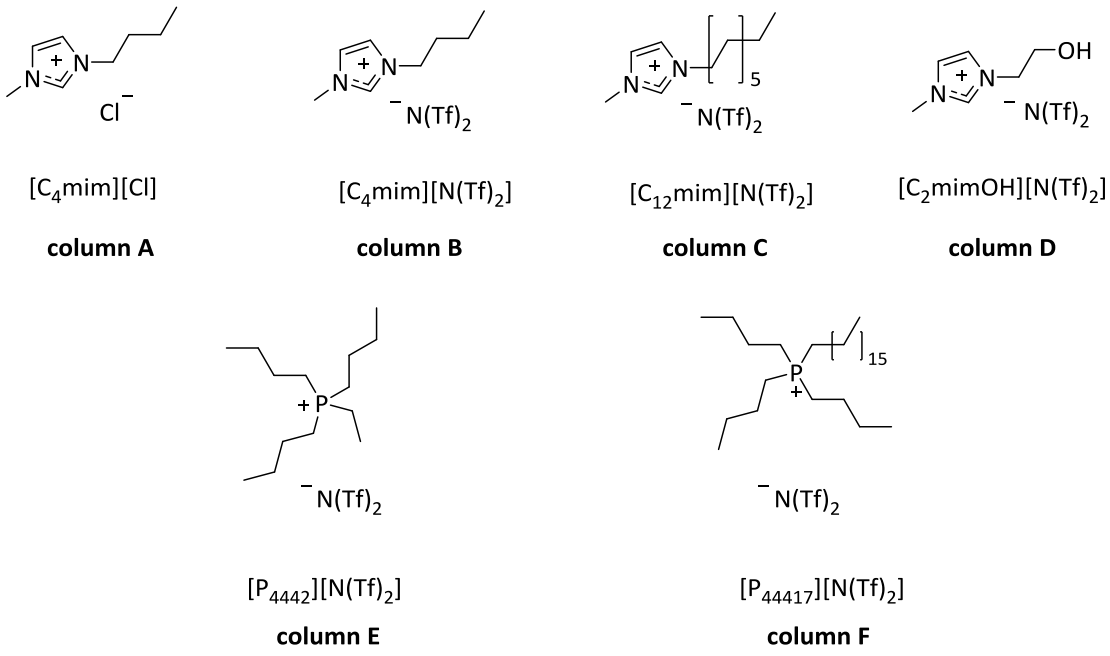


Figure 109: Ionic liquids used for coating of capillary columns

All ILs were synthesized according to literature procedures starting from commercially available 1-methylimidazole or trialkylphosphine using the corresponding alkylchloride or bromide under solvent-free conditions followed by anion exchange with lithium bis(trifluoromethane)sulfonimide.[3] Prior to application, the ILs were dried for 24-48 h at 50 °C under high vacuum and immediately used for the coating process.

III 3.1.3 Evaluation of column performance

After successful pretreatment and coating with various ionic liquids as described above, the obtained IL-coated capillary columns were evaluated according to literature using three parameters:[122]

- Plate number
- Kovats index
- Rohrschneider-McReynolds constant

The plate number was calculated using naphthalene as analyte and retention times at 100 °C according to following equation:

$$N = 5.54 \times \left(\frac{t_R}{b_{1/2}}\right)^2 \qquad \textbf{Equation 1}$$

t_R retention time for naphthalene

$b_{1/2}$ peak width at half height

Table 22: Plate number for IL used for coating of stationary phase

	column A (40 °C)	column B	column C	column D	column F	Lit.[122]
plate number /m	1228	1749	63	627	41	1700

As can been seen from Table 22, column B provided the best retention and the number of theoretical plates was even slightly higher than the one reported in literature for the same ionic liquid. These values were identical with 3 independently coated columns, indicating the good reproducibility of the coating method previously established. In contrast, only low plate numbers were obtained for all other IL-coated columns. However, since the plate number is calculated only for naphthalene, this low number could be either due to insufficient retention behaviour of the used IL but could be also traced back to bad affinity towards this compound. In case of column E it was not possible to elute naphthalene; hence the plate number could not be calculated. As column E showed hardly any significant retention for most of the analytes, it was not taken into consideration for further characterization.

For calculation of the Kovats indices, retention times for different linear alkanes were measured at constant temperature. This index allows comparing retention times of different analytes with each other and converts them in system-independent constants. Since the Kovats index is independent from film thickness, carrier gas velocity and column length it is often used to identify components by comparison with literature known values.[201] The Kovats index is calculated using equation 1 and is determined for a set of five analytes, including benzene, 1-butanol, 2-pentanone, 1-nitropropane and pyridine, therefore retention times of these analytes where identified.

$$I = 100 \times \left[n + (N - n) \frac{log(tr_{unknown}) - \log(tr_n)}{\log(tr_N) - \log(tr_n)} \right]$$ **Equation 2**

n C-number of the shortest *n*-alkane (octane)

N C-number of the longest *n*-alkane (hexadecane)

t_r corr. retention time

Table 23: Kovats indexes for IL used for coating of stationary phases

	column A (40 °C)	column B	column C	column D	column F	Lit.[122]	Squalan
benzene	782	1300				730	656
1-butanol	1256	1319	993	630	1068	1037	600
2-pentanone	925	1350	981	619	1100	742	629
1-nitropropane	1188	1548	1214	1012	1254	900	655
pyridine	1088	1491	1376	983	1229	912	700

As a third parameter, the Rohrschneider index is a major index for the evaluation of GC columns and an indication for the polarity of stationary phases. It is determined using the retention times of the five standard compounds mentioned before for the Kovats index, which are representatives for diverse functionalities and thus provide information about different interactions with the stationary phase (Table 24).

Table 24: Interaction types for analytes used in Rohrschneider index calculation[viii]

reference solute	Rohrschneider-McReynolds constant	type of interactions			typical for
		Dipole	π-interaction	H-bonding	
benzene	x'	-	donor	-	olefins, aromatic compounds
1-butanol	y'	✓	-	donor	alcohols, phenols, acids, amids,
2-pentanone	z'	✓	acceptor	-	aldehyds, ketones, esters, ethers
1-nitropropane	u'	✓	acceptor	-	nitro-,nitrilo compounds
pyridine	s'	✓	donor	-	amines, aromatics

The Rohrschneider-McReynolds constant is defined as the difference between the Kovats indices of the present stationary phase and an unpolar Squalan phase which can be found in literature.

$$\Delta I = I_{compound}^{polar} - I_{compound}^{Squalan} \qquad \textbf{Equation 3}$$

The Rohrschneider-McReynolds index is used for the evaluation of polarity of stationary phases and is the sum of all five constants, determined via the prior described equation.[201]

$$\sum(\Delta I) = x' + y' + z' + u' + s' \qquad \textbf{Equation 4}$$

[viii] http://www.univie.ac.at/rg_lindner/Analytische%20Chemie%20II%20Teil%20Laemmerhofer%20Unterlagen%20WS2009_2010.pdf, last accessed 1st August 2014.

A higher Rohrschneider-McReynolds index corresponds to a higher retention factor for the analyte and consequently to a higher polarity of the column. Two phases that differ in less than 200 units in Rohrschneider-McReynolds index are considered to have similar polarity.

Table 25: Components used for determination of Rohrschneider McReynolds constant and their interaction

	column A (40 °C)	column B	column C	column D	column F	Lit.[122]
benzene	126	644				74
1-butanol	656	719	393	30	468	437
2-pentanone	296	721	352	25	471	113
1-nitropropane	533	893	559	357	599	245
pyridine	388	791	676	283	529	212
Σ	1999	3768	1980	695	2067	1081

As apparent by Table 25, column B shows by far the highest polarity and reaches an almost three times higher value than the one described in literature based on $[C_2mim]Cl$. In case of benzene and 2-pentanone the affinity is particularly high, indicating that the bis(trifluoromethane)sulfonimide anion has a strong influence on the retention of aromatic and carbonyl compounds.

The rather low Rohrschneider-McReynolds constants of column D could also be explained by the low plate number of this column rather than its polarity. Column C and F have similar polarities as the literature IL; however, they also exhibit low plate numbers, thus the values are not fully comparable.

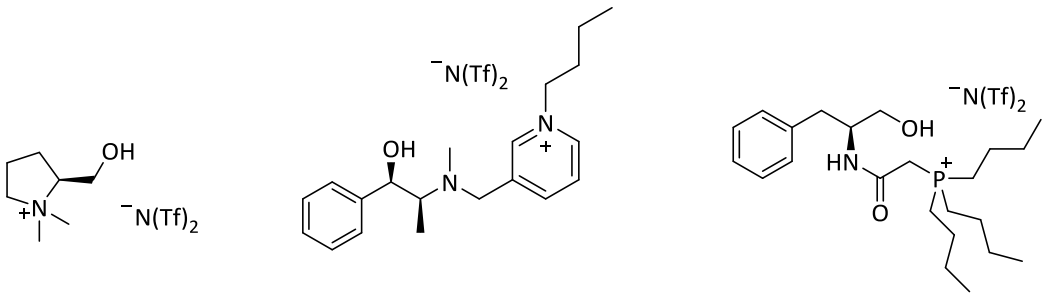
These initial coating experiments demonstrated that coating of capillary columns could be successfully performed and showed that the highest recognition strength was exhibited by imidazolium based $[C_4mim][NTf_2]$, which showed very high polarity and excellent number of theoretical plates. The high plate number is probably due to its low viscosity and thus good wettability.

IV Outlook

IV 1.1 Chiral Ionic Liquids as Stationary Phases in Gas Chromatography

Based on the successful preparation and evaluation of ionic liquid-coated GC columns, this strategy was expanded to chiral ionic liquids and preliminary experiments towards IL-coated stationary phases for the gas-chromatographic separation of racemates were made.

Three different chiral ionic liquids were selected for the consecutive preparation of chiral GC columns according to the previously optimized coating protocol (III 3.1).



column X column Y column Z

Figure 110: Chiral ionic liquids used for coating of capillary columns

The L-proline-based CIL **36** for column G was selected for column X because of its high temperature stability of 377 °C that was identified in thermogravimetrical (TGA) measurements. Furthermore, CILs **76** and **48** were selected for column Y and Z due to their high recognition strengths in the ^{19}F-NMR studies as previously described.

However, despite strictly following the previously optimized pretreatment and coating procedure, no successful coating could be achieved for column X as indicated by the retention behaviour of various analyts. No retention of naphthalene was observed, hence no calculation of plate number could be performed. This might be related to a higher viscosity or different wetting properties of this ionic liquid.

Further coating experiments in cooperation with Prof. J. Anderson with the aromatic chiral ionic liquids **76** and **48** were more successful and resulted in the preparation of two novel, chiral ionic liquid derived GC columns.[ix] Unfortunately, investigations towards the separation performance of column Y and Z for racemic analytes did not show any separation and no chiral resolution was obtained.

[ix] Performed in cooperation with Prof. Jared Anderson, University of Toledo, Ohio.

However, the evaluation of column performance revealed an unexpected behaviour for column Y when applied as secondary column in 2D-GC × GC. The CIL coated stationary phase was used for the separation of kerosene and fatty acid methyl esters (FAMEs): A rather unique resolution of aromatic compounds in the kerosene sample was observed (Figure 111), which might be due to the aromatic system of the CIL, and more investigations towards this behaviour will be performed in future.[x]

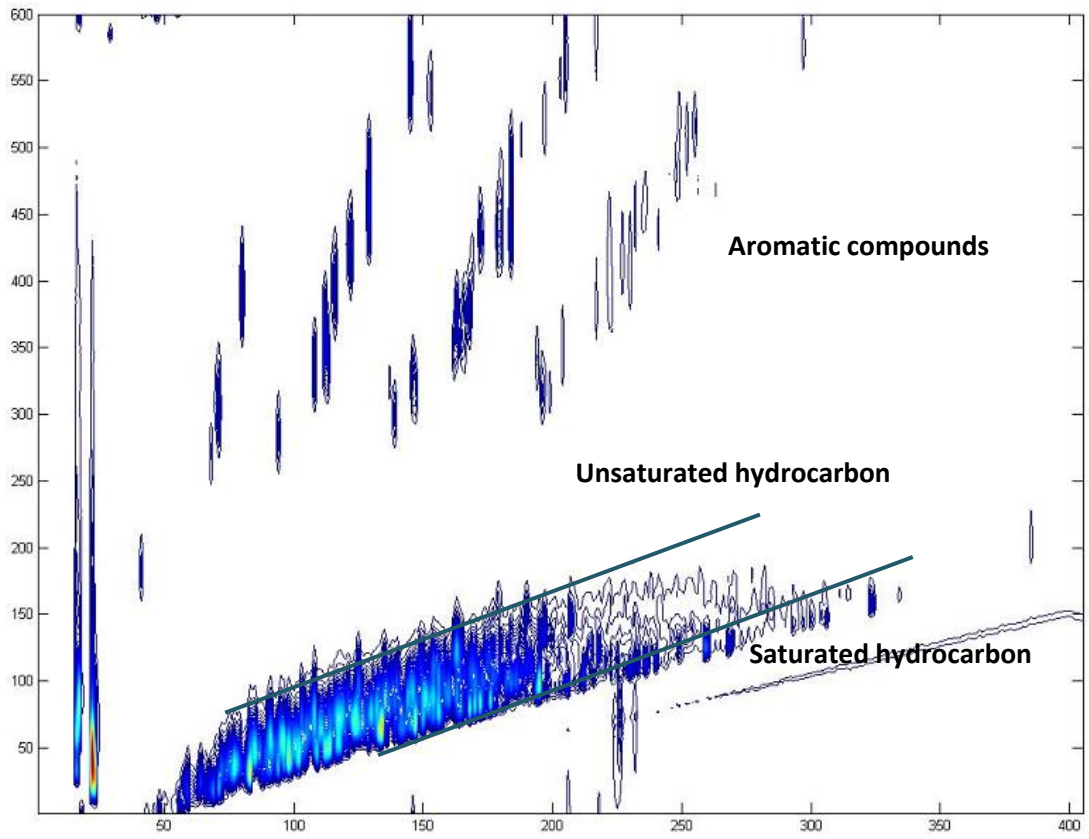


Figure 111: Resolution of kerosene sample using CIL coated column as 2nd column in 2D-GC x GC analysis

[x] The 2D-GC × GC experiments were performed using a 30 m × 250 µm, 0.25 µm Rtx-5 primary column and 1.2 m × 250 µm, 0.15 µm chiral IL-based column (plate number of 2300 plates/m), at an oven program from 40 °C to 120 °C at 2 °C min^{-1}, followed by a secondary ramp from 120 °C to 200 °C at 20 °C min^{-1}.

In a third experiment, the chiral phosphonium-based ionic liquid **48** that gave outstandingly strong chiral recognition behaviour with Mosher's acid salt as described in III 1 was investigated. Again, this ionic liquid could be successfully deposited after the pretreatment with sodium chloride and a high plate number of 2558 plates/m was found for column Z. A set of racemic analytes bearing various functionalities was selected as *e.g.* terpenes, alcohols, diols, amino alcohols, lactones and ketones, but unfortunately no chiral resolution could be observed so far.

Table 26: Retention times for racemic analytes on column Z

analyte (rac)	corr. retention times
fenchone	0.20
γ-butyrolatone	2.58
ibuprofen	-
2-pentanol	0.29
3-heptanol	0.98
3-octanol	1.64
phenylethanol	7.54
2,3-butandiol	3.19
1,3-cyclohexandiol	-
threitol	9.93
camphor	-
phenylethylamine	-

[a] No signal was observed after 30 minutes at 100 °C isothermal conditions.

IV 1.2 Chiral Ionic Liquids as Organocatalysts in Transfer Hydrogenation

Although asymmetric organocatalysis provides access to benign and highly selective reactions, this strategy suffers often from the necessity of very high catalyst amounts. The application of CILs could therefore be a good alternative as it opens the possibility of catalyst recycling.

One example for the high catalyst loading is the organocatalytic transfer hydrogenation of cyclic enones using Hantzsch esters as hydrogen source. This reaction has been shown to result in high enantioselectivities (86% ee) and conversions (93%); however, a large loading of using 20 mol% MacMillan catalysts as active organocatalyst in the presence of trichloroacetic acid was required.[202]

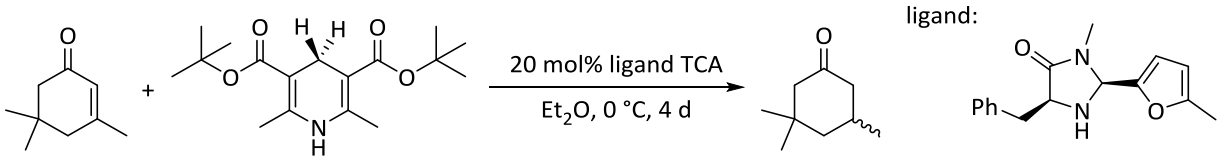


Figure 112: Transfer hydrogenation of a cyclic enone with MacMillan organocatalyst

The well-known MacMillan imidazolidinone structure offers the possibility of various modifications and functionalities to graft on an ionic liquid moiety, for example *via* the use of an appropriate amino acid, *e.g.* tryptophane as starting material followed by selective alkylation. Alternatively, ionic head groups can be introduced on positions 2 or 3 *via* covalent attachment to imidazolium or pyridinium systems using diverse synthetic strategies (Path 2 and 3). The consecutive adaptation of the counter anion as previously shown opens the possibility of catalyst recycling which would be of special interest regarding the high organocatalyst loading in this case.

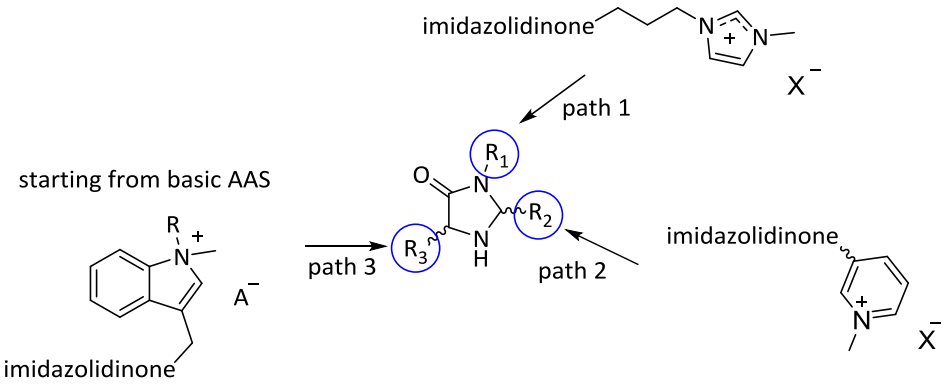


Figure 113: Possibilities of grafting MacMillan's imidazolidinone catalyst to ILs

Based on these divers possibilities to convert the MacMillan imidazolidinone in an IL preliminary attempts for the anchoring were made. Synthetic strategies based on path 1 and 2 were developed starting from commercially available phenylalanine.

For path 1 the amine functionality of L-phenylalanine was protected using *tert*-butyloxycarbonyl (BOC) group under literature conditions. The protected amino acid was converted to the corresponding amide using 1-(3-aminopropyl)imidazole according to Steglich protocol, using DCC/DMAP as amidation reagent in dichloromethane.[203] Deprotonation followed by acid-catalysis should give direct access to the MacMillan intermediate. Unfortunately cyclization did not occur, and optimization of reaction conditions, such as variation of temperature, acid catalyst or aldehyde/ketone did not give satisfactory results.

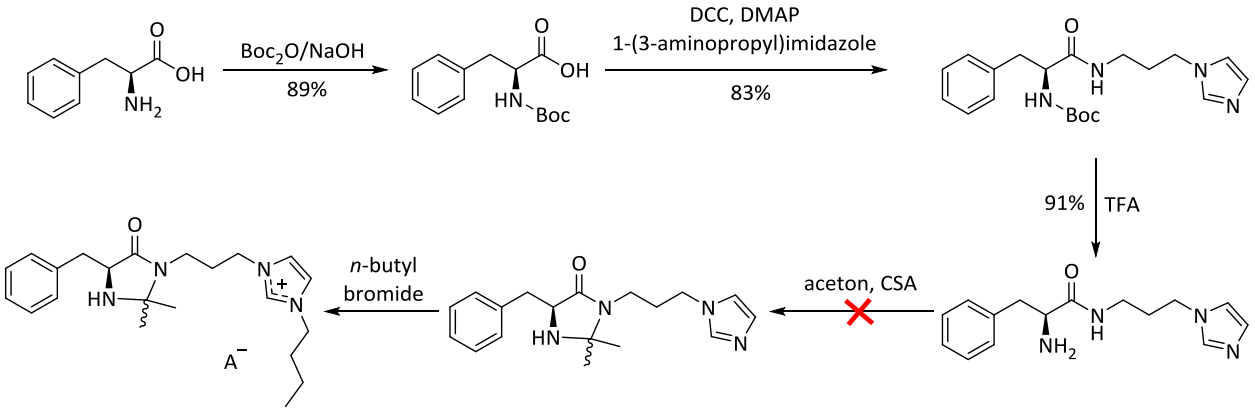


Figure 114: Synthetic strategy for Path 1

An alternative synthetic route for path 1 was proposed, starting from Boc-protected L-phenylalanine and amidation with 2-chloroethylamine hydrochloride. The product was deprotected and the intermediate was immediately used for the next step. Unfortunately also in this case, cyclization in the presence of acidic catalysts and acetone did not occur.

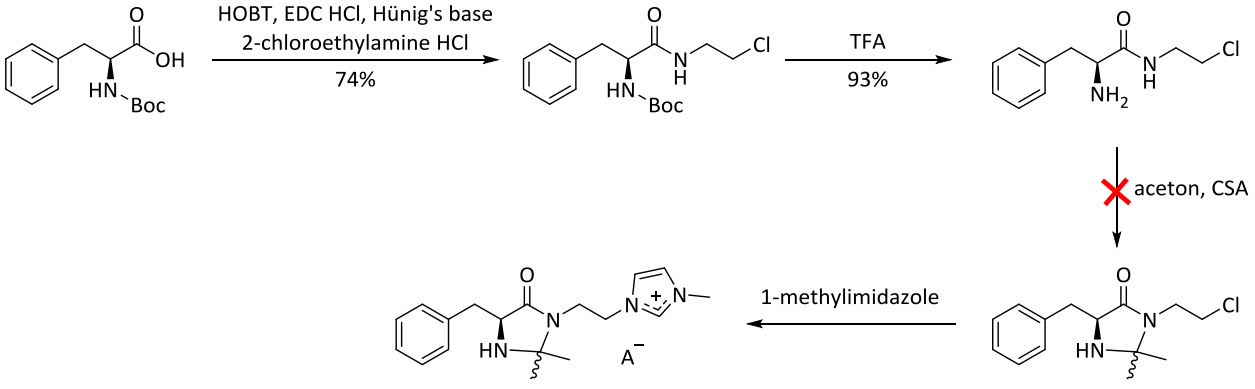


Figure 115: Synthetic strategy for Path 1

Therefore a synthetic route for path 2 was proposed starting from L-phenylalanine. After activation using sulfonyl chloride and immediate amidation, the amide was cyclized using freshly distilled 2-pyridinecarboxaldehyde in the presence of catalytic amounts of europium triflate in anhydrous chloroform. The product could be isolated as a mixture of diastereomers, which were separated on preparative HPLC using water/MeOH as mobile phase. Unfortunately the subsequent alkylation using *n*-butyl bromide, or more reactive methyl iodide did not result in the formation of the salt.

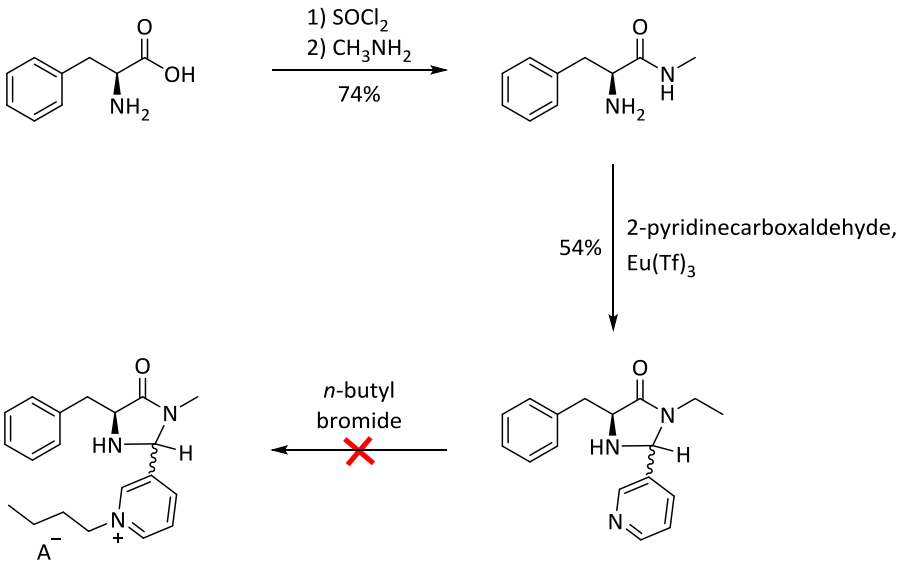


Figure 116: Synthetic strategy for Path 2

Although no desired product could be isolated, investigations toward the ideal alkylation conditions for path 2 are still ongoing, since this ionic liquid-tagged organocatalyst for asymmetric transfer hydrogenation might lead to a novel protocol for the reduction of α,β-unsaturated ketones and opens the possibility of catalyst recycling.

V Conclusion

Chiral ionic liquids can be efficiently synthesized from naturally occurring enantiopure starting materials and are able to exhibit a strong chiral interaction. This characteristic in combination with the tunable nature of ionic liquids opens novel solutions for synthesis and separations and makes them an attractive alternative to already established methods.

In the first part of this thesis, a set of novel, chiral-pool derived ionic liquids was prepared to investigate the strength of chiral induction properties when used as shift reagent in ^{19}F-NMR experiments. These investigations showed that diastereomeric interactions of CILs with a racemic substrate are highly dependent on concentration and structure of the ionic liquids, as the formed aggregates show a maximum of chiral induction at certain concentrations.

When used as chiral ligands in asymmetric synthesis the concept of grafting an ionic liquid moiety to an amino alcohol has shown to be a beneficial approach. In comparison to the conventional ligands, this strategy opens the possibility of catalyst recycling and adaptation of solubility *via* the choice of anion. Besides in some cases accelerated reaction rates and improved enantiomeric outcome can be observed.

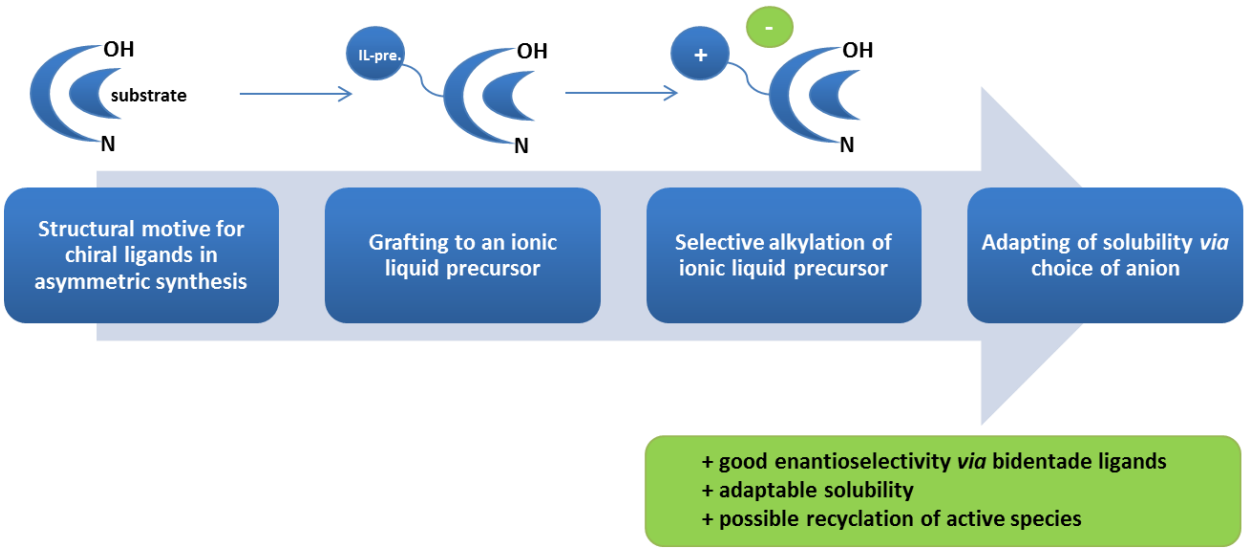


Figure 117: Strategy for novel ligand synthesis

The careful design of chiral ionic liquids with coordinating groups could expand the application of chiral pool derived ionic liquids towards a broad range of applications covering not only asymmetric synthesis but also separation sciences. A simple and efficient synthesis for novel CILs with an amino alcohol sub-unit was developed that could be successfully applied in asymmetric alkylations or transfer hydrogenations.

In the last part of this thesis, the use of ionic liquids as stationary phases in gas chromatography was further investigated. Coating protocols were developed to provide stationary phases with strong affinity towards polar and apolar substrates. Suitable chiral ionic liquids were identified and coated for the future evaluation of this novel, ionic liquid-based chiral GC columns, with higher thermal stability compared to commercially available phases. However, so far no chiral separation could be obtained and more investigations towards the chiral resolution of racemic substrates are currently ongoing.

VI Experimental Part

VI 1 Materials and Methods – Chemical Synthesis

All reagents were purchased from commercial suppliers and used without further purification unless noted otherwise. CH_2Cl_2, Et_2O, MeOH, THF and toluene intended for water-free reactions were pre-distilled and desiccated on Al_2O_3 columns (PURESOLV, Innovative Technology). Anhydrous triethylamin was stored over KOH and distilled from calcium hydride prior to use.

Chromatography solvents were distilled prior to use. Column chromatography was performed on a Büchi Sepacore Flash System (2 x Büchi Pump Module C-605, Büchi Pump Manager C-615, Büchi UV Photometer C-635, Büchi Fraction Collector C-660) or standard manual glass columns using silica gel from Merck (40-63 µm) with PE/EtOAc or MeOH/CH_2Cl_2 mixtures as eluates.

Preparative HPLC was performed on a Shimazu preparative HPLC equipped with SDP20A PDA detector using a C18(2) column (250 cm x 21.20 cm ID) and MeOH/H_2O as eluent at a flowrate of 20 ml/min.

TLC-analysis was carried out using precoated aluminum-backed plates purchased from Merck (silica gel 60 F_{254}). UV active compounds were detected at 254 nm.

Table 27: TLC staining solutions

TLC staining solution 1 (general purpose)		TLC staining solution 2 (general purpose)	
2 g	$KMnO_4$	4.5 g	phosphomolybdic acid hydrate
1 g	NaOH	0.1 g	cerium ammonium nitrate
40 g	K_2CO_3	100 ml	H_2SO_4 (10%)
320 mL	deion. H_2O	300 mL	EtOH

^1H, ^{13}C and ^{19}F NMR spectra were recorded from $CDCl_3$, CD_2Cl_2, MeOD or d_6-DMSO solutions on a Bruker AC 200 (200 MHz) or Bruker Advance UltraShield 400 (400 MHz) spectrometer and chemical shifts (δ) are reported in ppm using tetramethylsilane as internal standard coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet, brs = broad.

GC analysis was conducted with a Thermo Finnigan Focus GC / DSQ II equipped with a FID detector using a standard capillary column BGB5 (30m x 0.32 mm ID) at a flow rate of 2.0 ml/min and a split ratio of 20 with Helium as carrier gas.

Enantiomeric excess was determined *via* GC using a BGB175 (30 m x 0.25 mm ID, 0.25 µm film) or BGB173 (30 m x 0.25 mm ID, 0.25 µm film) chiral column on a ThermoQuest Trace GC 2000 and a on a ThermoFocus GC equipped with FID detector.

Alternatively, enantiomeric composition was determined *via* HPLC on a Thermo Finnigan Surveyor chromatograph or DAIONEX UPLC, equipped with a PDA plus detector (190-360 nm) using DAICEL IA, IC or AS-H columns (250x 4.60 mm) as stationary phase and mixtures of *n*-heptane/*i*-PrOH as solvent and flow rates of 0.5-1.0 ml/min.

Optical rotation was measured on an Anton Paar MCP500 polarimeter at the specified conditions.

TLC/MS analysis was performed on a Bruker Esquire HTC ion trap mass spectrometer equipped with a camag TLC-MS interface.

Thermal stabilities were determined on a Netzsch TGA in a range of 25 to 500 °C with a heating rate of 10 °C/min. Decomposition temperatures ($T_{5\%onset}$) were reported from onset to 5 wt% mass loss. Melting points above room temperature were measured on a Kofler hot-stage microscope or on an automated melting point system OPTI MELT of Stanford ResearchSystems and are uncorrected.

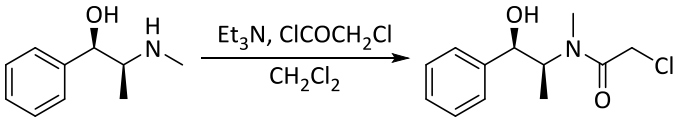
Infrared spectra were recorded on a Perkin-Elmer Spectrum 65 FT IR spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.

Elemental analysis was performed at Vienna University, Department of Physicochemistry-Laboratory for Microanalysis, Währingerstraße 42, A-1090 Vienna.

VI 2 Amido Alcohol-Derived Chiral Ionic Liquids

VI 2.1 Synthesis of Ephedrine-Derived Ionic Liquids

VI 2.1.1 2-Chloro-*N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylacetamide 2



$C_{12}H_{16}ClNO_2$
241.71

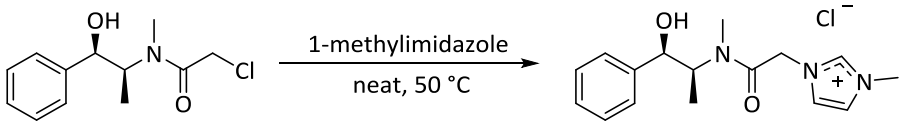
1 **2**

(1*R*,2*S*)-Ephedrine **1** (10.00 g, 60.51 mmol) was dissolved in dry CH_2Cl_2 before anhydrous triethylamine (8.40 ml, 60.50 mmol) was added under vigorous stirring. The reaction mixture was cooled to 0 °C, then freshly distilled chloroacetyl chloride (4.80 ml, 60.50 mmol) was added and the solution was further stirred at rt until TLC showed full conversion. After extraction of the reaction mixture with H_2O, 2N HCl, $NaHCO_3$ solution and brine, the combined organic layers were dried and the solvent was removed under reduced pressure. Purification by crystallization from EtOH or *via* MPLC (CH_2Cl_2/MeOH) gave compound **2** as pale yellow crystals.

Analytical data was in accordance to literature.[152]

Yield	12.3 g (84%) yellow crystals
Mp	79-81 °C
Major rotamer	
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 7.36-7.30 (m, 5H, H-arom), 4.90 (d, J = 3.98 Hz, 1H, C*H*-OH), 4.50-4.43 (m, 1H, C*H*-CH_3), 4.02 (s, 2H, CH_2-Cl), 3.20 (brs, 1H, O*H*), 2.86 (s, 3H, CH_3-N), 1.22 (d, J = 7.08 Hz, 3H, CH_3-CH)

VI 2.1.2 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride 3



$C_{16}H_{22}ClN_3O_2$
323.82

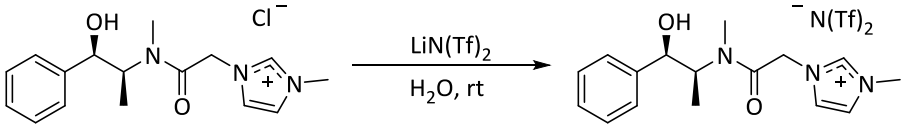
2 **3**

To compound **2** (3.06 g, 12.40 mmol) freshly distilled 1-methylimidazole (0.98 ml, 12.40 mmol) was added *via* syringe. The reaction mixture was stirred for 48 hours at 50 °C and remaining volatile materials were removed under reduced pressure ($1x10^{-2}$ mbar overnight). Crystallization from acetonitrile gave product **3** as yellow crystals.

Analytical data was in accordance to literature.[152]

Yield	3.61 g (90%) yellow crystals
Mp	135-138 °C
Major rotamer	
^{1}H-NMR (200 MHz, DMSO)	δ_H = 9.02 (s, 1H, C*H*-imidazole), 7.68 (s, 1H, C*H*-imidazole), 7.52 (s, 1H, C*H*-imidazole), 7.48-7.17 (m, 5H, *H*-arom), 5.56 (d, J = 5.69 Hz, 1H, C*H*-OH), 5.22 (s, 2H, CH_2-N-imidazole), 4.79-4.68 (m, 1H, C*H*-CH_3), 3.90 (s, 3H, CH_3-N-imidazole), 2.95 (s, 3H, CH_3-N), 1.08 (d, J = 6.95 Hz, 3H, CH_3-CH)
$T_{5\%\ onset}$	90 °C
ν_{max}/cm^{-1}	3085 (O-H), 1621 (C-C), 1570 (C=C), 1370 (C-H)

VI 2.1.3 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 4



$C_{18}H_{22}F_6N_4O_6S_2$
568.51

3 **4**

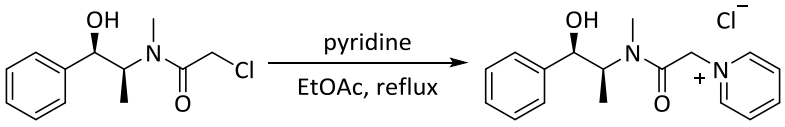
Compound **3** (1.06 g, 3.25 mmol) was dissolved in 20 ml H_2O before a solution of lithium bis(trifluoromethane)sulfonimide (1.03 g, 3.57 mmol) in 10 ml H_20 was added. The reaction mixture was stirred at rt for 1 hour followed by multiple extraction of the aqueous layer with CH_2Cl_2. The combined organic layers were subsequently washed with water until no chloride could be detected in the organic

phase (tested with $AgNO_3$ solution). After the organic layers were dried and the solvent removed under reduced pressure, the product **4** was dried at high vacuum ($1x10^{-2}$ mbar overnight) and could be collected as a colorless liquid.

Analytical data was in accordance to literature.[152]

Yield	1.65 g (90%) colorless liquid
Major rotamer	
^{1}H-NMR (200 MHz, DMSO)	δ_H = 8.93 (s, 1H, C*H*-imidazole), 7.66 (s, 1H, C*H*-imidazole), 7.47 (s, 1H, H C*H*-imidazole), 7.43-7.20 (m, 5H, *H*-arom), 5.48 (d, J = 4.69 Hz, 1H, C*H*-OH), 5.16 (s, 1H, CH_2-N-imidazole), 4.76-4.67 (m, 1H, C*H*-CH_3), 3.89 (s, 3H, CH_3-N-imidazole), 2.93 (s, 3H, CH_3-N), 1.05 (d, J = 6.85 Hz, 3H, CH_3-CH).
$T_{5\%\ onset}$	173 °C
ν_{max}/cm^{-1}	3163 (O-H), 1653 (C-C), 1574 (C=C), 1347 (C-H), 1176 (C-F_3), 1051 (NH-CH_3)

VI 2.1.4 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)pyridin-1-ium chloride 5



$C_{17}H_{21}ClN_2O_2$
320.82

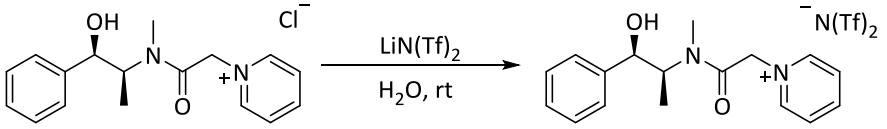
2 **5**

Compound **2** (2.00 g, 8.27 mmol) was dissolved in 15 ml of anhydrous EtOAc under inert atmosphere before pyridine (0.67 ml, 8.27 mmol) was added at rt. The reaction mixture was heated to reflux until TLC showed full conversion. After cooling to 0 °C product **5** could be collected *via* filtration and washing with cold PE to obtain as light yellow solid.

Yield	2.3 g (87%) light yellow solid
Mp	155-159 °C
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.75-8.61 (m, 2H, *H*-pyridine), 3.39-8.36 (m, 1H, *H*-pyridine), 8.12-8.05 (m, 2H, *H*-pyridine), 7.50-7.30 (m, 5H, *H*-arom), 5.75-5.50 (m, 2H, C*H*-OH, C*H*-CH_3), 4.94-4.60 (m, 2H, CH_2-N^+), 3.08 (s, 3H, CH_3-N), 1.27 (d, J = 6.88, CH_3-CH)

^{13}C-NMR (100 MHz, MeOD)	δ_C = 147.6 (s, *C*=O), 142.5 (s, C-arom), 129.7-127.0 (10d, C-arom), 71.8 (d, *C*H-OH), 66.9 (d, *C*H-CH_3), 61.4 (t, *C*H_2-N^+), 31.5 (q, *C*H_3-N), 10.0 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -27.35 (*c* 1.02, MeOH)
$T_{5\%\ onset}$	148 °C
ν_{max}/cm^{-1}	2960 (O-H), 1638 (C-C), 1485 (C=C), 1352 (C-H)
Elemental analysis	calculated: w-% C: 63.64, w-% H: 6.60, w-% N: 8.73 calculated: 1.58xH_2O = w-% C: 58.46, w-% H: 6.97, w-% N: 8.02 measured: w-% C: 58.69, w-% H: 6.84, w-% N: 7.68

VI 2.1.5 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)pyridin-1-ium bis(trifluoromethane)sulfonimide 6



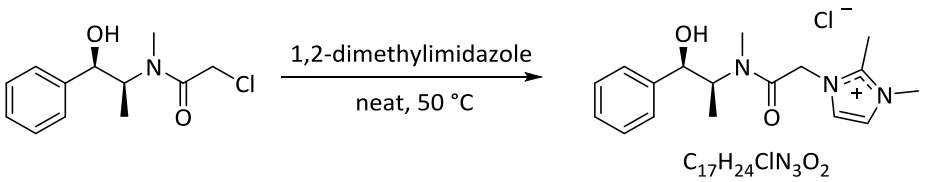
$C_{19}H_{21}F_6N_3O_6S_2$
565.50

5 **6**

According to procedure VI 2.1.3, compound **6** was prepared from **5** (2.27 g, 8.00 mmol) and lithium bis(trifluoromethane)sulfonimide (2.53 g, 8.88 mmol) to yield the product as yellow liquid.

Yield	2.15 g (48%) yellow liquid
Major rotamer	
^{1}H-NMR (200 MHz, MeOD)	δ_H = 8.67-8.57 (m, 2H, *H*-pyridine), 8.32-8.29 (m, 1H, *H*-pyridine), 8.14-8.02 (m, 2H, *H*-pyridine), 7.49-7-28 (m, 5H, *H*-arom), 5.66-5.40 (m, 2H, C*H*-OH, C*H*-CH_3), 4.88-4.59 (m, 2H, CH_2-N^+), 2.86 (s, 3H, CH_3-N), 1.25 (d, J = 6.85 Hz, 3H, CH_3-CH)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 165.8 (s, *C*=O), 147.4 (2d, C-pyridine), 143.8 (s, *C*-arom), 129.7-128.7 (5d, C-arom), 127.8 (2d, CH-pyridine), 118.4 (q, J = 320.5 Hz, CF_3), 76.6 (d, *C*H-OH), 62.9 (t, *C*H_2-N^+), 57.7 (d, *C*H-CH_3), 30.9 (q, *C*H_3-N), 12.5 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -15.55 (*c* 1.00, CH_2Cl_2)
$T_{5\%\ onset}$	129 °C
ν_{max}/cm^{-1}	3093 (O-H), 1654 (C-C), 1492(C=C), 1347 (C-H), 1180 (C-F_3), 1050 (NH-CH_3)
Elemental analysis	calculated: w-% C: 40.35, w-% H: 3.74, w-% N: 7.43 measured: w-% C: 40.34, w-% H: 3.65, w-% N: 7.21

VI 2.1.6 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium chloride 7



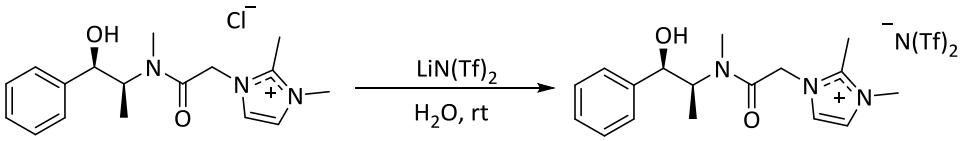
$C_{17}H_{24}ClN_3O_2$
337.85

2 **7**

Compound **7** was prepared according to procedure VI 2.1.2 using **2** (2.00 g, 8.27 mmol) and 1,2-dimethylimidazole (0.79 g, 8.27 mmol) to give the product as light yellow solid.

Yield	2.65 g (95%) yellow solid
Mp	115-119 °C
Major rotamer	
^{1}H-NMR (200 MHz, MeOD)	δ_H = 7.59 (s, 1H, C*H*-imidazole), 7.29 (m, 6H, C*H*-imidazole, *H*-arom), 5.57 (d, J = 4.70 Hz, 1H, C*H*-OH), 5.11 (q, J = 17.67 Hz, 2H, CH_2-N-imidazole), 5.15-5.50 (m, 1H, C*H*-N), 3.77 (s, 3H, CH_3-N-imidazole), 2.95 (s, 3H, CH_3-N), 2.19 (s, 3H, CH_3-CH-imidazole), 1.15 (d, J = 6.84 Hz, 3H, CH_3-CH)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 166.2 (s, *C*=O), 143.9 (s, *C*-arom), 129.8 (d, *C*H-imidazole), 129.3 (d, *C*H-arom), 128.3 (d, *C*H-arom), 127.9/126.4 (2d, *C*H-imidazole), 127.9 (d, *C*H-arom), 126.4 (d, *C*H-arom), 123.24 (d, *C*H-arom), 76.6 (d, *C*H-OH), 57.2 (d, *C*H-CH_3), 50.7 (t, *C*H_2-N-imidazole), 35.5 (q, *C*H_3-N-imidazole), 30.6 (q, *C*H_3-N), 13.4 (q, *C*H_3-CH-imidazole), 9.68 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -7.39 (*c* 0.98, MeOH)
$T_{5\%\ onset}$	79 °C
ν_{max}/cm^{-1}	2922 (O-H), 1647 (C-C), 1593 (C=C), 1312 (C-H)
Elemental analysis	calculated: w-% C: 60.44, w-% H: 7.16, w-% N: 12.44 calculated: 0.55xH_2O = w-% C: 58.72, w-% H: 7.28, w-% N: 12.08 measured: w-% C: 58.33, w-% H: 7.04, w-% N: 13.11

VI 2.1.7 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 8



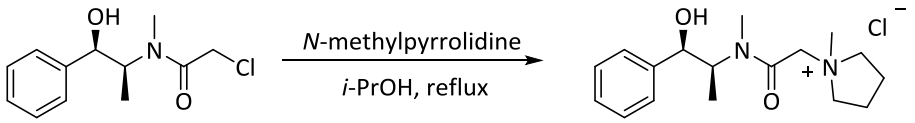
$C_{19}H_{24}F_6N_4O_6S_2$
582.54

7 **8**

According to procedure VI 2.1.3, compound **8** was prepared from **7** (2.7 g, 8 mmol) and lithium bis(trifluoromethane)sulfonimide (2.53 g, 8.8 mmol) to yield the product as colorless liquid.

Yield	4.30 g (90%) colorless liquid
Major rotamer	
^{1}H-NMR (200 MHz, MeOD)	δ_H = 7.46-7.00 (m, 7H, *H*-arom, *H*-imidazole), 5.19-4.78 (m, 2H, CH_2-N-imidazole), 4.68-4.67 (m, 2H, C*H*-OH, C*H*-CH_3), 3.79 (s, 3H, CH_3-N-imidazole), 2.99 (s, 3H, C*H*$_3$-N), 2.17 (s, 3H, C*H*$_3$-C-imidazole), 1.34 (d, J = 5.70 Hz, 3H, C*H*$_3$-CH)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 166.1 (s, C-13), 147.5 (s, *C*-arom), 143.9 (s, *C*-imidazol), 129.8 (d, *C*H-arom), 129.4 (2d, *C*H-arom), 128.8 (d, *C*H-arom), 127.8/127.8 (2d, *C*H-imidazole), 123.4 (d, *C*H-arom), 119.8 (q, J = 320.5 Hz, CF_3), 76.6 (d, *C*H-OH), 57.2 (d, *C*H-CH_3), 50.6 (t, *C*H_2-N-imidazole), 35.5 (q, *C*H_3-N-imidazole), 30.4 (q, *C*H_3-N), 13.6 (q, *C*H_3-CH-imidazole), 9.6 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -10.73 (*c* 1.07, CH_2Cl_2)
$T_{5\%\ onset}$	173 °C
ν_{max}/cm^{-1}	3152 (O-H), 1651 (C-C), 1594 (C=C), 1347 (C-H), 1180 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 39.17, w-% H: 4.15, w-% N: 9.62 measured: w-% C: 39.37, w-% H: 4.00, w-% N: 9.45

VI 2.1.8 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-1-methylpyrrolidin-1-ium chloride 9



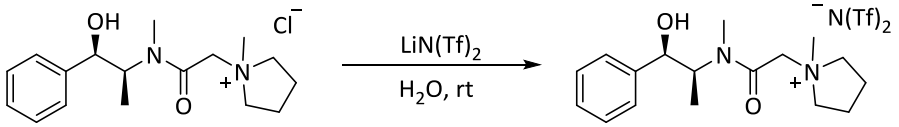
$C_{17}H_{27}ClN_2O_2$
326.87

2 **9**

Compound **2** (2.00 g, 8.27 mmol) was dissolved under inert atmosphere in 15 ml *i*-PrOH before *N*-methylpyrrolidine (0.97 ml, 9.10 mmol) was added. The reaction mixture was stirred under reflux until TLC showed no starting material. The mixture was cooled to 0 °C and the crystallized product **9** could be collected after filtration and washing with cold PE.

Yield	2.03 g (75%) colorless solid
Mp	42-45 °C
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.48-7.25 (m, 5H, *H*-arom), 4.70-4.68 (m, 1H, C*H*-OH), 4.52-4.21 (m, 2H, CH_2-N^+), 3.76-3.29 (m, 4H, CH_2-CH_2-pyrrolidine), 4.38 (d, J = 7.67 Hz, 1H, C*H*-CH_3), 2.907 (s, 3H, CH_3-N^+), 2.93 (s, 3H, CH_3-N), 2.24-2.06 (m, 5H, CH_2-CH_2-pyrrolidine, OH), 1.32 (d, J = 6.72 Hz, 3H, CH_3-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 165.0 (s, *C*=O), 143.9 (s, *C*H-arom), 129.6 (d, *C*-arom), 129.3 (2d, *C*-arom), 129.2 (s, *C*-arom), 128.7 (s, *C*-arom), 127.9 (s, *C*-arom), 76.6 (s, *C*-OH), 66.7 (2t, C-*C*H_2-pyrrolidine), 63.8 (t, CH_2-N^+), 56.3 (d, *C*H-CH_3), 50.2 (q, CH_3-N^+), 25.3 (q, CH_3-N), 22.6 (2t, *C*H_2-pyrrolidine), 13.4 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -8.80 (*c* 1.04, MeOH)
$T_{5\%\ onset}$	107 °C
ν_{max}/cm^{-1}	2970 (O-H), 1655 (C-C), 1498 (C=C), 1318 (C-H)
Elemental analysis	calculated: w-% C: 62.47, w-% H: 8.33, w-% N: 8.57 calculated: 0.50xH_2O w-% C: 62.79, w-% H: 8.40, w-% N: 8.34 measured: w-% C: 62.47, w-% H: 8.33, w-% N: 8.57

VI 2.1.9 1-(2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-1-methylpyrrolidin-1-ium bis(trifluoromethane)sulfonimide 10



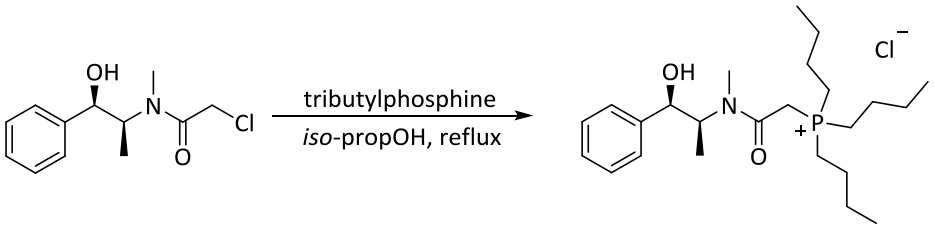
$C_{19}H_{27}F_6N_3O_6S_2$
571.55

9 **10**

According to procedure VI 2.1.3, compound **10** was prepared from **9** (2.28 g, 7.00 mmol) and lithium bis(trifluoromethane)sulfonimide (2.21 g, 7.77 mmol) to yield the product as colorless liquid.

Yield	3.67 g (91%) colorless liquid
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.38 (m, 5H, H-arom), 4.7-4.47 (m, 1H, C*H*-OH), 4.67-4.64 (m, 1H, C*H*-CH_3), 4.31-4.06 (m, 2H, CH_2-N-pyrrolidine), 3.69-3.32 (m, 4H, CH_2-pyrrolidine), 3.01 (s, 3H, CH_3-N^+), 2.87 (s, 3H, CH_3-N), 2.22-2.03 (m, 4H, CH_2-pyrrolidine), 1.34 (d, J = 6.92 Hz, 3H, CH_3-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.0 (s, *C*=O), 142.4 (s, *C*H-arom), 127.96 (2d, *C*-arom), 127.4 (d, *C*-arom), 126.5 (2d, *C*-arom), 119.8 (q, J = 320.5 Hz, CF_3), 75.3 (s, *C*H-OH), 65.3 (2t, C-*C*H_2-pyrrolidine), 62.6 (t, CH_2-N^+), 54.8 (d, *C*H-CH_3), 50.2 (q, CH_3-N^+), 29.1 (q, CH_3-N), 21.3 (2t, *C*H_2-pyrrolidine), 12.16 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -17.49 (*c* 1.00, MeOH)
$T_{5\%\ onset}$	199 °C
ν_{max}/cm^{-1}	2989 (O-H), 1651 (C-C), 1454 (C=C), 1347 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 39.93, w-% H: 4.76, w-% N: 7.35 measured: w-% C: 39.81, w-% H: 4.67, w-% N: 7.28

VI 2.1.10 Tributyl(2-(((1*R*, 2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)phosphonium chloride 11



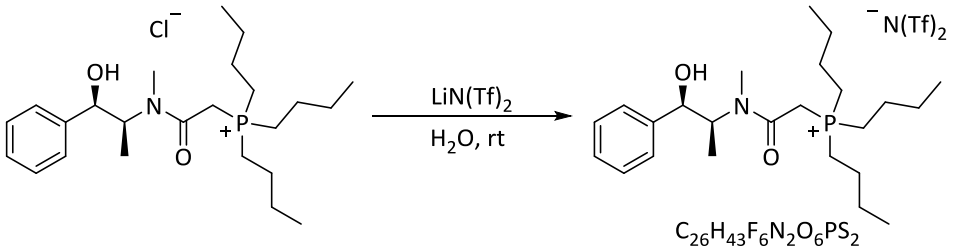
$C_{24}H_{43}ClNO_2P$
444.04

2 **11**

Compound **2** (1.67 g, 6.90 mmol) was dissolved in 15 ml *i*-PrOH before tributylphosphine (1.70 ml, 6.90 mmol) was added and the reaction mixture was heated to reflux until TLC showed no starting material. The solvent was evaporated under reduced pressure to yield product **11** as light yellow liquid.

Yield	2.41 g (79%) light yellow liquid
Major rotamer	
^{1}H-NMR (200 MHz, MeOD)	δ_H = 7.44-7.25 (m, 5H, *H*-arom), 4.71-4.00 (m, 2H, C*H*-OH, C*H*-CH_3), 2.96 (s, 2H, CH_2-P^+), 2.21-2.04 (m, 6H, CH_2-P^+), 1.87-1.01 (m, 15H, C*H*$_2$-C*H*$_2$-C*H*$_2$, C*H*$_3$-N), 0.99-0.84 (m, 9H, CH_2-CH_2-CH_2-C*H*$_3$)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 143.8 (s, C=O), 129.7 (s, C-arom), 129.3 (2d, C-arom), 128.8 (2d, C-arom), 127.9 (d, C-arom), 76.6 (d, *C*H-OH), 56.3 (d, *C*H-CH_3), 32.2 (q, C*H*$_3$-N), 24.4 (3t, *C*H_2-CH_2-CH_2), 20.8 (3t, CH_2-*C*H_2-CH_2), 20.7 (3t, CH_2-CH_2-*C*H_2), 13.7 (3d, q, *C*H_3-CH_2-CH_2-CH_2, *C*H_3-CH)
Specific Rotation	α_D^{20} = -18.09 (*c* 0.97, MeOH)
$T_{5\%\ onset}$	97 °C
ν_{max}/cm^{-1}	2958 (O-H), 1627 (C-C), 1449 (C=C), 1230 (C-H)
Elemental analysis	calculated: w-% C: 64.92, w-% H: 9.76, w-% N: 3.15
	calculated: 0.30xH_2O = w-% C: 64.14, w-% H: 9.78, w-% N: 3.12
	measured: w-% C: 64.20, w-% H: 9.64, w-% N: 2.87

VI 2.1.11 Tributyl(2-(((1*R*, 2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)phosphonium bis(trifluoromethane)sulfonimide 12



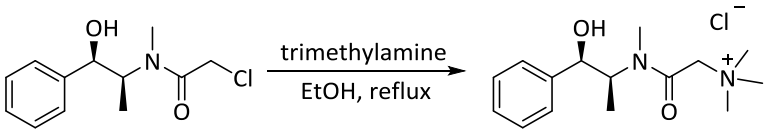
$C_{26}H_{43}F_6N_2O_6PS_2$
688.72

11 **12**

According to procedure VI 2.1.3, cmp **12** was prepared from **11** (3.64 g, 8.20 mmol) and lithium bis(trifluoromethane)sulfonimide (2.59 g, 9.02 mmol) to yield the product as colorless liquid.

Yield	4.60 g (79%) colorless liquid
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.32-7.21 (m, 5H, *H*-arom), 4.23-4.19 (m, 1H, C*H*-OH),), 3.63-3.52 (m, 2H, C*H*-CH_3, OH), 2.98-2.68 (m, 2H, CH_2-P^+), 2.20-2.17 (m, 6H, 3CH_2-P^+), 1.50-1.47 (m, 15H, 3CH_2-CH_2-CH_2, CH_3-N), 1.00-0.97 (m, 9 H, CH_2-CH_2-CH_2-CH_3)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 139.6 (s, *C*=O), 130.3 (s, C-arom), 129.5 (2d, C-arom), 127.6 (2d, C-arom), 119.8 (q, J = 320.6 Hz, CF_3), 64.3 (d, *C*H-OH), 54.7 (d, *C*H-CH_3), 43.2 (s, C-7), 38.0 (q, CH_3-N), 28.5 (3t, *C*H_2-CH_2-CH_2), 25.3 (3t, CH_2-*C*H_2-CH_2), 20.4/19.4 (t, CH_2-CH_2-*C*H_2), 13.6 (3d, q, *C*H_3-CH_2-CH_2-CH_2, *C*H_3-CH)
Specific Rotation	α_D^{20} = -13.68 (*c* 1.10, CH_2Cl_2)
$T_{5\%\ onset}$	134°C
ν_{max}/cm^{-1}	2963 (O-H), 1667 (C-C), 1536 (C=C), 1348 (C-H), 1185 (C-F_3), 1054 (NH-CH_3)
Elemental analysis	calculated: w-% C: 45.34, w-% H: 6.26, w-% N: 4.07 measured: w-% C: 46.49, w-% H: 6.21, w-% N: 3.91

VI 2.1.12 2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium chloride 13



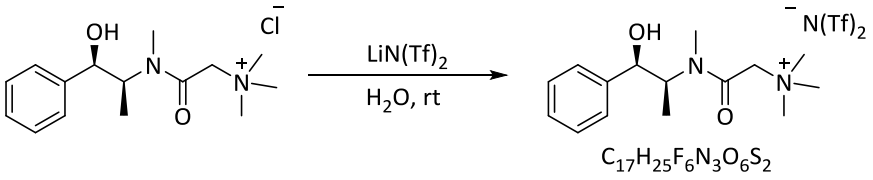
$C_{15}H_{25}ClN_2O_2$
300.83

2 **13**

Compound **2** (1.00 g, 4.14 mmol) was dissolved under inert atmosphere in anhydrous EtOH before trimethylamine as 33% solution in EtOH (1.08 ml, 4.55 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour prior heating to reflux for 24 hours until TLC showed full conversion. The reaction mixture was cooled to 0 °C to accelerate crystallization of product **13**, which could be collected from the reaction mixture as colorless solid after filtration.

Yield	1.09 g (88%) colorless solid
Mp	52-55 °C
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.44-7.23 (m, 5H, *H*-arom), 4.76-4.71 (m, 1H, C*H*-OH), 4.22 (d, J = 4.70 Hz, 2H, CH_2-N), 3.61 (q, J = 7.02 Hz, 1H, C*H*-CH_3), 3.19 (s, 9H, CH_3-N^+), 2.89 (s, 3H, CH_3-N), 1.15 (d, J = 4.48 Hz, 3H, CH_3-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.2 (s, *C*=O), 142.6 (s, *C*-arom), 129.7 -127.8 (5d, *C*-arom), 76.6 (d, *C*H-OH), 54.5 (d, CH_2-N^+), 50.3 (d, *C*H-CH_3), 30.6 – 13.3 (2q, *C*H_3)
Specific Rotation	α_D^{20} = -9.37 (*c* 1.02, MeOH)
$T_{5\%\ onset}$	120 °C
ν_{max}/cm^{-1}	2994 (O-H), 1651 (C-C), 1491 (C=C), 1454 (C-H)
Elemental analysis	calculated: w-% C: 59.89, w-% H: 8.38, w-% N: 9.31
	calculated: 1.30xH_2O = w-% C: 55.56, w-% H: 8.58, w-% N: 8.64
	measured: w-% C: 55.56, w-% H: 8.16, w-% N: 8.16

VI 2.1.13 2-(((1*R*, 2*S*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium bis(trifluoromethane)sulfonimide 14



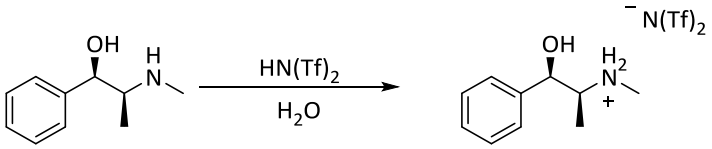
$C_{17}H_{25}F_6N_3O_6S_2$
545.52

13 **14**

According to procedure VI 2.1.3, compound **14** was prepared from **13** (0.90 g, 3.00 mmol) and lithium bis(trifluoromethane)sulfonimide (0.95 g, 3.33 mmol) to yield the product as colorless liquid.

Yield	1.38 g (85%) colorless liquid
Major rotamer	
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.47-7.27 (m, 5H, *H*-arom), 4.68 (d, J = 7.84 Hz, 1H, C*H*-OH), 4.16 (m, 2H, CH_2-N), 3.36-3.31 (m, 1H, C*H*-CH_3), 3.10 (s, 9H, CH_3-N^+), 2.90 (s, 3H, CH_3-N), 1.35 (d, J = 6.84 Hz, 3H, CH_3-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.1 (s, *C*=O), 142.6 (s, *C*-arom), 127.8 (2d, *C*-arom), 127.4 (d, *C*-arom), 126.4 (2d, *C*-arom), 119.8 (q, J = 320.0 Hz, CF_3), 75.3 (d, *C*H-OH), 62.8 (t, CH_2-N^+), 58.2 (d, *C*H-CH_3), 53.4 (q, *C*H_3-N^+), 29.1 (q, CH_3-N), 12.1 (q, *C*H_3-CH)
Specific Rotation	α_D^{20} = -15.01 (*c* 1.03, CH_2Cl_2)
$T_{5\%\ onset}$	185 °C
ν_{max}/cm^{-1}	2990 (O-H), 1652 (C-C), 1491 (C=C), 1347 (C-H), 1180 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 37.43, w-% H: 4.62, w-% N: 7.70 measured: w-% C: 37.63, w-% H: 4.24, w-% N: 7.39

VI 2.1.14 (1*R*,2*S*)-1-Hydroxy-*N*,*N*-dimethyl-1-phenylpropan-2-aminium bis(trifluoromethan)sulfonimide 29



$C_{12}H_{16}F_6N_2O_5S_2$
446.38

1 **29**

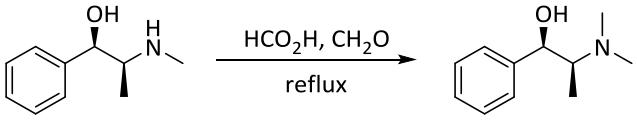
(1*R*,2*S*)-Ephedrin **1** (0.50 g, 3.00 mmol) was dissolved in 10 ml H_2O and bis(tr(fluoromethane)sulfonimide (0.84 g, 3.00 mmol) was added as solution in 2 ml H_2O. The reaction mixture was stirred at rt for 1 hour followed by lyophilization of the excessive water.

Analytical data was in accordance to literature.[110]

Yield 1.32 g (98%) white solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.34-7.26 (m, 5H, H-arom), 7.01 (brs, 1H, N*H*), 6.67 (brs, 1H, N*H*), 5.23 (d, J = 2.64 Hz, 1H, C*H*-OH), 3.46-3.43 (m, 1H, C*H*-CH_3), 2.88 (t, J = 5.67 Hz, 3H, C*H*$_3$-NH_2), 1.11 (d, J = 6.65 Hz, C*H*$_3$-CH)

VI 2.1.15 (1*R*,2*S*)-2-(Dimethylamino)-1-phenylpropan-1-ol 30



$C_{11}H_{17}NO$
179.26

1 **30**

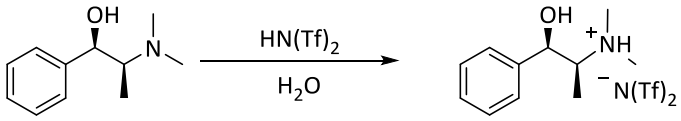
(1*R*,2*S*)-Ephedrine **1** (5.00 g, 30.26 mmol) was dissolved in formic acid (11.40 ml, 302.60 mmol) and formaldehyde was added as 37% solution (6.60 ml, 181.56 mmol). After the reaction mixture was refluxed for 24 hours, it was cooled to rt, basificated with aqueous NaOH to pH 10 and extracted with EtOAc. The combined organic layers were dried and concentrated under reduced pressure. Recrystallization from EtOH afforded the product **30** as colorless solid.

Analytical data was in accordance to literature.[204]

Yield 4.6 g (79%) colorless solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.27-7.19 (m, 5H, H-arom), 4.89 (d, J = 3.62 Hz, 1H, C*H*-OH), 3.53 (brs, 1H, OH), 2.50-2.40 (m, 1H, C*H*-NH), 2.29 (s, 6H, CH_3-N), 0.75 (d, J = 6.78 Hz, 3H, CH_3-CH)

VI 2.1.16 (1*R*, 2*S*)-1-Hydroxy-*N*,*N*-dimethyl-1-phenylpropan-2-aminium bis(trifluoromethane)sulfonimide 31



$C_{13}H_{18}F_6N_2O_5S_2$
460.41

30 **31**

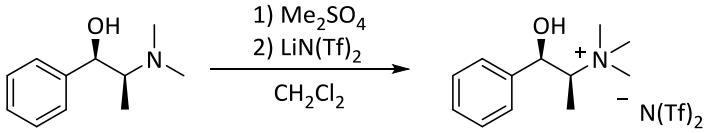
According to procedure VI 2.1.14 compound **31** was prepared from (1*R*,2*S*)-methylephedrine (0.45 g, 2.52 mmol) **30** and bis(trifluoromethane)sulfonimide (0.70 g, 2.52 mmol).

Analytical data was in accordance to literature.[110]

Yield 1.14 g (99%) colorless solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.33-7.26 (m, 5H, H-arom), 5.33 (d, J = 2.24 Hz, 1H, C*H*-OH), 4.28 (brs, 2H, N*H*, O*H*), 3.42-3.32 (m, 1H, C*H*-CH_3), 2.95 (s, 6H, CH_3-NH), 1.14 (d, J = 6.85 Hz, CH_3-CH)

VI 2.1.17 (1*R*, 2*S*)-1-Hydroxy-*N*,*N*,*N*-trimethyl-1-phenylpropan-2-aminium bis(trifluoromethane)sulfonimide 32



$C_{14}H_{20}F_6N_2O_5S_2$
474.43

30 **32**

Compound **30** (3.06 g, 17.05 mmol) was dissolved in anhydrous CH_2Cl_2 and cooled to 0 °C before dimethylsulfate (1.62 ml, 17.05 mmol) was slowly added *via* syringe. The reaction mixture was vigorously stirred at rt for 1 hour. After evaporation of the solvent under reduced pressure, the residue was dissolved in 10 ml H_2O and a solution of lithium bis(trifluoromethane)sulfonimide (5.38 g,

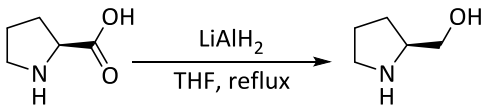
18.76 mmol) in 5 ml H_2O was added. The resulting second phase, which contains the CIL, was extracted with CH_2Cl_2, dried and concentrated in vacuo to yield the product **32** as colorless liquid.

Analytical data was in accordance to literature.[94]

Yield	2.31 g (75%) colorless liquid
^{1}H-NMR (200 MHz, DMSO)	δ_H = 7.42-4.29 (m, 5H, H-arom), 6.00 (brs, 1H, OH), 5.47 (s, 1H, C*H*-OH), 3.69-3.59 (m, 1H, C*H*-CH_3), 3.20 (s, 9H, C*H*$_3$-N), 1.10 (d, J = 6.46 Hz, 3H, C*H*$_3$-CH)

VI 2.2 Synthesis of L-Prolinol-Derived Ionic Liquids

VI 2.2.1 (*S*)-Pyrrolidin-2-ylmethanol 15



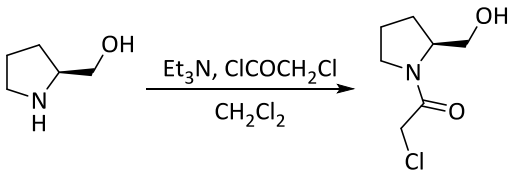
$C_5H_{11}NO$
101.15
15

Compound **15** was prepared according to procedure VI 2.3.1 using L-proline (25.00 g, 217.00 mmol) and lithiumaluminiumhydride (12.35, 325.50 mmol) in 300 ml anhydrous THF. The product was purified by distillation at 70-73 °C and 5 mbar.

Analytical data was in accordance with literature.[205]

Yield	17.19 g (78%) colorless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H= 3.90 (brs, 1H, NH), 3.44-3.17 (m, 2H, C*H*$_2$-OH), 3.11-2.98 (m, 1H, C*H*-NH), 2.80-2.69 (m, 2H, C*H*$_2$-NH), 1.70-1.53 (m, 3H, C*H*$_2$-pyrrol, C*H*$_{2a}$-pyrrol), 1.32-1.19 (m, 1H, C*H*$_{2b}$-pyrrol)

VI 2.2.2 (*S*)-2-Chloro-1-(2-(hydroxymethyl)pyrrolidin-1-yl)ethanone 16



$C_7H_{12}ClNO_2$
177.63

15 **16**

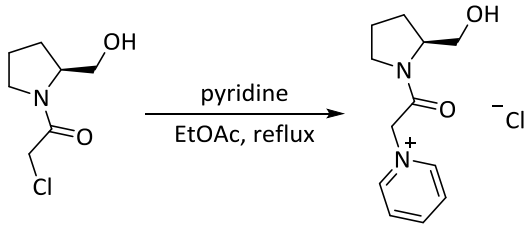
Compound **16** was prepared according to procedure VI 2.1.1 using L-prolinol **15** (7.02 g, 69 mmol), anhydrous triethylamine (9.62 ml, 69 mmol) and chloroacetyl chloride (5.52 ml, 69 mmol) in 100 ml anhydrous CH_2Cl_2. The product was purified by MPLC using CH_2Cl_2/MeOH= 30:1.

Analytical data were in accordance with literature.[206]

Yield 5.70 g (46%) colourless solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 4.21-4.16 (m, 1H, C*H*-NH), 4.05 (s, 2H, CH_2-Cl), 3.84 (brs, 1H, NH), 3.67-3.54 (m, 4H, CH_2-NH, CH_2-OH), 2.07-1.81 (m, 3H, CH_2-pyrrol, CH_{2a}-pyrrol), 1.73-1.61 (m, 1H, CH_{2b}-pyrrol)

VI 2.2.3 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)pyridin-1-ium chloride 17



$C_{12}H_{17}ClN_2O_2$
256.73

16 **17**

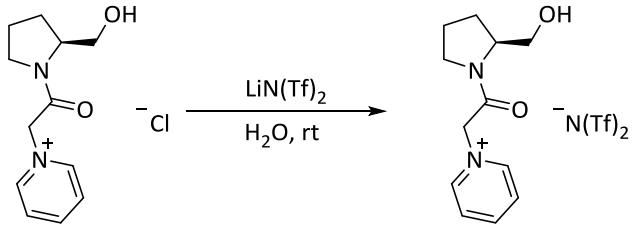
Product **17** was prepared according to VI 2.1.4 using compound **16** (0.51 g, 2.86 mmol) and pyridine (0.23 ml, 2.86 mmol) in 10 ml EtOAc to afford the product as colorless liquid.

Yield 0.69 g (94%) colorless liquid

^{1}H-NMR (400 MHz, MeOD) δ_H = 8.96-8.93 (m, 2H, C*H*-pyridine), 8.72-8.63 (m, 1H, C*H*-pyridine), 8.20-8.13 (m, 2H, C*H*-pyridine), 6.04-5.66 (m, 1H, CH_2-OH), 4.36-4.07 (m, 1H, C*H*-NH), 3.70-3.62 (m, 4H, CH_2-N-pyrrolidine, CH_2-N$^+$), 2.20-1.92 (m, 4H, CH_2-CH_2-pyrrolidine, CH_2-CH_2-pyrrolidine)

^{13}C-NMR (100 MHz, MeOD)	δ_C = 164.92 (s, *C*=O), 147.8/147.74 (2d, d, *C*H-pyridine), 129.4 (2d, *C*H-pyridine), 64.8 (t, CH_2-OH), 62.8 (d, *C*H_2-N-pyrrolidine), 61.63 (d, *C*H-CH_2-OH), 48.0 (t, *C*H_2-N^+), 28.3 (t, *C*H_2-CH_2-N-pyrrolidine), 25.3 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -53.07 (*c* 0.62, MeOH)
$T_{5\%\ onset}$	170 °C
ν_{max}/cm^{-1}	3313 (O-H), 2878 (C-H), 1638 (C=O), 1446 (C=C)
Elemental analysis	calculated: w-% C: 54.14, w-% H: 6.67, w-% N: 10.91 calculated: 0.46xH_2O = w-% C: 54.39, w-% H: 6.82, w-% N: 10.57 measured: w-% C: 54.39, w-% H: 6.76, w-% N: 10.44

VI 2.2.4 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)pyridin-1-ium bis(trifluoromethane)sulfonimide 18



$C_{14}H_{17}F_6N_3O_6S_2$
501.42

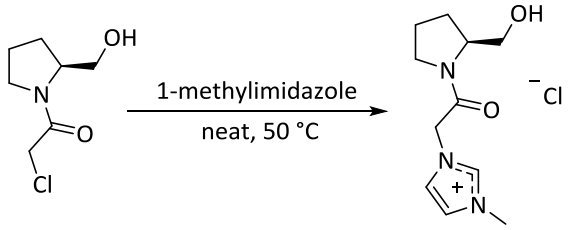
17 **18**

Product **18** was prepared according to VI 2.1.3 using compound **17** (0.42 g, 1.63 mmol) and lithium bis(trifluoromethane)sulfonimide (0.51 g, 1.63 mmol).

Yield	0.72 g (88%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.84-8.82 (m, 2H, C*H*-pyridine), 8.67-8.63 (m, 1H, C*H*-pyridine), 8.16-8.12 (m, 2H, C*H*-pyridine), 5.98-5.56 (m, 2H, CH_2-OH), 4.26-4.10 (m, 1H, C*H*-NH), 3.67-3.48 (m, 4H, CH_2-N-pyrrolidine, CH_2-N^+), 2.15-1.96 (m, 4H, CH_2-CH_2-pyrrolidine, CH_2-CH_2-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.3 (s, *C*=O), 146.2/146.2 (2d, d, *C*H-pyridine), 127.5 (2d, *C*H-pyridine), 119.8 (q, J = 320.5 Hz, CF_3), 63.4 (t, CH_2-OH), 61.8 (d, *C*H_2-N-pyrrolidine), 60.2 (d, *C*H-CH_2-OH), 46.4 (t, *C*H_2-N^+), 26.7 (t, *C*H_2-CH_2-N-pyrrolidine), 23.6 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -29.00 (*c* 0.77, MeOH)
$T_{5\%\ onset}$	242 °C
ν_{max}/cm^{-1}	3098 (O-H), 1653 (C-C), 1455 (C=C), 1347 (C-H), 1177 (C-F_3)

Elemental analysis	calculated: w-% C: 33.53, w-% H: 3.42, w-% N: 8.38
	calculated: 0.67xH_2O = w-% C: 32.75, w-% H: 3.60, w-% N: 8.18
	measured: w-% C: 31.17, w-% H: 3.18, w-% N: 7.94

VI 2.2.5 (*S*)-1-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride 19



$C_{11}H_{18}ClN_3O_2$
259.73

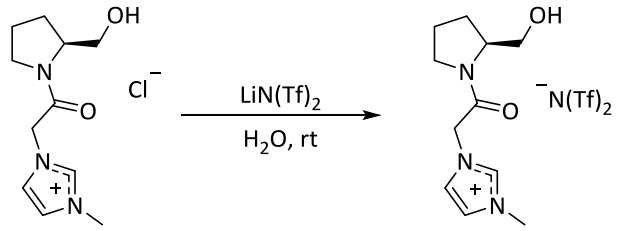
16 **19**

Product **19** was prepared according to VI 2.1.2 using compound **16** (1.00 g, 4.46 mmol) and 1-methylimidazole (0.35 ml, 4.46 mmol).

Analytical data was in accordance with literature.[152]

Yield	1.90 g (96%) colorless solid
Mp	110-115 °C
^{1}H-NMR (400 MHz, MeOH)	δ_H = 7.60-7.58 (m, 2H, C*H*-imidazole), 5.57-5.18 (m, 2H, CH_2-OH), 4.26-4.11 (m, 1H, C*H*-NH), 3.98 (s, 3H, CH_3-N), 3.67-3.58 (m, 4H, CH_2-N-imidazol, CH_2-N), 2.15-1.91 (m, 4H, CH_2-CH_2- pyrrolidine)
$T_{5\%\ onset}$	237 °C
ν_{max}/cm^{-1}	3381 (O-H), 2922 (C-H), 1634 (C=O)
Elemental analysis	calculated: w-% C: 50.83, w-% H: 6.99, w-% N: 16.18
	calculated: 0.41xH_2O = w-% C: 49.46, w-% H: 7.10, w-% N: 15.73
	measured: w-% C: 49.51, w-% H: 7.27, w-% N: 15.67

VI 2.2.6 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 20



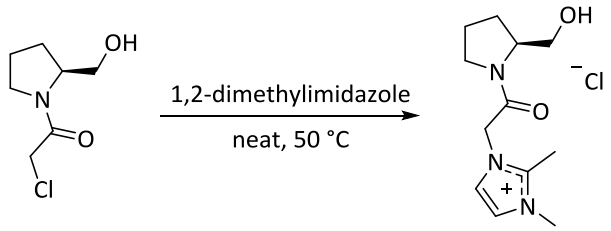
$C_{13}H_{18}F_6N_4O_6S_2$
504.42

19 **20**

Product **20** was prepared according to VI 2.1.3 using compound **19** (0.50 g, 1.93 mmol) and lithium bis(trifluoromethane)sulfonimide (0.61 g, 2.12 mmol).

Yield	0.82 g (63%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 9.03-8.99 (m, 1H, C*H*-imidazole), 7.66 (s, 1H, C*H*-imidazole), 7.60 (s, 1H, C*H*-imidazole), 5.29-5.17 (m, 1H, CH_2-OH), 4.09-4.07 (m, 1H, C*H*-NH), 3.89 (s, 3H, CH_3-N), 3.46-3.36 (m, 4H, CH_2-N-imidazol, CH_2-N), 2.07-1.81 (m, 4H, CH_2-CH_2-pyrrol)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.5 (s, *C*=O), 123.8 (2d, *C*H-imidazole), 122.8 (2d, *C*H-imidazole), 119.4 (q, J = 321.9 Hz, CF_3), 60.5 (t, CH_2-OH), 59.3 (d, *C*H-CH_2-OH), 50.4 (d, *C*H_2-N-pyrrolidine), 45.8 (*C*H_2-N-imidazole), 35.7 (q, CH_3-N^+), 26.4 (t, *C*H_2-CH_2-N-pyrrolidine), 23.4 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -28.24 (*c* 1.09, MeOH)
$T_{5\%\ onset}$	275.5 °C
ν_{max}/cm^{-1}	2962 (O-H), 1650 (C=O), 1175 (C-F_3)
Elemental analysis	calculated: w-% C: 30.95, w-% H: 3.60, w-% N: 11.11 measured: w-% C: 30.85, w-% H: 3.10, w-% N: 10.88

VI 2.2.7 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium chloride 21



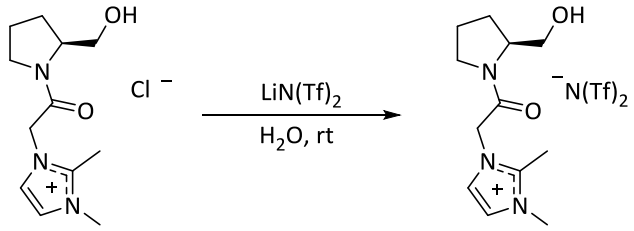
$C_{12}H_{20}ClN_3O_2$
273.76

16 **21**

Product **21** was prepared according to VI 2.1.6 using compound **16** (0.52 g, 2.93 mmol) and 1,2-dimethylimidazole (0.27 g, 2.93 mmol).

Yield	0.77 g (96%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.53-7.45 (m, 2H, C*H*-imidazole), 5.64-5.24 (m, 2H, CH_2-OH), 4.25-4.09 (m, 1H, C*H*-N), 3.87 (s, 3H, CH_3-N), 3.68-3.60 (m, 4H, CH_2-N-imidazole, CH_2-N), 2.59-2.58 (m, 3H, CH_3-CH-imidazole), 2.07-1.97 (m, 4H, CH_2-CH_2-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 164.7 (s, *C*=O), 146.4 (s, *C*-imidazole), 122.2 (d, *C*H-imidazole), 121.9 (d, *C*H-imidazole), 61.3 (t, *C*H_2-OH), 60.0 (d, *C*H-CH_2-OH), 49.7 (d, *C*H_2-N-pyrrolidine), 46.4 (*C*H_2-N-imidazole), 34.2 (q, CH_3-N^+), 26.7 (t, *C*H_2-CH_2-N-pyrrolidine), 23.7 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -46.79 (*c* 1.05, MeOH)
$T_{5\%\ onset}$	180 °C
ν_{max}/cm^{-1}	3365 (O-H), 2956 (C-H), 1638 (C=O)
Elemental analysis	calculated: w-% C: 52.56, w-% H: 7.36, w-% N: 15.35 calculated: 0.50xH_2O = w-% C: 50.97, w-% H: 7.49, w-% N: 14.86 measured: w-% C: 51.10, w-% H: 7.17, w-% N: 14.38

VI 2.2.8 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 22

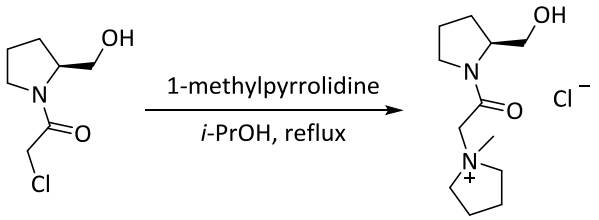


21 $C_{14}H_{20}F_6N_4O_6S_2$ 518.45 **22**

Product **22** was prepared according to VI 2.1.3 using compound **21** (0.77 g, 2.81 mmol) and lithium bis(trifluoromethane)sulfonimide (0.88 g, 3.09 mmol).

Yield	1.21 g (83%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.50-7.39 (m, 2H, C*H*-imidazole), 5.61-5.11 (m, 2H, CH_2-OH), 4.25-4.11 (m, 1H, C*H*-N), 3.87 (s, 3H, CH_3-N), 3.67-3.46 (m, 4H, CH_2-N-imidazole, CH_2-N), 2.57-2.58 (m, 3H, CH_3-CH-imidazole), 2.16-1.83 (m, 4H, CH_2-CH_2-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.9 (s, *C*=O), 146.3 (s, *C*-imidazole), 122.2 (d, *C*H-imidazole), 121.9 (d, *C*H-imidazole), 119.8 (q, J = 320.48 Hz, CF_3), 61.3 (t, *C*H_2-OH), 60.5 (d, *C*H-CH_2-OH), 49.6 (d, *C*H_2-N-pyrrolidine), 46.4 (*C*H_2-N-imidazole), 34.1 (q, CH_3-N^+), 26.6 (t, *C*H_2-CH_2-N-pyrrolidine), 23.6 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -27.57 (*c* 0.83, MeOH)
$T_{5\%\ onset}$	281 °C
ν_{max}/cm^{-1}	2956 (O-H), 1650 (C-C), 1542 (C=C), 1347 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 32.43, w-% H: 3.89, w-% N: 10.81 calculated: 0.16xH_2O = w-% C: 32.25, w-% H: 3.93, w-% N: 10.75 measured: w-% C: 32.32, w-% H: 3.49, w-% N: 10.26

VI 2.2.9 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-1-methylpyrrolidin-1-ium chloride 23



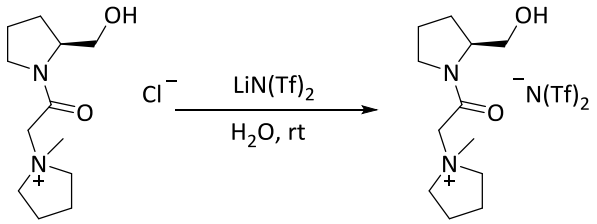
16

$C_{12}H_{23}ClN_2O_2$
262.78
23

Product **23** was prepared according to VI 2.1.8 using compound **16** (0.50 g, 2.83 mmol) and 1-methylpyrrolidine (0.29 ml, 3.83 mmol) in 10 ml *i*-PrOH, to afford the product as colorless liquid.

Yield	0.52 g (70%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 4.80-4.46 (m, 2H, C*H*$_2$-OH), 4.14-4.12 (m, 1H, C*H*-NH), 3.80-3.42 (m, 8H, C*H*$_2$-N pyrrolidine, C*H*$_2$-C*H*$_2$-N pyrrolidine, C*H*$_2$-N), 3.32-3.31 (m, 3H, C*H*$_3$-N), 2.28-1.91 (m, 8H, C*H*$_2$-C*H*$_2$-pyrrolidine, C*H*$_2$-C*H*$_2$-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 162.9 (s, *C*=O), 65.6 (t, CH_2-OH), 62.8 (t, *C*H_2-N-pyrrolidine), 63.4 (d, *C*H-CH_2-OH), 61.3 (2t, *C*H_2-N^+), 59.8 (q, CH_3-N^+), 49.1 (*C*H_2-N-pyrrolidine), 46.5 (t, *C*H_2-CH_2-N-pyrrolidine), 26.5 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine), 23.7 (t, *C*H_2-CH_2-N-pyrrolidine), 21.3/21.2 (2t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -34.06 (*c* 0.75, MeOH)
$T_{5\%\ onset}$	222.1 °C
ν_{max}/cm^{-1}	3359 (O-H), 2482 (C-H), 1643 (C=O)
Elemental analysis	calculated: w-% C: 54.85, w-% H: 8.l83, w-% N: 1.66 calculated: 1.93xH_2O = w-% C: 48.44, w-% H: 9.10, w-% N: 9.41 measured: w-% C: 48.49, w-% H: 9.11, w-% N: 9.22

VI 2.2.10 (*S*)-1-(2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)-1-methylpyrrolidin-1-ium bis(trifluoromethane)sulfonimide 24



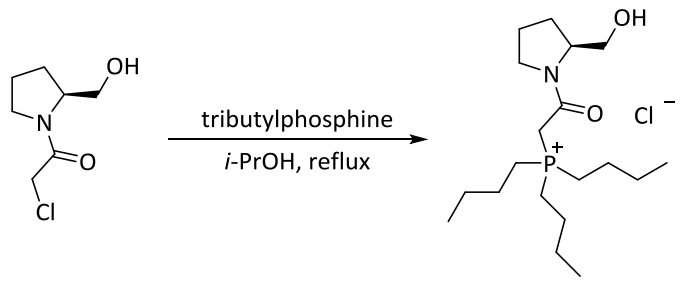
$C_{14}H_{23}F_6N_3O_6S_2$
507.47

23 **24**

Product **24** was prepared according to VI 2.1.3 using compound **23** (0.49 g, 1.90 mmol) and lithium bis(trifluoromethane)sulfonimide (0.60 g, 2.09 mmol).

Yield	0.62 g (64%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 4.78-4.33 (m, 1H, C*H*$_2$-OH), 4.18-4.08 (m, 1H, C*H*-NH), 3.84-3.46 (m, 8H, C*H*$_2$-N-pyrrolidine, C*H*$_2$-C*H*$_2$-N-pyrrolidine, C*H*$_2$-N), 3.39-3.32 (m, 3H, C*H*$_3$-N), 2.28-2.24 (m, 4H, C*H*$_2$-C*H*$_2$-pyrrolidine), 2.13-1.80 (m, 4H, C*H*$_2$-C*H*$_2$-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 162.7 (s, *C*=O), 119.8 (q, J = 320.41 Hz, CF_3), 65.7 (t, CH_2-OH), 62.8 (t, *C*H_2-N-pyrrolidine), 61.4 (2t, *C*H_2-N^+), 59.8 (q, CH_3-N^+), 58.9 (d, *C*H-CH_2-OH), 49.1 (*C*H_2-N-pyrrolidine), 46.4 (t, *C*H_2-CH_2-N-pyrrolidine), 27.6 (t, *C*H_2-CH_2-CH_2-N-pyrrolidine), 23.6 (t, *C*H_2-CH_2-N-pyrrolidine), 21.3/21.2 (2t, *C*H_2-CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -23.11 (*c* 0.96, MeOH)
$T_{5\%\ onset}$	276 °C
ν_{max}/cm^{-1}	2961 (O-H), 1648 (C-C), 1452 (C-H), 1177 (C-F_3)
Elemental analysis	calculated: w-% C: 29.94, w-% H: 4.40, w-% N: 8.73 measured: w-% C: 30.28, w-% H: 3.96, w-% N: 8.21

VI 2.2.11 (*S*)-Tributyl(2-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)phosphonium chloride 25



$C_{19}H_{39}ClNO_2P$
379.95

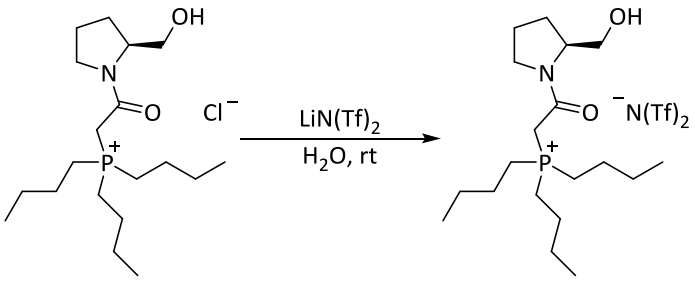
16 **25**

Product **25** was prepared according to VI 2.1.8 using compound **26** (0.51 g, 2.89 mmol) and tributylphosphine (1.71 ml, 2.89 mmol) in 10 ml *i*-PrOH, to afford the product as colorless liquid.

Yield	0.65 g (59%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 4.49-4.18 (m, 2H, CH_2-OH), 4.16-4.09 (m, 1H, C*H*-NH), 3.64-3.43 (m, 8H, 3CH_2-P^+, CH_2-N-pyrrolidine), 2.38-2.29 (m, 8H, C*H*$_2$-CH_2-pyrrolidine, CH_2-C*H*$_2$-pyrrolidine), 2.11-2.19 (m, 19H, CH-N-pyrrolidine, P^+-C*H*$_2$-C*H*$_2$-C*H*$_2$), 1.04-0.97 (m, 9H, P^+-CH_2-CH_2-CH_2-C*H*$_3$)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.9 (s, C=O), 63.6 (t, *C*H_2-OH), 61.4 (t, CH_2-P^+), 59.5 (d, *C*H-N-pyrrolidine), 45.5 (t, *C*H_2-N-pyrrolidine), 42.0 (t, *C*H_2-CH_2-N-pyrrolidine 23.2/26.7 (2t, *C*H_2-CH_2-CH_2-CH_3), 24.4/24.3 (3t, CH_2-*C*H_2-CH_2-CH_3), 19.1.4/18.6 (2t, CH_2-CH_2-*C*H_2-CH_3), 12.5 (q, CH_2-CH_2-*C*H_3)
Specific Rotation	α_D^{20} = -25.85 (*c* 0.79, MeOH)
$T_{5\%\ onset}$	195 °C
ν_{max}/cm^{-1}	3287 (O-H), 2958 (C-H), 1630 (C=O)
Elemental analysis[xi]	

[xi] Caused by the hygroscopy of phosphonium chloride **25**, we were not able to obtain a matching elemental analysis. The compound was therefore directly used for anion exchange towards bis(trifluoromethane)sulfonimide **26** that was completely characterized.

VI 2.2.12 (*S*)-Tributyl(2-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-oxoethyl)phosphonium bis(trifluoromethane)sulfonimide 26



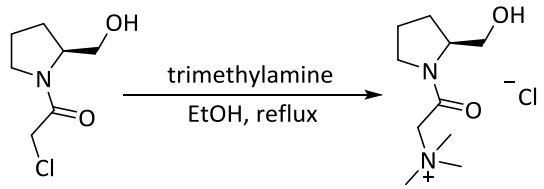
$C_{21}H_{39}F_6N_2O_6PS_2$
624.64

25 **26**

Product **26** was prepared according to VI 2.1.3 using compound **25** (0.55 g, 1.45 mmol) and lithium bis(trifluoromethane)sulfonimide (0.46 g, 1.59 mmol).

Yield	0.81 g (70%) colourless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 4.16-4.07 (m, 1H, C*H*-NH), 3.69-3.42 (m, 6H, CH_2-OH, CH_2-N-pyrrolidine, CH_2-P^+), 2.25-2.19 (m, 4H, CH_2-CH_2-pyrrolidine, CH_2-CH_2-pyrrolidine), 2.05-1.91 (m, 6H, P^+-CH_2-CH_2-CH_2-CH_3,), 1.49-1.40 (m, 12H, P^+-CH_2-CH_2-CH_2, P^+-CH_2-CH_2-CH_2), 0.96-0.90 (m, 9H, P^+-CH_2-CH_2-CH_2-CH_3)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 164.3 (s, C=O), 119.8 (q, J = 321.4 Hz, CF_3), 63.2 (t, *C*H_2-OH), 61.8 (d, *C*H-N-pyrrolidine), 49.0 (t, CH_2-P^+), 45.7 (t, *C*H_2-N-pyrrolidine), 42.5 (t, *C*H_2-CH_2-N-pyrrolidine), 23.2/26.7 (3t, *C*H_2-CH_2-CH_2-CH_3), 24.4/24.3 (3t, CH_2-*C*H_2-CH_2-CH_3), 19.1/18.6 (3t, CH_2-CH_2-*C*H_2-CH_3), 13.2 (q, CH_2-CH_2-*C*H_3)
Specific Rotation	α_D^{20} = -17.85 (*c* 1.01, MeOH)
$T_{5\%\ onset}$	220 °C
ν_{max}/cm^{-1}	2962 (O-H), 1637 (C-C), 1437 (C=C), 1348 (C-H), 1180 (C-F_3)
Elemental analysis	calculated: w-% C: 40.38, w-% H: 6.29, w-% N: 4.48 calculated: 0.06xH_2O = w-% C: 40.31, w-% H: 6.30, w-% N: 4.48 measured: w-% C: 40.33, w-% H: 6.40, w-% N: 4.38

VI 2.2.13 (*S*)-2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium chloride **27**



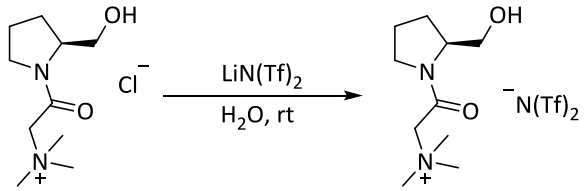
$C_{10}H_{21}ClN_2O_2$
236.74

16 **27**

Product **27** was prepared according to VI 2.1.12 using compound **16** (0.53 g, 3.01 mmol) and trimethylamine (0.30 ml, 3.90 mmol) in 10 ml anhydrous EtOH to afford the product as colorless solid.

Yield	0.71 g (99%) colorless solid
Mp	124-127 °C
^{1}H-NMR (200 MHz, MeOD)	δ_H = 4.68-4.42 (m, 1H, C*H*$_2$-OH), 4.17-4.12 (m, 1H, C*H*-NH), 3.67-3.47 (m, 4H, C*H*$_2$-N-imidazole, C*H*$_2$-N), 3.37-3.35 (m, 9H, C*H*$_3$-N), 2.06-1.87 (m, 4H, C*H*$_2$-C*H*$_2$-pyrrolidine)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 162.4 (s, *C*=O), 62.6 (t, *C*H$_2$-OH), 60.18 (d, *C*H$_2$-N-pyrrolidine), 59.0 (d, *C*H-CH$_2$-OH), 52.9 (3q, *C*H$_3$-N$^+$), 46.0 (*C*H$_2$-N$^+$), 26.2 (t, *C*H$_2$-CH$_2$-N-pyrrolidine), 23.4 (t, *C*H$_2$-CH$_2$-CH$_2$-N-pyrrolidine)
Specific Rotation	α_D^{20} = -35.37 (*c* 0.89, MeOH)
$T_{5\%\ onset}$	192.1 °C
ν_{max}/cm^{-1}	3230 (O-H), 2951 (C-H), 1645 (C=O)
Elemental analysis	calculated: w-% C: 50.73, w-% H: 8.49, w-% N: 11.83 calculated: 0.37xH_2O = w-% C: 49.35, w-% H: 9.00, w-% N: 11.51 measured: w-% C: 49.48, w-% H: 8.80, w-% N: 10.94

VI 2.2.14 (*S*)-2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium bis(trifluoromethane)sulfonimide 28



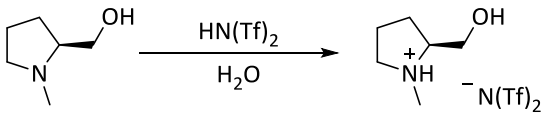
$C_{12}H_{21}F_6N_3O_6S_2$
481.43

27 **28**

Product **28** was prepared according to VI 2.1.3 using compound **27** (0.54 g, 2.26 mmol) and lithium bis(trifluoromethane)sulfonimide (0.71 g, 2.49 mmol).

Yield	0.96 g (86%) colorless liquid
^{1}H-NMR (200 MHz, MeOD)	δ_H = 4.67-4.29 (m, 1H, C*H*$_2$-OH), 4.17-4.12 (m, 1H, C*H*-NH), 3.65-3.42 (m, 4H, C*H*$_2$-N-imidazole, C*H*$_2$-N), 3.37-3.33 (m, 9H, C*H*$_3$-N), 2.01-1.94 (m, 4H, C*H*$_2$-C*H*$_2$-pyrrol)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 162.3 (s, *C*=O), 119.3 (q, J = 320.5 Hz, CF_3), 63.3 (t, *C*H$_2$-OH), 61.2 (d, *C*H$_2$-N-pyrrolidine), 59.7 (d, *C*H-CH$_2$-OH), 53.4 (3q, *C*H$_3$-N$^+$), 46.4 (*C*H$_2$-N$^+$), 26.5 (t, *C*H$_2$-CH$_2$-N-pyrrolidine), 23.5 (t, *C*H$_2$-CH$_2$-CH$_2$-N-pyrrolidine)
Specific Rotation	α_D^{20} = -17.59 (*c* 1.01, MeOH)
$T_{5\%\ onset}$	257 °C
ν_{max}/cm^{-1}	2969 (O-H), 1682 (C-C), 1347 (C-H), 1179 (C-F_3)
Elemental analysis	calculated: w-% C: 29.94, w-% H: 4.40, w-% N, 8.73 measured: w-% C: 30.28, w-% H: 3.96, w-% N: 8.21

VI 2.2.15 (2*S*)-2-(Hydroxymethyl)-1-methylpyrrolidin-1-ium bis(trifluoromethan)sulfonimide 35



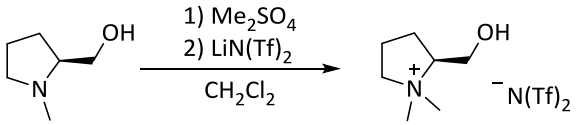
$C_8H_{14}F_6N_2O_5S_2$
396.32

34 **35**

Product **35** was prepared according to VI 2.1.16 using commercially available *N*-methylprolinol **34** (0.51 g, 5.00 mmol) and bis(trifluoromethan)sulfonimide (1.41 g, 5.00 mmol) in 25 ml H_2O_{dest}.

Yield	1.90 g (99%) light yellow liquid
^{1}H-NMR (200 MHz, DMSO)	δ_H = 3.66-3.64 (m, 2H, C*H*$_2$-OH), 3.38-3.27 (m, 1H, C*H*$_{2a}$-N-pyrrolidine), 3.19-3.01 (m, 1H, C*H*$_{2b}$-N-pyrrolidine), 2.92-2.79 (m, C*H*-CH$_2$-OH), 2.69 (s, 3H, CH$_3$-N$^+$), 2.06-1.59 (m, 4H, C*H*$_2$-CH$_2$-pyrrolidine, CH$_2$-C*H*$_2$-pyrrolidine)
^{13}C-NMR (50 MHz, DMSO)	δ_C = 119.4 (q, J = 321.9 Hz, CF$_3$), 68.4 (q, CH$_3$-N$^+$), 59.4 (t, CH$_2$-OH), 59.3 (t, CH$_2$-N-pyrrolidine), 39.6 (d, CH-CH$_2$-OH), 26.0 (t, CH$_2$ *C*H$_2$-CH$_2$-N-pyrrolidine), 21.7 (t, *C*H$_2$ CH$_2$-CH$_2$-N-pyrrolidine)
Specific Rotation	α_D^{20} = -14.21 (*c* 0.95, MeOH)
$T_{5\%\ onset}$	298 °C
ν_{max}/cm^{-1}	3001 (O-H), 1423 (C-C), 1051 (C-F$_3$)
Elemental analysis	calculated: w-% C: 24.25, w-% H: 3.56, w-% N: 7.07
	measured: w-% C: 24.18, w-% H: 3.63, w-% N: 6.99

VI 2.2.16 (*S*)-2-(Hydroxymethyl)-1,1-dimethylpyrrolidin-1-ium bis(trifluoromethane)sulfonimide 36



$C_9H_{16}F_6N_2O_5S_2$
410.35

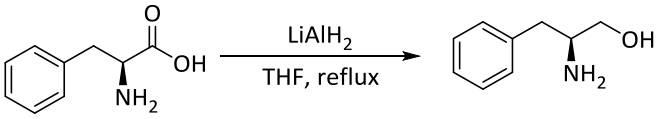
34 **36**

Product **36** was prepared according to VI 2.1.17 using compound **34** (1.02 ml, 8.60 mmol), dimethylsulfate (0.81 ml, 8.60 mmol) and lithium bis(trifluoromethane)sulfonimide (2.72 g, 9.46 mmol).

Yield	3.04 g (86%) colourless solid
Mp	109-110 °C
^{1}H-NMR (200 MHz, CH_2Cl_2)	δ_H = 4.13-4.05 (m, C*H*-CH_2-OH), 3.94-3.79 (m, 2H, C*H*$_2$-OH), 3.60-3.50 (m, 2H, C*H*$_2$-N-pyrrolidine), 3.31 (s, 3H, CH_3-N^+), 3.04 (s, 3H, CH_3-N^+), 2.38-2.12 (m, 3H, C*H*$_2$-CH_2-pyrrolidine, CH_2-C*H*$_{2a}$-pyrrolidine), 1.96-1.80 (m, 1H, CH_2-C*H*$_{2b}$-pyrrolidine)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 119.8 (q, J = 320.47 Hz, CF_3), 75.9 (q, *C*H_3-N^+), 67.6 (q, *C*H_3-N^+), 58.7 (t, CH_2-OH), 52.8 (t, *C*H_2-N-pyrrolidine), 44.3 (d, *C*H-CH_2-OH), 23.8 (t, CH_2 *C*H_2-CH_2-N-pyrrolidine), 19.5 (t, *C*H_2 CH_2-CH_2-N-pyrrolidine)
Specific Rotation	α_D^{20} = -30.01 (*c* 0.85, MeOH)
$T_{5\%\ onset}$	377 °C
ν_{max}/cm^{-1}	2938 (O-H), 1473 (C-C)
Elemental analysis	calculated: w-% C: 26.34, w-% H: 3.93, w-% N: 6.83 measured: w-% C: 26.42, w-% H: 3.91, w-% N: 6.73

VI 2.3 Synthesis of L-Phenylalanine-Derived Ionic liquids

VI 2.3.1 (*S*)-2-Amino-3-phenylpropan-1-ol 37



$C_9H_{13}NO$
151.21
37

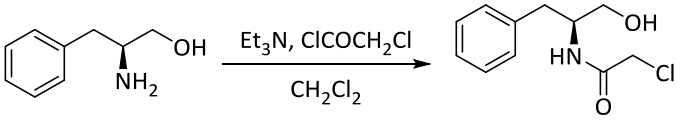
L- Phenylalanine (5.00 g, 30.26 g) was suspended in 200 ml of dry THF and cooled to 0 °C using an ice bath under inert atmosphere. Lithiumaluminiumhydride (3.45 g, 90.78 mmol) was added in small portion and the reaction mixture was heated to reflux for 24 hours. After full conversion the reaction mixture was cooled to 0 °C and 4 ml H_2O and 4 ml NaOH were added slowly to hydrolyze the successive $LiAlH_4$ and additional water was added until no evolution of gas could be observed. After filtration of the aluminum hydroxide and evaporation of the solvent under reduced pressure the product **37** could be collected as yellow crystals.

Analytical data was in accordance to literature.[207]

Yield 4.47 g (97%) yellow solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.22-7.07 (m, 5H, H-arom), 3.54 (dd, J_1 = 3.84 Hz, J_2 = 10.79 Hz, 1H, CH_{2b}-OH), 3.35-3.26 (m, 1H, CH_{2a}-OH), 3.08-2.96 (m, 1H, CH-NH_2), 2.70 (dd, J_1 = 5.12 Hz, J_2 = 13.63 Hz, 1H, Ph-CH_{2a}), 2.48-2.37 (m, 4H, Ph-C$H_{2b,}$ OH, NH_2)

VI 2.3.2 (*S*)-2-Chloro-N-(1-hydroxy-3-phenylpropan-2-yl)acetamide 38



$C_{11}H_{14}ClNO_2$
227.69

37 **38**

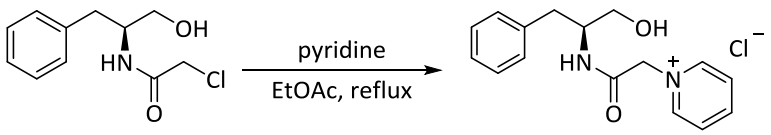
Compound **38** was prepared according to procedure VI 2.1.1 using L-phenylalaninol **37** (4.48 g, 31 mmol), anhydrous triethylamine (4.30 ml, 31 mmol) and chloroacetyl chloride (2.47 ml, 31 mmol) in 100 ml anhydrous CH_2Cl_2. The product was purified by MPLC using CH_2Cl_2/MeOH= 8:1

Analytical data was in accordance to literature.[206]

Yield 5.21 g (70%) colorless solid

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.30-7.12 (m, 5H, H-arom), 6.83 (brs, 1H, OH), 4.20-4.15 (m, 1H, CH-NH), 4.02 (s, 2H, CH_2-Cl), 3.65 (m, 2H, CH_2-OH), 2.94 (d, J = 8.85 Hz, 2H, CH_2-CH), 2.75 (brs, 1H, NH)

VI 2.3.3 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium chloride 39



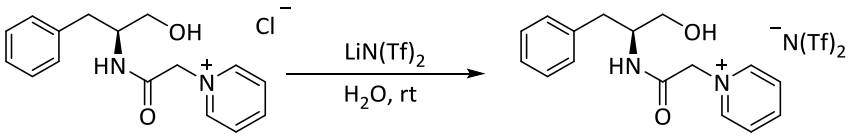
$C_{16}H_{19}ClN_2O_2$
306.79

38 **39**

Product **39** was prepared according to VI 2.1.4 using compound **38** (1.00 g, 4.46 mmol) and pyridine (0.37 ml, 4.46 mmol) in 15 ml EtOAc, to afford the product as colorless solid.

Yield	1.24 g (90%) colorless solid
Mp	111-114 °C
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.79 (d, J = 5.50 Hz, 1H, *CH*-N$^+$-pyridine), 8.63 (t, J= 7.24 Hz, 1H, C*H*-pyridine), 7.16 (t, J = 7.16 Hz, 2H, C*H*-pyridine) 7.27-7.18 (m, 5H, H-arom), 5.48-5.29 (m, 2H, CH_2-N$^+$), 4.22-4.10 (m, 1H, C*H*-NH), 3.68-3.46 (m, 2H, CH_2-OH), 3.00-2.70 (m, 2H, CH_2-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 165.6 (s, *C*=O), 147.5/147.3 (2d, *C*H-N$^+$-pyridine), 139.6 (s, *C*-arom), 130.4 (2d, *C*H-arom), 129.5 (2d, *C*H-arom), 128.9 (2d, *C*H-arom), 127.5 (2d, *C*H-arom), 64.0 (t, CH_2-N$^+$), 63.1 (t, CH_2-OH), 55.1 (d, *C*H-NH), 38.1 (t, *C*H_2-CH)
Specific Rotation	α_D^{20} = -14.26 (*c* 1.00, MeOH)
$T_{5\%\ onset}$	113.4 °C
ν_{max}/cm^{-1}	3052 (O-H), 1668 (C-C), 1567 (C=C), 1481 (C-H)
Elemental analysis	calculated: w-% C: 62.64, w-% H: 6.24, w-% N: 9.13 calculated: 0.35xH_2O = w-% C: 61.38, w-% H: 6.34, w-% N: 8.95 measured: w-% C: 61.38, w-% H: 5.99, w-% N: 8.74

VI 2.3.4 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bis(trifluoromethane)sulfonimide 40



$C_{18}H_{19}F_6N_3O_6S_2$
551.48

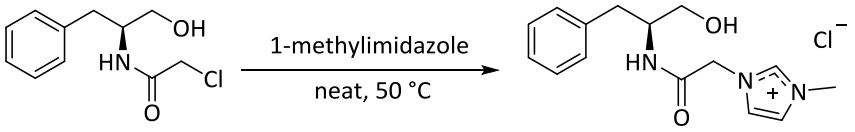
39 **40**

Product **40** was prepared according to VI 2.1.3 using compound **39** (0.83 g, 2.71 mmol) and lithium bis(trifluoromethane)sulfonimide (0.86 g, 2.98 mmol).

Yield	0.83 g (56%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.96-8.49 (m, 3H, *CH*- pyridine), 8.13-8.09 (m, 3H, C*H*-pyridine), 7.31-7.21 (m, 5H, H-arom), 5.40-5.29 (m, 2H, CH_2-N$^+$), 4.47-4.15 (m, 1H, C*H*-NH), 3.61 (ddd, J_1 = 34.04 Hz, J_2 = 11.17 Hz, J_3 = 5.57 Hz, 2H, CH_2-OH), 2.87 (ddd, J_1 = 72.28 Hz, J_2 = 13.74 Hz, J_3 = 7.36 Hz, 2H, CH_2-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 162.6 (s, *C*=O), 145.3/144.4 (2d, *C*H-N$^+$-pyridine), 136.6 (s, *C*-arom), 127.5 (2d, *C*H-arom), 126.7 (2d, *C*H-arom), 126.1 (2d, *C*H-arom), 124.7 (2d, *C*H-arom), 118.3 (q, J = 320.5 Hz, CF_3), 61.1 (t, CH_2-N$^+$), 60.2 (t, CH_2-OH), 52.2 (d, *C*H-NH), 35.2 (t, *C*H_2-CH)

Specific Rotation	α_D^{20} = -17.49 (*c* 1.05, CH_2Cl_2)
$T_{5\% onset}$	165 °C
ν_{max}/cm^{-1}	2923 (O-H), 1688 (C-C), 1545 (C=C), 1346 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 39.20, w-% H: 3.47, w-% N: 7.62 measured: w-% C: 39.03, w-% H: 3.35, w-% N: 7.26

VI 2.3.5 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride 41



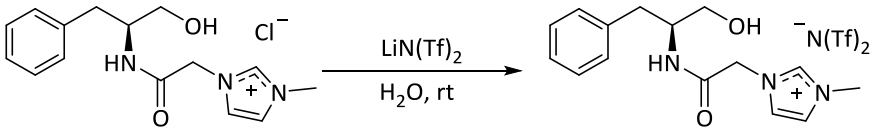
$C_{15}H_{20}ClN_3O_2$
309.79

37 **41**

Product **41** was prepared according to VI 2.1.2 using compound **17** (1.00 g, 4.46 mmol) and 1-methylimidazole (0.35 ml, 4.46 mmol).

Yield	1.90 g (96%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.89 (s, 1H, C*H*-imidazole), 7.58-7.57 (m, 1H, C*H*-imidazole), 7.48-7.47 (m, 1H, C*H*-imidazole), 7.29-7.21 (m, 5H, *H*-arom), 4.96 (q, J = 14.63 Hz, 2H, CH_2-N-imidazole), 4.20-4.14 (m, 1H, C*H*-NH), 3.94 (s, 3H, CH_3-N$^+$), 3.60 (ddd, J_1 = 29.79 Hz, J_2 = 11.17 Hz, J_3 = 5.35 Hz, 2H, CH_2-OH), 2.97-2.74 (m, 2H, CH_2-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 166.5 (s, *C*=O), 139.6 (s, *C*-arom), 130.3 (2d, *C*-arom), 129.5 (2d, *C*-arom), 127.5 (d, *C*-arom), 124.8 (d, *C*-arom), 124.4 (d, *C*-arom), 64.1 (t, *C*H_2-OH), 54.9 (d, *C*H-NH), 52.0 (s, *C*H_2-N), 38.0 (t, *C*H_2-CH), 36.6 (q, CH_3-N$^+$)
Specific Rotation	α_D^{20} = -7.52 (*c* 0.85, MeOH)
$T_{5\% onset}$	86 °C
ν_{max}/cm^{-1}	2950 (O-H), 1676 (C-C), 1562 (C=C), 1265 (C-H)
Elemental analysis	calculated: w-% C: 58.16, w-% H: 6.51, w-% N: 13.56 calculated: 0.55xH_2O = w-% C: 56.35, w-% H: 6.65, w-% N: 13.14 measured: w-% C: 56.37, w-% H: 6.53, w-% N: 13.36

VI 2.3.6 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 42



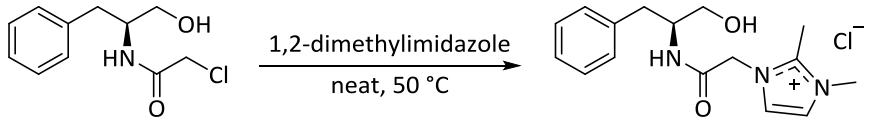
$C_{17}H_{20}F_6N_4O_6S_2$
554.48

41 **42**

Product **42** was prepared according to VI 2.1.3 using compound **41** (0.51 g, 1.64 mmol) and lithium bis(trifluoromethane)sulfonimide (0.52 g, 1.80 mmol).

Yield	0.61 g (67%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.80 (s, 1H, C*H*-imidazole), 7.55-7.54 (m, 1H, C*H*-imidazole), 7.42-7.41 (m, 1H, C*H*-imidazole), 7.31-7-21 (m, 5H, H-arom), 4.70-4.77 (m, 2H, CH_2-N-imidazole), 4.19-4.16 (m, 1H, C*H*-NH), 3.93 (s, 3H, CH_3-N^+), 3.59 (ddd, J_1 = 29.89 Hz, J_2 = 11.13 Hz, J_3 = 5.39 Hz, 2H, CH_2-OH), 2.85 (ddd, J_1 = 80.48 Hz, J_2 = 10.31 Hz, J_3 = 7.67 Hz, 2H, CH_2-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 165.1 (s, *C*=O), 138.2 (s, *C*-arom), 137.7 (d, C-arom), 128.9 (2d, *C*-arom), 128.1 (2d, *C*-arom), 126.1 (d, *C*-arom), 123.5 (d, C-arom), 123.1 (d, C-arom), 119.8 (q, J = 320.4 Hz, CF_3), 62.6 (t, *C*H_2-OH), 53.4 (d, *C*H-NH), 50.5 (s, *C*H_2-N), 38.0 (t, *C*H_2-CH), 36.6 (q, CH_3-N^+)
Specific Rotation	α_D^{20} = -12.95 (*c* 0.98, CH_2Cl_2)
$T_{5\%\ onset}$	141 °C
ν_{max}/cm^{-1}	3160 (O-H), 1686 (C-C), 1547 (C=C), 1346 (C-H), 1176 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 36.82, w-% H: 3.64, w-% N: 10.10 measured: w-% C: 36.50, w-% H: 3.64, w-% N: 9.86

VI 2.3.7 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium chloride 43



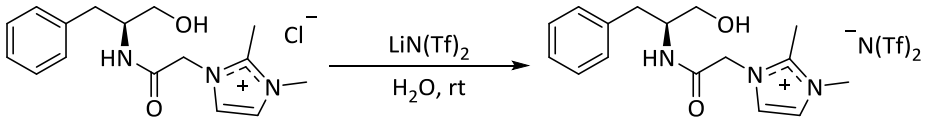
$C_{16}H_{22}ClN_3O_2$
323.82

37 **43**

Product **43** was prepared according to VI 2.1.6 using compound **37** (1.00 g, 4.46 mmol) and 1,2-dimethylimidazole (0.42 ml, 4.46 mmol).

Yield	1.34 g (93%) yellow liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.46 (d, J = 2.01 Hz, 1H, *H*-imidazole), 7.35 (d, J = 2.12 Hz, 1H, *H*-imidazole) 7.26 (m, 6H, *H*-imidazole, *H*-arom), 4.93 (m, 2H, C*H*$_2$-N-imidazole), 4.23-4.13 (m, 1H, C*H*-NH), 3.81 (s, 3H, C*H*$_3$-N$^+$), 3.68-347 (m, 2H, C*H*$_2$-OH), 3.00-2.71 (m, 2H, C*H*$_2$-CH), 2.36 (s, 3H, CH$_3$-imidazole)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 165.1 (s, *C*=O), 139.7 (s, *C*-arom), 130.4 (2d, C-arom), 129.5 (2d, *C*-arom), 127.48 (d, *C*-arom), 126.1 (d, *C*-arom), 123.5 (2d, C-arom), 64.3 (t, *C*H$_2$-OH), 50.9 (d, *C*H-NH), 38.2 (t, *C*H$_2$-CH), 35.5 (q, CH$_3$-N$^+$), 9.6 (q, CH$_3$-imidazole)
Specific Rotation	α_D^{20} = -6.80 (*c* 1.06, MeOH)
$T_{5\%\ onset}$	176 °C
ν_{max}/cm^{-1}	3240 (O-H), 1676 (C-C), 1579 (C=C), 1452 (C-H)
Elemental analysis	calculated: w-% C: 59.35, w-% H: 6.85, w-% N: 12.98 calculated: 0.85xH_2O = w-% C: 56.67, w-% H: 7.04, w-% N: 12.39 measured: w-% C : 56.62, w-% H: 6.88, w-% N: 12.38

VI 2.3.8 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2,3-dimethyl-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide 44



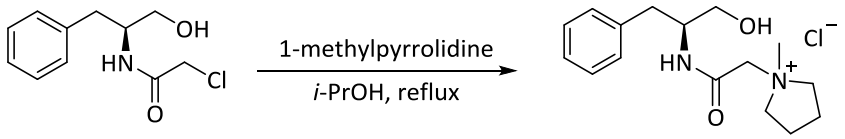
$C_{18}H_{22}F_6N_4O_6S_2$
568.51

43 **44**

Product **44** was prepared according to VI 2.1.3 using compound **43** (0.64 g, 2.00 mmol) and lithium bis(trifluoromethane)sulfonamide (0.63 g, 2.20 mmol).

Yield	0.56 g (50%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.43 (d, J = 2.01 Hz, 1H, *H*-imidazole), 7.31-7.19 (m, 6H, *H*-imidazole, *H*-arom), 4.93 (m, 2H, C*H*$_2$-N-imidazole), 4.23-4.19 (m, 1H, C*H*-NH), 3.81 (s, 3H, C*H*$_3$-N$^+$), 3.60 (ddd, J_1 = 30.49 Hz, J_2 = 11.09 Hz, J_3 = 5.47 Hz, 2H, C*H*$_2$-OH), 2.84 (ddd, J_1 = 101.46 Hz, J_2 = 13.71 Hz, J_3 = 7.45 Hz, 2H, C*H*$_2$-CH), 2.35 (s, 3H, CH$_3$-imidazole)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 164.9 (s, *C*=O), 145.9 (s, *C*-arom), 138.3 (s, *C*-imidazole), 128.9 (2d, *C*H-arom), 128.1 (2d, *C*H-arom), 126.1 (d, *C*-arom), 121.4 (2d, *C*-arom), 119.8 (q, J = 320.5 Hz, CF_3), 62.9 (t, *C*H$_2$-OH), 53.4 (d, *C*H-NH), 49.5 (t, *C*H$_2$-N), 36.8 (t, *C*H$_2$-CH), 34.1 (q, *C*H$_3$-N$^+$), 8.2 (q, *C*H$_3$-imidazole)
Specific Rotation	α_D^{20} = -12.91 (*c* 1.07, CH_2Cl_2)
$T_{5\%\ onset}$	180 °C
ν_{max}/cm^{-1}	2958 (O-H), 1680 (C-C), 1541 (C=C), 1346 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 38.03, w-% H: 3.90, w-% N: 9.86 measured: w-% C: 38.31, w-% H: 3.77, w-% N: 9.45

VI 2.3.9 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1-methylpyrrolidin-1-ium chloride 45



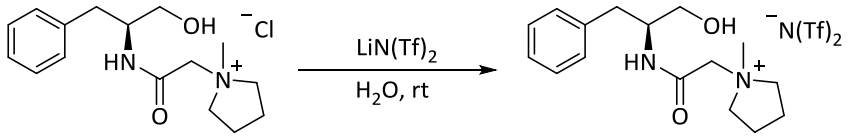
$C_{16}H_{25}ClN_2O_2$
312.84

37 **45**

Product 45 was prepared according to VI 2.1.8 using compound 37 (1.00 g, 4.46 mmol) and trimethylamine (0.55 ml, 4.91 mmol) in 15 ml *i*-PrOH, to afford the product as yellow solid.

Yield	0.56 g (50%) yellow solid
Mp	151-154 °C
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.28-7.16 (m, 5H, *H*-arom), 4.23-4.25 (m, 1H, C*H*-NH), 4.02 (q, J = 12.97 Hz, 2H, CH_2-N$^+$), 3.69-3.45 (m, 6H, CH_2-N-pyrrolidine, CH_2-OH), 3.04 (s, 3H, CH_3-N$^+$), 2.84 (ddd, J_1 = 107.34 Hz, J_2 = 13.77 Hz, J_3 = 7.55 Hz, 2H, CH_2-CH), 2.17-2.14 (m, 4H, CH_2-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 161.8 (s, *C*=O), 136.9 (s, *C*-arom), 127.6 (2d, *C*H-arom), 126.6 (2d, *C*H-arom), 124.6 (d, *C*H-arom), 63.7/63.6 (2t, *C*H_2-N$^+$-pyrolidine), 61.6 (t, *C*H_2-OH), 51.6 (q, *C*H_3-N$^+$), 47.5 (d, *C*H-NH), 35.2 (t, *C*H_2-CH), 19.7/19.6 (t, CH_2-pyrrolidine)
Specific Rotation	α_D^{20} = -29.15 (*c* 1.02, MeOH)
$T_{5\%\ onset}$	182 °C
ν_{max}/cm^{-1}	2959 (O-H), 1666 (C-C), 1576 (C=C), 1492 (C-H)
Elemental analysis	calculated: w-% C: 61.43, w-% H: 8.05, w-% N: 8.95 measured: w-% C: 61.33, w-% H: 7.81, w-% N: 8.61

VI 2.3.10 (*S*)-1-(2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1-methylpyrrolidin-1-ium bis(trifluoromethane)sulfonimide 46



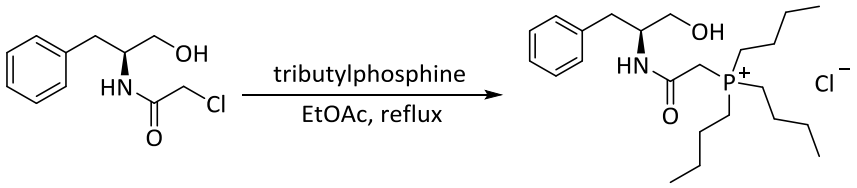
$C_{18}H_{25}F_6N_3O_6S_2$
557.52

45 **46**

Product **46** was prepared according to VI 2.1.3 using compound **45** (1.17 g, 3.75 mmol) and lithium bis(trifluoromethane)sulfonimide (1.18 g, 4.13 mmol).

Yield	1.43 g (68%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.28-7.16 (m, 5H, *H*-arom), 4.34-4.21 (m, 1H, C*H*-NH), 4.02 (q, J = 12.97 Hz, 2H, CH_2-N$^+$), 3.69-3.45 (m, 6H, CH_2-N-pyrrolidine, CH_2-OH), 3.04 (s, 3H, CH_3-N$^+$), 2.96-2.63 (m, 2H, CH_2-CH), 2.17-2.14 (m, 4H, CH_2-pyrrolidine)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 164.5 (s, *C*=O), 139.6 (s, *C*-arom), 130.4 (2d, *C*H-arom), 129.5 (2d, *C*H-arom), 127.5 (d, *C*H-arom), 121.6 (q, J = 294.3 Hz, CF_3), 66.7/66.6 (t, CH_2-N$^+$-pyrrolidine), 64.3 (t, *C*H_2-OH), 54.3 (q, *C*H_3-N$^+$), 50.3 (d, *C*H-NH), 47.8 (d, *C*H-NH) 38.1 (t, *C*H_2-CH), 22.5/22.4 (t, CH_2-pyrrolidine)
Specific Rotation	α_D^{20} = -22.98 (*c* 1.06, CH_2Cl_2)
$T_{5\%\ onset}$	203 °C
ν_{max}/cm^{-1}	2969 (O-H), 1682 (C-C), 1544 (C=C), 1347 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 38.78, w-% H: 4.52, w-% N: 7.54 measured: w-% C: 39.12, w-% H: 4.055, w-% N: 7.47

VI 2.3.11 (*S*)-Tributyl(2-((1-hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)phosphonium chloride 47



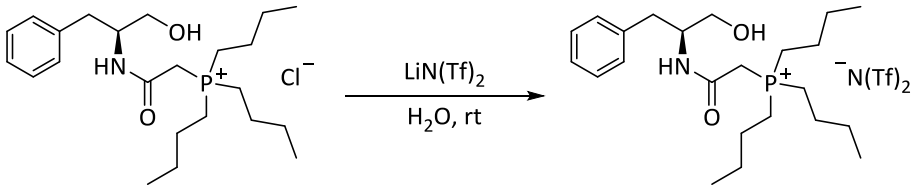
$C_{23}H_{41}ClNO_2P$
430.01

37 **47**

Product **47** was prepared according to VI 2.1.8 using compound **37** (1.00 g, 4.46 mmol) and tributylphosphine (1.16 ml, 4.46 mmol) in 15 ml EtOAc, to afford the product as colorless liquid.

Yield	1.45 g (76%) colorless liquid
^{1}H-NMR (200 MHz, MeOD)	δ_H = 7.30-7.19 (m, 5H, *H*-arom), 4.26-4.09 (m, 1H, C*H*-NH), 3.65-3.49 (m, 2H, CH_2-OH), 2.99-2.66 (m, 2H, CH_2-CH), 2.28-2.02 (m, 6H, $3CH_2$-P^+), 1.53-1.46 (m, 14H, $3CH_2$-CH_2-CH_3, CH_2-P^+), 0.99-0.91 (m, 9H, $3CH_2$-CH_2-CH_3)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 163.7 (s, C=O), 138.3 (s, C-arom), 128.9 (2d, *C*H-arom), 128.1 (2d, *C*H-arom), 126.1 (d, *C*H-arom), 62.9 (t, CH_2-OH), 53.5 (d, *C*H-NH), 36.6 (t, CH_2-CH), 26.8/26.7 (3t, CH_2-CH_2-CH_2-CH_3), 24.4/24.3 (3t, CH_2-CH_2-CH_2-CH_3), 20.4/19.5 (3t, CH_2-CH_2-CH_2-CH_3), 12.6 (3q, CH_2-CH_2-CH_3)
Specific Rotation	α_D^{20} = -14.79 (*c* 1.04, MeOH)
$T_{5\%\ onset}$	131 °C
ν_{max}/cm^{-1}	2958 (O-H), 1664 (C-C), 1555 (C=C), 1455 (C-H)
Elemental analysis	calculated: w-% C: 64.24, w-% H: 9.61, w-% N: 3.26 calculated: 0.45xH_2O = w-% C: 63.05, w-% H: 9.64, w-% N: 3.20 measured: w-% C: 63.11, w-% H: 8.85, w-% N: 2.87

VI 2.3.12 (*S*)-tributyl(2-((1-hydroxy-3-phenylpropan-2-yl)amino)-2-oxoethyl)phosphonium bis(trifluoromethane)sulfonimide 48



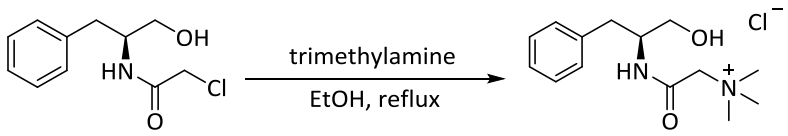
$C_{25}H_{41}F_6N_2O_6PS_2$
674.70

47 **48**

Product **48** was prepared according to VI 2.1.3 using compound **47** (0.72 g, 1.67 mmol) and lithium bis(trifluoromethane)sulfonimide (0.53 g, 1.84 mmol).

Yield	0.59 g (53%) colorless liquid
^{1}H-NMR (400 MHz, $CDCl_3$)	δ_H = 7.25-7.08 (m, 5H, *H*-arom), 4.13-4.06 (m, 1H, C*H*-NH), 3.66-3.41 (m, 2H, CH_2-OH), 3.33-3.10 (m, 2H, CH_2-CH), 2.85-2.64 (m, 2H, CH_2-P^+), 2.45 (brs, 1H, N*H*), 2.12-1.97 (m, 6H, 3CH_2-P^+), 1.41-1.34 (m, 14H, 3CH_2-CH_2-CH_3, CH_2-P^+), 0.91-0.85 (m, 9H, 3CH_2-CH_2-CH_3)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 163.7 (s, C=O), 139.6 (s, C-arom), 130.3 (2d, *C*H-arom), 129.5 (2d, *C*H-arom), 127.6 (d, *C*H-arom), 119.8 (q, J = 320.6 Hz, CF_3), 64.3 (t, *C*H_2-OH), 54.7 (d, *C*H-NH), 38.0 (t, *C*H_2-CH), 28.5/27.2 (2t, *C*H_2-CH_2-CH_2-CH_3), 25.3/25.0 (2t, CH_2-*C*H_2-CH_2-CH_3), 20.4/19.5 (2t, CH_2-CH_2-*C*H_2-CH_3), 13.9 (q, CH_2-CH_2-*C*H_3)
Specific Rotation	α_D^{20} = -13.68 (*c* 1.10, CH_2Cl_2)
$T_{5\%\ onset}$	134 °C
ν_{max}/cm^{-1}	2963 (O-H), 1667 (C-C), 1536 (C=C), 1348 (C-H), 1185 (C-F_3), 1054 (NH-CH_3)
Elemental analysis	calculated: w-% C: 45.34, w-% H: 6.29, w-% N: 4.07 measured: w-% C: 46.49, w-% H: 6.21, w-% N: 3.93

VI 2.3.13 (*S*)-2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium chloride 49



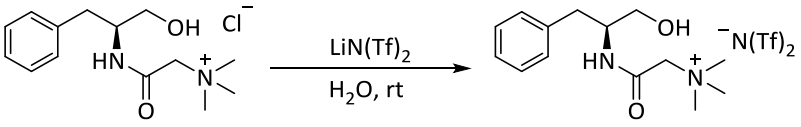
$C_{14}H_{23}ClN_2O_2$
286.80

37 **49**

Product **49** was prepared according to VI 2.1.12 using compound **37** (1.00 g, 4.46 mmol) and trimethylamine (1.23 ml, 4.91 mmol) in 10 ml anhydrous EtOH to afford the product as colorless solid.

Yield	0.56 g (50%) colorless solid
Mp	60-64 °C
^{1}H-NMR (200 MHz, MeOD)	δ_H = 7.29-7.15 (m, 5H, *H*-arom), 4.38-4.23 (m, 1H, C*H*-NH), 3.97 (q, J = 13.03 Hz, 2H, CH_2-N$^+$), 3.63-3.56 (m, 2H, CH_2-OH), 3.15 (s, 9H, CH_3-N$^+$), 3.02-2.64 (m, CH_2-CH)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 161.4 (s, *C*=O), 136.8 (s, *C*-arom), 127.6 (2d, *C*-arom), 126.6 (2d, *C*-arom), 124.6 (d, *C*-arom), 63.2 (t, *C*H_2-OH), 61.5 (t, *C*H_2-N$^+$), 51.8 (q, CH_3-N$^+$), 51.5 (d, CH_2-*C*H), 35.1 (t, *C*H_2-CH)
Specific Rotation	α_D^{20} = -31.07 (*c* 0.85, MeOH)
$T_{5\%\ onset}$	159 °C
ν_{max}/cm^{-1}	2956 (O-H), 1674 (C-C), 1566 (C=C), 1454 (C-H)
Elemental analysis	calculated: w-% C: 58.63, w-% H: 8.08, w-% N: 9.77 calculated: 0.20xH_2O = w-% C: 57.90, w-% H: 8.12, w-% N: 9.65 measured: w-% C: 57.92, w-% H: 7.95, w-% N: 9.50

VI 2.3.14 (*S*)-2-((1-Hydroxy-3-phenylpropan-2-yl)amino)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium bis(trifluoromethane)sulfonimide 50



$C_{16}H_{23}F_6N_3O_6S_2$
531.49

49 **50**

Product **50** was prepared according to VI 2.1.3 using cmp **49** (1.66 g, 5.80 mmol) and lithium bis(trifluoromethane)sulfonimide (1.83 g, 6.38 mmol).

Yield	2.85 g (92%) colorless liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 7.29-7.18 (m, 5H, *H*-arom), 4.33-4.24 (m, 1H, C*H*-NH), 3.91 (q, J = 14.70 Hz, 2H, CH_2-N^+), 3.67-3.49 (m, 2H, CH_2-OH), 3.13 (s, 9H, CH_3-N^+), 3.02-2.62 (m, CH_2-CH)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 164.1 (s, *C*=O), 139.5 (s, *C*-arom), 130.4 (2d, *C*H-arom), 129.5 (2d, *C*H-arom), 127.6 (d, *C*-arom), 121.5 (q, J = 312.12 Hz, CF_3), 66.1 (t, *C*H_2-OH), 64.3 (t, *C*H_2-N), 54.7 (3q, CH_3-N^+), 54.3 (d, *C*H-NH), 38.2 (t, *C*H_2CH)
Specific Rotation	α_D^{20} = -23.72 (*c* 1.03, CH_2Cl_2)
$T_{5\%\ onset}$	155 °C
ν_{max}/cm^{-1}	2969 (O-H), 1682 (C-C), 1544 (C=C), 1347 (C-H), 1179 (C-F_3), 1051 (NH-CH_3)
Elemental analysis	calculated: w-% C: 36.16, w-% H: 4.36, w-% N: 7.91 measured: w-% C: 36.43, w-% H: 3.99, w-% N: 7.69

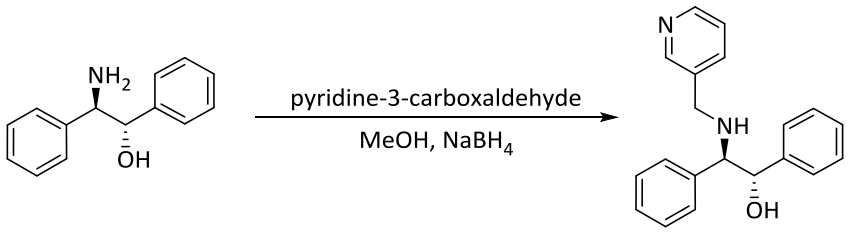
VI 2.3.15 Procedure von ^{19}F-NMR experiments

Racemic Mosher's acid potassium salt was synthesized by stirring *rac*-Mosher's acid (100 mg, 4.20 mmol) with an equimolar amount KOH (21 mg, 4.20 mmol) in 20 ml H_2O for 1 hour and subsequent lyophilization of the excessive H_2O.

Racemic Mosher's acid potassium salt (13.61 mg, 0.05 mmol) and 18-crown-6 (13.22 mg, 0.05 mmol) ether were mixed in a NMR tube, followed by addition if a solution of CIL in CD_2Cl_2. The mixture was sonificated for 10 minutes to accelerate the dissolution of the starting materials.

VI 3 Amino-Alcohol Chiral Ionic Liquids in Diethylzinc-addition

VI 3.1.1 (1*S*,2*R*)-1,2-Diphenyl-2-[(pyridin-3-ylmethyl)amino]ethanol 52



51

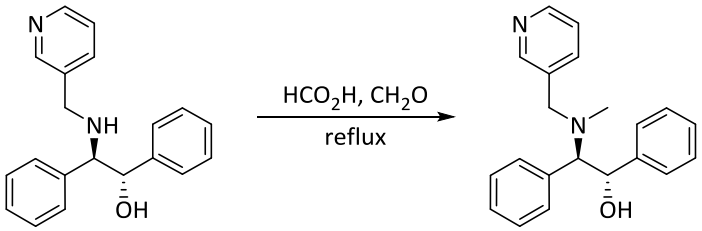
$C_{20}H_{20}N_2O$
304.39
52

Freshly distilled pyridine-3-carboxaldehyde (0.88 ml, 9.33 mmol) was added to a mixture of (1*S*,2*R*)-2-amino-1,2-diphenylethanol **51** (2.00 g, 9.33 mmol) and activated molecular sieve 3 Å (5.00 g) in 100 ml of anhydrous methanol and refluxed for 14 h. Sodium borohydride (0.35 g, 9.33 mmol) was added in small portions and the mixture was stirred at room temperature until TLC indicated complete conversion. The reaction mixture was filtered over silica and hydrolyzed with H_2O_{dest}. Methanol was removed under reduced pressure and the aqueous layer was extracted with CH_2Cl_2. The product, was further purified via FMPLC (200 g silica, CH_2Cl_2:MeOH 40:1 + Et_3N) to yield **52** as colorless solid in 89% yield. Crystallization from toluene gave colorless crystals.

Yield	2.54 g (89%) colorless crystals
Mp	144-146 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.38 (d, J = 4.78 Hz, 1H, *H*-pyridine), 8.28 (s, 1H, *H*-pyridine), 7.42-7.38 (m, 1H, *H*-pyridine), 7.18-7.10 (m, 11H, *H*-arom), 4.71 (d, J = 6.06 Hz, 1H, C*H*-OH), 3.81 (d, J = 6.06 Hz, 1H, C*H*-NH), 3.60 (d, J = 13.67 Hz, 1H, CH_2-NH), 3.43 (d, J = 13.69 Hz, 1H, CH_2), 2.80 (brs, 1H, O*H*), 1.68 (brs, 2H, NH_2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 149.6 (d, *C*-arom), 148.4 (d, *C*-arom), 140.6 (s, *C*-arom), 138.9 (s, *C*-arom), 135.7 (s, *C*-arom), 135.2 (d, *C*-arom), 128.4 (d, *C*-arom), 128.1 (d, *C*-arom), 127.9 (d, *C*-arom), 127.8 (d, *C*-arom), 127.2 (d, *C*-arom), 126.9 (d, *C*-arom), 123.3 (d, *C*-arom), 76.4 (d, *C*H-OH), 68.1 (d, *C*H-NH), 48.4 (t, *C*H_2-NH)
Specific Rotation	α_D^{20} = +17.80 (*c* 0.83, CH_2Cl_2)
$T_{5\%\ onset}$	177 °C
ν_{max}/cm^{-1}	3028 (N-H), 1578 (C=C), 1450 (C-H), 752 (C-H-arom)
Elemental analysis	calculated: w-% C: 78.92, w-% H: 6.62

calculated: 0.15xH_2O: w-% C: 78.22, w-% H: 6.66
measured: w-% C: 78.12, w-% H: 6.34

VI 3.1.2 (1*S*,2*R*)-2-[Methyl(pyridin-3-ylmethyl)amino]-1,2-diphenylethanol 53



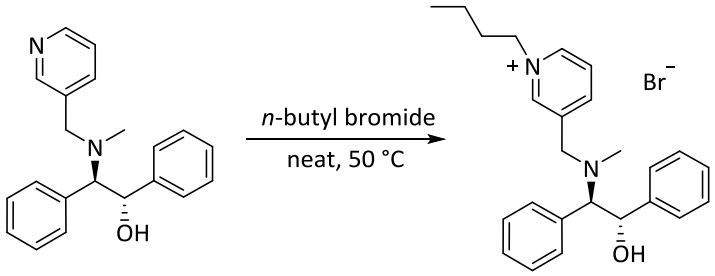
$C_{21}H_{22}N_2O$
318.42

52 **53**

Compound **52** (1.34 g, 4.40 mmol) was dissolved in 9 ml of concentrated formic acid and stirred for 30 minutes. Formaldehyde (7.5 ml, 37% solution in H_2O) was added and the mixture was refluxed overnight. Remaining formaldehyde was removed under reduced pressure, a 4 M NaOH solution in H_2O was added until pH>7 and the reaction mixture was extracted with CH_2Cl_2. The pooled organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Crystallization from toluene gave **53** as colorless crystals in 65% yield.

Yield	0.90 g (65%) colorless crystals
Mp	103-106 °C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.36 (dd, J_1 = 1.64 Hz, J_2 = 4.75 Hz, 1H, *H*-pyridine), 8.22 (d, J = 1.72 Hz, 1H, *H*-pyridine), 7.23-7.12 (m, 12H, *H*-arom), 5.26 (d, J = 6.65 Hz, 1H, C*H*-OH), 3.58-3.48 (m, 2H, C*H*-NH, N-CH_2), 3.37 (d, J = 13.88 Hz, 2H, N-CH_2), 2.63 (brs, 1H, O*H*), 2.18 (s, 3H, NH-CH_3)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 149.9 (d, *C*-arom), 148.4 (s, *C*-arom), 142.0 (d, *C*-arom), 136.3 (s, *C*-arom), 135.6 (s, *C*-arom), 134.5 (d, *C*-arom), 129.5 (d, *C*-arom), 128.0 (d, *C*-arom), 127.9 (d, *C*-arom), 127.7 (d, *C*-arom), 127.4 (d, *C*-arom), 126.7 (d, *C*-arom), 123.3 (d, *C*-arom), 74.5 (d, *C*-OH), 72.8 (d, *C*-NH), 56.8 (d, *C*H_2), 38.6 (q, NH-*C*H_3)
Specific Rotation	α_D^{20} = +61.10 (*c* 1.17, CH_2Cl_2)
$T_{5\%\ onset}$	215 °C
ν_{max}/cm^{-1}	3269 (O-H), 1574 (C=C), 1480 (C-H), 1027 (NH-CH_3), 756 (C-H-arom)
Elemental analysis	calculated: w-% C: 79.21, w-% H: 6.96 calculated: 0.05xH_2O: w-% C: 78.99, w-% H: 6.98 measured: w-% C: 79.08, w-% H: 6.52

VI 3.1.3 1-Butyl-3-[[[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]methyl-amino]methyl]pyridinium bromide 54



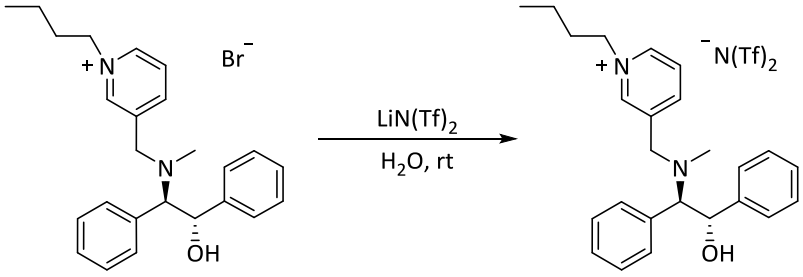
$C_{25}H_{31}BrN_2O$
455.44

53 **54**

Compound **53** (0.50 g, 1.56 mmol) and freshly distilled *n*-butylbromide (0.47 ml, 4.40 mmol) were mixed in a round-bottom flask, sealed, and stirred at 60 °C for 24 hours. Excess *n*-butyl bromide was evaporated and the brown oil was washed twice with anhydrous ethyl acetate. Remaining volatile materials were removed under reduced pressure at 60 °C to yield pyridinium bromide **54** as light brown liquid in 99% yield.

Yield	0.70 g (99%) brown liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 9.18 (d, J = 5.42 Hz, 1H, *H*-pyridine), 8.73 (s, 1H, *H*-pyridine), 7.82-7.76 (m, 2H, *H*-pyridine), 7.21-7.10 (m, 10H, *H*-arom), 5.32 (d, J = 7.04 Hz, 1H, C*H*-OH), 4.68 (t, J = 7.46 Hz, 1H, C*H*-N), 3.71-3.65 (m, 3H, CH_2-N, OH), 2.15 (s, 3H, N-CH_3), 1.86-1.81 (m, 2H, CH_2-CH_2-CH_2), 1.30-1.26 (m, 2H, CH_2-CH_2-CH_2), 0.87 (t, J = 7.25 Hz, 3H, CH_3-CH_2-CH_2)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 144.1 (d, *C*-arom), 143.5 (d, *C*-arom), 142.7 (s, *C*-arom), 135.3 (d, *C*-arom), 129.9 (s, *C*-arom) 128.2 (s, *C*-arom), 128.0 (d, *C*-arom), 127.9 (d, *C*-arom), 127.3 (d, *C*-arom), 127.0 (d, *C*-arom), 74.9 (d, *C*H-OH), 72.7 (d, *C*H-N), 61.5 (t, *C*H_2-CH_2-CH_2), 55.7 (t, *C*H_2), 39.3 (q, N-*C*H_3), 33.8 (t, CH_2-*C*H_2-CH_2), 19.3 (t, CH_2-CH_2-*C*H_2), 13.6 (q, *C*H_3-CH_2-CH_2)
Specific Rotation	α_D^{20} = +52.02 (*c* 0.77, CH_2Cl_2)
$T_{5\%\ onset}$	220 °C
ν_{max}/cm^{-1}	3284 (O-H), 1631 (C-C), 1495 (C=C), 1480 (C-H), 1025 (NH-CH_3), 753 (C-H arom)
Elemental analysis	calculated: w-% C: 65.93, w-% H: 6.86 calculated: 0.55xH_2O: w-% C: 64.53, w-% H: 6.95 measured: w-% C: 64.53, w-% H: 6.95

VI 3.1.4 1-Butyl-3-[[[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]-methylamino]methyl]pyridinium bis(trifluoromethane)sulfonimide 55



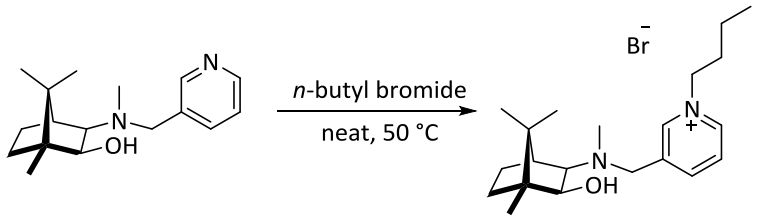
$C_{27}H_{31}F_6N_3O_5S_2$
655.67

54 **55**

Product **55** was prepared according to VI 2.1.3 using compound **54** (0.60 g, 1.30 mmol) and lithium bis(trifluoromethane)sulfonimide (0.41 g, 1.43 mmol) to yield the product as yellow oil.

Yield	0.84 g (98%) yellow liquid
^{1}H-NMR (400 MHz, $CDCl_3$)	δ_H = 8.47 (d, J = 5.98 Hz, 1H, *H*-pyridine), 7.81 (s, 2H, *H*-pyridine), 7.70 (s, 1H, *H*-pyridine), 7.35-7.30 (m, 10H, *H*-arom), 5.28 (d, J = 8.67 Hz, 1H, C*H*-OH), 4.31-4.26 (m, 2H, CH_2-N arom), 3.82 (d, J = 8.81 Hz, 1H, C*H*-NH), 3.72/3.58 (2d, J = 14.99 Hz, 2H, N-CH_2), 2.13 (s, 3H, N-CH_3), 1.78-1-71 (m, 2H, CH_2-CH_2-CH_3), 1.38-1.29 (m, 2H, CH_2-CH_2-CH_3), 0.97 (t, J = 7.21 Hz, 3H, CH_3-CH_2-CH_2)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ_C = 144.6 (d, *C*-arom), 143.0 (d, *C*-arom), 142.8 (d, *C*-arom), 142.5 (s, *C*-arom), 142.4 (d, *C*-arom), 134.7 (s, *C*-arom), 129.3 (2d, *C*-arom), 128.6 (2d, *C*-arom), 128.4 (2d, *C*-arom), 128.2 (s, *C*-arom), 127.9 (2d, *C*-arom), 127.3 (2d, *C*-arom), 119.7 (q, J = 321.48 Hz, *C*F_3), 74.4 (d, *C*H-OH), 73.1 (d, *C*H-NCH_3), 62.0 (t, *C*H_2-CH_2-CH_2), 55.4 (t, *C*H_2-NCH_3), 38.3 (q, NH-*C*H_3), 33.2 (t, CH_2-*C*H_2-CH_3), 19.3 (t, CH_2-*C*H_2-CH_3), 13.4 (q, *C*H_3-CH_2-CH_2)
Specific Rotation	α_D^{20} = +43.73 (*c* 1.01, CH_2Cl_2)
$T_{5\%\ onset}$	258 °C
ν_{max}/cm^{-1}	3529 (O-H), 1633 (C-C), 1498 (C=C), 1453 (C-H), 1178 (C-F_3), 1133 (S=O), 1035 (NH-CH_3), 703 (C-H-arom)
Elemental analysis	calculated: w-% C: 49.46, w-% H: 4.77 calculated: 0.05xH_2O: w-% C: 49.39, w-% H: 4.77 measured: w-% C: 49.41, w-% H: 4.66

VI 3.1.5 1-Butyl-3-[[[[(1*S*,2-*exo*,3-*exo*)-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl]amino]methyl]-pyridinium bromide 59



$C_{21}H_{35}BrN_2O$
411.43

58 **59**

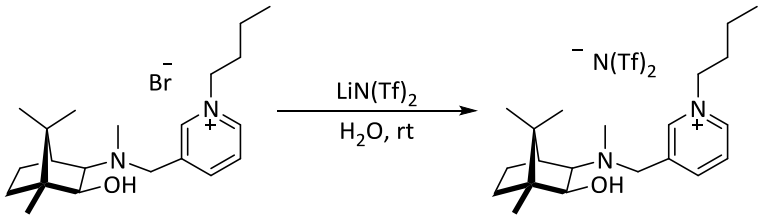
Preparation from **58**[xii] (2.91 g, 10.60 mmol) according to procedure VI 3 with *n*-butyl bromide (1.13 ml, 10.60 mmol) and gave the crude product as light brown solid. Crystallization from acetonitrile/ethyl acetate gave **59** colorless crystals.

Analytical data was in accordance with literature.[86]

Yield	4.32 g (99%) colorless crystals
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 9.38 (s, 1H, H-pyridine), 9.29 (d, J = 6.12 Hz, 1H, H-pyridine), 8.30 (d, J = 7.84 Hz, 1H, H-pyridine), 7.96 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, H-pyridine), 4.78 (t, J = 7.34 Hz, 2H, N-C*H*$_2$-CH$_2$), 3.97 (d, J = 14.48 Hz, 1H, C*H*$_2$-NCH$_3$), 3.49 (m, 3H, C*H*$_2$-NCH$_3$, C*H*-OH and O*H*), 2.51 (d, 1H, J = 6.26 Hz, C*H*-NCH$_3$), 2.07 (s, 3H, C*H*$_3$-N), 1.88 (m, 3H, CH$_2$-C*H*$_2$-CH$_2$, C*H*-C-CH$_3$), 1.59-1.28 (m, 4H, H-6$_{exo}$, H-5$_{exo}$, CH$_2$-C*H*$_2$-CH$_3$), 1.03 (s, 3H, C*H*$_3$-C), 0.94-0.75 (m, 5H, H-6$_{endo}$, H-5$_{endo}$, CH$_2$-CH$_2$-C*H*$_3$), 0.81/0.61 (2s, 6H, 2 C*H*$_3$)
$T_{5\%\ onset}$	187 °C
ν_{max}/cm^{-1}	3272 (O-H), 2958 (N-H), 1638 (C-N), 1370 (C-CH3), 1282 (C-H)

[xii] Compound **58** was synthesized according to literature and available in our lab. [164]

VI 3.1.6 1-Butyl-3-[[[[(1*S*,2-exo,3-exo)-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl]amino]methyl]-pyridinium bis(trifluoromethane)sulfonimide 60



$C_{23}H_{35}F_6N_3O_5S_2$
611.66

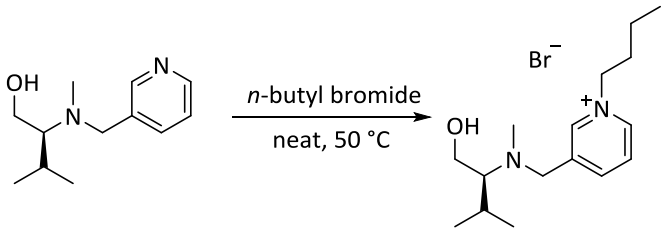
59 **60**

Product **60** was prepared according to VI 2.1.3 using compound **59** (0.99 g, 2.43 mmol) and lithium bis(trifluoromethane)sulfonimide (0.86 g, 3.00 mmol) to yield the product as light yellow viscous liquid.

Analytical data was in accordance with literature.[86]

Yield	1.39 g (93%) yellow liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.72 (s, 1H, *H*-pyridine), 8.68 (d, J = 6.06 Hz, 1H, *H*-pyridine), 8.40 (d, J = 7.83 Hz, 1H, *H*-pyridine), 7.95 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, *H*-pyridine), 4.55 (t, J = 7.34 Hz, 3H, C*H*$_3$), 3.95 (d, J = 14.48 Hz, 1H, C*H*$_2$-NCH_3), 3.56 (m, 2H, C*H*-OH, C*H*$_2$-N CH_3), 3.21 (brs, OH), 2.62 (d, 1H, J = 6.26 Hz, C*H*-NCH_3), 2.16 (s, 3H, C*H*$_3$-N), 2.14-1.15 (m, 7H, C*H*-C-2CH_3, H-6$_{exo}$, H-5$_{exo}$, C*H*$_2$-CH_2-CH_3, CH_2-C*H*$_2$-CH_3), 1.16 (s, 3H, CH_3-C), 1.02-0.85 (m, 5H, H-6$_{endo}$, H-5$_{endo}$, CH_2-CH_2-C*H*$_3$), 0.96/0.78 (2s, 6H, 2 CH_3)
$T_{5\%\ onset}$	191 °C
ν_{max}/cm^{-1}	2879 (N-H), 1636 (C-N), 1348 (C-CH_3), 1179 (C-F_3), 1133 (S=O), 1052 (NH-CH_3)

VI 3.1.7 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]methylamino]methyl]pyridinium bromide 63



$C_{16}H_{29}BrN_2O$
345.33

62 **63**

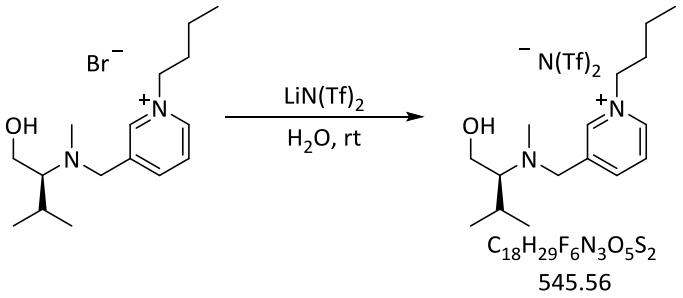
Preparation of **62**[xiii] (0.81 g, 2.36 mmol) according to procedure VI 3 with *n*-butyl bromide (0.25 ml, 2.36 mmol) and gave **63** as viscous brown oil.

Analytical data was in accordance with literature.[86]

Yield	0.57 g (99%) brown liquid
^{1}H-NMR (200 MHz, MeOD)	δ_H = 8.98 (s, 1H, *H*-pyridine), 8.90 (d, J = 5.87 Hz, 1H, *H*- pyridine), 8.57 (d, J = 8.02 Hz, 1H, *H*-pyridine), 8.06 (t, J = 7.03 Hz, 1H, H-pyridine), 4.66 (t, J = 7.53 Hz, 2H, C*H*$_2$-N-arom), 4.13 (s, 2H, C*H*$_2$-N), 3.80-3.76 (m, 2H, C*H*$_2$-OH), 2.41-2.38 (m, 4H, CH_2-CH_2, CH_2-C*H*$_2$-CH_2), 2.11-1.75 (m, 3H C*H*$_3$-N), 1.42 (sext, J = 7.43 Hz, 2H, CH_3-C*H*$_2$-CH_3), 1.16-0.96 (m, 9H, 2 C*H*$_3$-CH_2-C*H*$_3$, C*H*$_3$-CH_2-CH_2)
$T_{5\%\ onset}$	223 °C
ν_{max}/cm^{-1}	3338 (O-H), 2933 (N-C), 1633 (C-C), 1465 (C-H), 1049 (NH-CH_3)

[xiii] Compound **62** was synthesized according to literature and available in our lab.[164]

VI 3.1.8 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-2-methyl-propyl]methyl-amino]methyl]pyridinium bis(trifluoromethane)sulfonimide 64



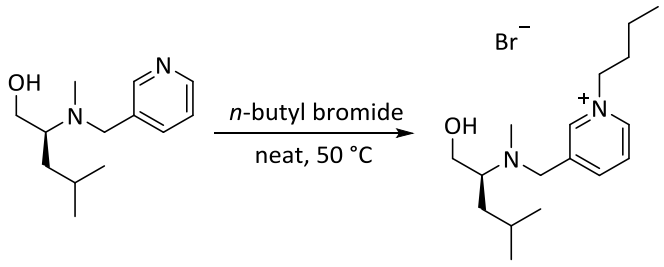
63 **64**

Product **64** was prepared according to VI 2.1.3 using compound **63** (0.48 g, 1.39 mmol) and lithium bis(trifluoromethane)sulfonimide (0.44 g, 1.52 mmol) to yield the product as yellow oil.

Analytical data was in accordance with literature.[86]

Yield	0.72 g (95%) yellow liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.76 (s, 1H, *H*-pyridine), 8.63 (d, J = 5.87 Hz, 1H, *H*-pyridine), 8.40 (d, J = 7.83 Hz, 1H, *H*-pyridine), 7.98-7.93 (m, 1H, *H*-pyridine), 4.56 (t, J = 7.53 Hz, 2H, CH_2-N-arom), 4.11 (s, 2H, CH_2-N), 3.71-3.45 (m, 2H, CH_2-OH), 2.46-2.39 (m, 1H, C*H*-NCH_3), 2.35 (s, 3H, N-CH_3), 1.99-1.69 (m, 1H, CH_2-CH_2-CH_2), 1.68-1.03 (m, 3H, CH_2-CH_2, CH_2-CH_2-CH_2), 1.37 (sext, J = 7.42 Hz, 2H, CH_3-CH_2-CH_3), 1.19- 0.71 (m, 9H, 2 CH_3, CH_3-CH_2-CH_2)
$T_{5\%\ onset}$	226 °C
ν_{max}/cm^{-1}	3310 (O-H), 1627 (C-C), 1469 (C=C), 1466 (C-H), 1230 (C-F_3), 1134 (S=O), 1045 (NH-CH_3)

VI 3.1.9 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-3-methyl-butyl]methylamino]methyl]pyridinium bromide 68



$C_{17}H_{31}BrN_2O$
359.35

67 **68**

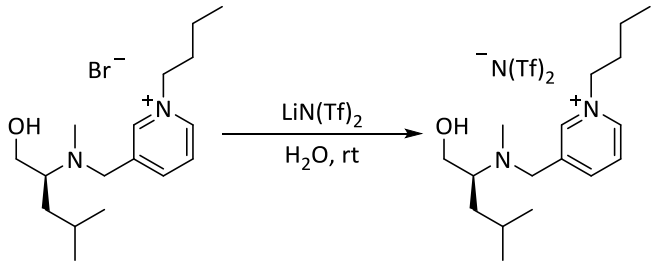
Preparation from **67**[xiv] (0.67 g, 3.00 mmol) according to procedure VI 3 with *n*-butyl bromide (0.32 ml, 3.00 mmol) gave **68** as viscous brown oil.

Analytical data was in accordance with literature.[86]

Yield	1.07 g (99%) yellow liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 9.40 (d, J = 5.87 Hz, 1H, *H*-pyridine), 9.19 (d, J = 5.89 Hz, 1H, *H*-pyridine), 8.28 (d, J = 8.02 Hz, 1H, *H*-pyridine), 7.94 (dd, J_1 = 7.63 Hz, J_2 = 6.06 Hz, 1H, *H*-pyridine), 4.76 (t, J = 7.34 Hz, 2H, C*H*$_2$-N-arom), 3.96/3.71 (2d, J = 15.26 Hz, 2H, C*H*$_2$-N), 3.39-3.26 (m, 2H, C*H*$_2$-OH), 2.66-2.61 (m, 1H, C*H*-NCH_3), 2.11 (s, 3H, N-C*H*$_3$), 1.85 (q, J = 7.5 Hz, 2H, C*H*$_2$-CH_2-CH_2), 1.58-1.05 (m, 4H, C*H*$_2$-CH_2-CH_3, CH_2-C*H*$_2$-CH_3), 0.94-0.88 (m, 1H, CH_3-C*H*-CH_3), 0.75 (t, J = 7.53 Hz, 3H, C*H*$_3$-CH_2-CH_2), 0.68/0.64 (2d, 6H, J = 6.45 Hz, 2 C*H*$_3$)
$T_{5\%\ onset}$	188 °C
ν_{max}/cm^{-1}	3330 (OH), 2957 (NH), 1643 (C-N), 1367 (C-CH_3), 1055 (C-H)

[xiv] Compound **67** was synthesized according to literature and available in our lab. [164]

VI 3.1.10 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-3-methylbutyl]methylamino]methyl]pyridinium bis(trifluoromethane)sulfonimide 69



$C_{19}H_{31}F_6N_3O_5S_2$
559.58

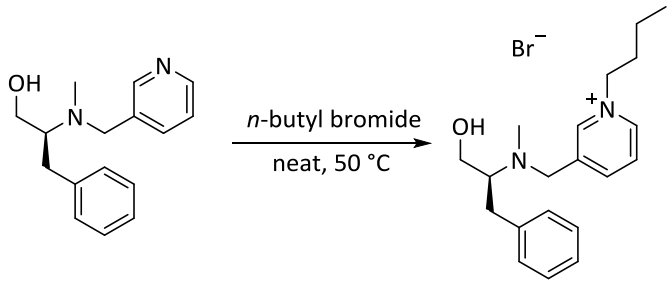
68 **69**

Product **69** was prepared according to VI 2.1.3 using compound **68** (0.85 g, 2.36 mmol) and lithium bis(trifluoromethane)sulfonimide (0.75 g, 2.60 mmol) to yield the product as yellow oil.

Analytical data was in accordance with literature.[86]

Yield	1.21 g (92%) yellow liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.74 (s, 1H, *H*-pyridine), 8.60 (d, J = 6.60 Hz, 1H, *H*-pyridine), 8.37 (d, J = 8.02 Hz, 1H, *H*-pyridine), 7.90 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, *H*-pyridine), 4.51 (t, J = 7.63 Hz, 2H, C*H*$_2$-N-arom), 3.96/3.81 (2d, J = 15.26 Hz, 2H, C*H*$_2$-N), 3.49 (m, 2H, C*H*$_2$-OH), 2.79-2.70 (m, 2H, C*H*-NCH_3, OH), 2.21 (s, 3H, N-C*H*$_3$), 1.90 (q, J = 7.53 Hz, 2H, C*H*$_2$-CH_2-CH_2), 1.68-0.99 (m, 5 H, CH_2-C*H*$_2$, CH_2-C*H*$_2$-CH_2, CH_3-C*H*-CH_3), 0.89 (t, J = 7.14 Hz, 3H, C*H*$_3$-CH_2-CH_2), 0.95-0.87 (m, 2H, CH_3-C*H*$_2$-CH_3), 0.91/0.83 (2d, 6H, J = 6.45 Hz, 2 C*H*$_3$)
$T_{5\%\ onset}$	244 °C
ν_{max}/cm^{-1}	3562 (OH), 2969 (NH), 1635 (C-N), 1348 (C-CH_3), 1179 (C-F_3), 1132 (S=O), 1052 (NH-CH_3)

VI 3.1.11 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-2-phenylethyl]methylamino]methyl]pyridinium bromide 72



$C_{20}H_{29}BrN_2O$
393.37

71 **72**

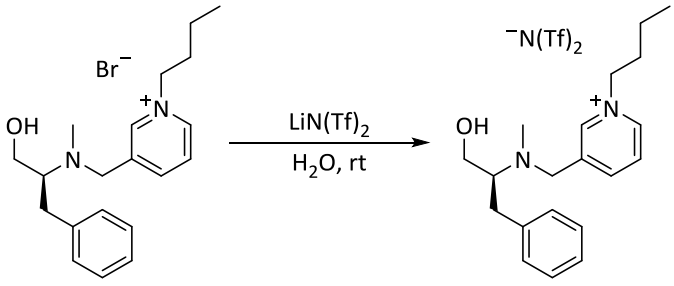
Preparation from **71**[xv] (0.37 g, 2.67 mmol) according to procedure VI 3 with *n*-butyl bromide (0.32 ml, 3.00 mmol) gave **72** as viscous brown oil.

Analytical data was in accordance with literature.[86]

Yield	1.04 g (99%) brown oil
^{1}H-NMR (200 MHz, MeOD)	δ_H = 8.82 (d, J = 8.80 Hz, 1H, *H*-pyridine), 8.60 (s, 1H, *H*-pyridine), 8.26 (d, J = 8.02 Hz, 1H, *H*-pyridine), 7.92 (t, 1H, *H*-pyridine), 7.41-7.21 (m, 5H, *H*-arom), 4.50 (t, J = 7.53 Hz, 2H, CH-N-arom), 4.03 (s, 2H, C*H*$_2$-OH), 3.86-3.50 (m, 2H, C*H*$_2$-NCH$_3$), 3.13-3.01 (m, 1H, C*H*$_2$-CH$_2$-OH), 2.92-2.64 (m, 2H, C*H*$_2$-Ph), 2.52-2.31 (m, 3H, C*H*$_3$-N), 1.93 (quin, J = 3.59 Hz, 2H, CH$_2$-C*H*$_2$-CH$_2$), 1.40 (sext, J = 4.96 Hz, 2H, CH$_2$-CH$_2$-C*H*$_2$), 1.02 (t, J = 3.91, 3H, CH$_2$-CH$_2$-C*H*$_3$)
Specific Rotation	α_D^{20} = -2.28 (*c* 0.27, CH_2Cl_2)
$T_{5\%\ onset}$	225 °C
ν_{max}/cm^{-1}	3309 (O-H), 2872 (N-C), 1632 (C-C), 1495 (C=C), 1453 (C-H), 1031 (NH-CH$_3$)

[xv] Compound **71** was synthesized according to literature and available in our lab.[164]

VI 3.1.12 1-Butyl-3-[[[(1*S*)-1-(hydroxymethyl)-2-phenylethyl]methylamino] methyl]pyridinium bis(trifluoromethane)sulfonimide 73



$C_{22}H_{29}F_6N_3O_5S_2$
593.60

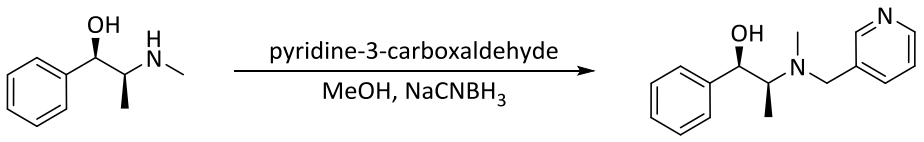
72 **73**

Product **73** was prepared according to VI 2.1.3 using compound **72** (1.28 g, 5.00 mmol) and lithium bis(trifluoromethane)sulfonimide (1.58 g, 5.50 mmol) to yield the product as yellow oil.

Analytical data was in accordance with literature.[86]

Yield	2.94 g (99%) yellow oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.48 (d, J = 6.10 Hz, 1H, *H*-pyridine), 8.26 (s, 1H, *H*-pyridine), 8.03 (d, J = 8.00 Hz, 1H, *H*-pyridine), 7.91-7.62 (m, 1H, *H*-pyridine), 7.31-7.05 (m, 5H, *H*-arom.), 4.34 (t, J = 7.62 Hz, 2H, C*H*-N arom), 3.92 (dd, J_1 = 15.61 Hz, J_2 = 14.48 Hz, 2H, CH_2-N), 3.80-3.51 (m, 2H, CH_2-OH), 2.99-2.71 (m, 1H, C*H*-CH_2-OH), 2.69-2.21 (m, 2H, CH_2-Ph), 2.32 (s, 3H, N-CH_3), 1.80 (q, J = 7.62 Hz, 2H, CH_2-CH_2-CH_3), 1.25 (sext, J = 7.50 Hz, 2H, CH_3-CH_2-CH_2), 0.89 (t, J = 7.30 Hz, 3H, CH_3-CH)
$T_{5\%\ onset}$	265 °C
ν_{max}/cm^{-1}	2855 (O-H), 1577 (C-C), 1453 (C=C), 1328 (C-H), 1284 (C-F_3), 1027 (NH-CH_3)

VI 3.1.13 (1*R*,2*S*)-2-(Methyl(pyridin-3-ylmethyl)amino)-1-phenylpropan-1-ol 74



$C_{16}H_{20}N_2O$
256.35

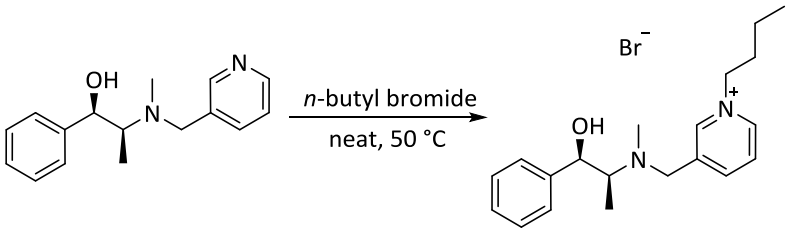
1 **74**

To a suspension of (1*R*,2*S*)-ephedrine **1** (4.95 g, 30 mmol) and molecular sieve 4 Å (10 g) in 100 ml anhydrous MeOH, freshly distilled pyridine-2-carboxaldehyde (3.21 g, 30 mmol) was added dropwise. The reaction mixture was refluxed for 15 hours until TLC showed complete conversion. The mixture was filtrated over celite to remove the molecular sieve and acetic acid (9.00 g, 150 mmol) and $NaCNBH_3$ (5.65 g, 90 mmol) were added to the solution. The mixture was stirred 2 h at room temperature until TLC showed full conversion of the intermediate. Solid $NaHCO_3$ (15 g) was added and the mixture was allowed to rest for 2 hours. Methanol was removed under reduced pressure and ethyl acetate was added to the residue. The organic layer was extracted three times with small amounts of water, dried over Na_2SO_4, filtrated and the remaining solvent was removed. The obtained raw material was purified *via* MPLC (CH_2Cl_2:MeOH 10:1) and gave **73** in 68% yield as colorless liquid.

Analytical data was in accordance with literature.[164]

Yield	5.23 g (68%) colorless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.38-3.35 (m, 1H, *H*-pyridine), 8.39 (d, J = 1.76 Hz, 1H, *H*-pyridine), 7.40 (td, J_1 = 7.77 Hz, J_2 = 1.79 Hz, 1H, *H*-pyridine), 7.26-7.08 (m, 6H, *H*-arom, *H*-pyridine), 4.80 (d, J = 5.24 Hz, 1H, C*H*-OH), 3.55 (s, brs, J = 7.63 Hz, 3H, CH_2-N, OH), 2.93-2.81 (m, 1H, H-NCH_3), 2.14 (s, 3H, CH_3-N), 0.99 (d, J = 6.76 Hz, 3H, CH_3-CH)

VI 3.1.14 1-Butyl-3-[[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]methylamino]methyl]pyridinium bromide 75



$C_{20}H_{29}BrN_2O$
393.37

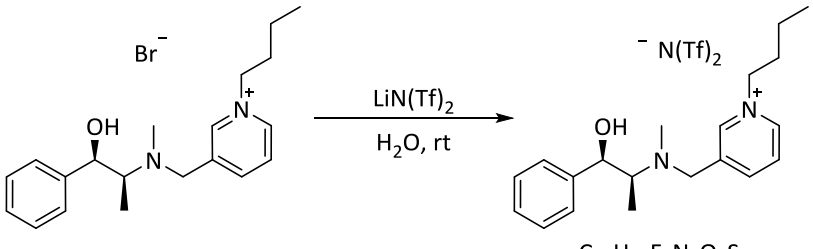
74 **75**

Preparation from **74** (0.77 g, 3.00 mmol) according to procedure VI 3 with *n*-butyl bromide (0.32 ml, 3.00 mmol) and gave **75** as viscous brown oil.

Analytical data was in accordance with literature.[86]

Yield	1.05 g (89%) brown oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 9.20 (d, J = 5.87 Hz, 1H, *H*-pyridine), 8.90 (d, J = 1.96 Hz, 1H, *H*-pyridine), 7.90 (d, J = 7.83 Hz, 1H, *H*-pyridine), 7.81 (dd, J_1 = 7.53 Hz, J_2 = 6.36 Hz, 1H, *H*-pyridine), 7.20-7.15 (m, 5H, *H*-arom), 4.88 (d, J = 5.28 Hz, 1H, C*H*-OH), 4.67 (t, J = 7.63 Hz, 2H, C*H*-N arom), 4.12 (brs, 1H, OH), 4.13/3.67 (2d, J = 15.45 Hz/J = 15.26 Hz, 2H, CH_2-N), 2.90-2.86 (m, 1H, H-NCH_3), 2.18 (s, 3H, CH_3-N), 1.84 (q, J = 7.73 Hz, 1H, CH_2-CH_2-CH_2), 1.31 (sext, J = 7.73 Hz, 2H, CH_2-CH_2-CH_2), 1.07 (d, J = 6.85 Hz, 3H, CH_3-CH_2-CH_2), 0.90 (t, J = 7.24 Hz, 3H, CH_3-CH)
$T_{5\%\ onset}$	213 °C
ν_{max}/cm^{-1}	3374 (O-H), 2873 (N-H), 1638 (C-N), 1371 (C=C), 1201(C-H), 703 (C-H arom)

VI 3.1.15 1-Butyl-3-[[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]methylamino]methyl]pyridinium bis(trifluoromethane)sulfonimide 76



$C_{22}H_{29}F_6N_3O_5S_2$
593.60

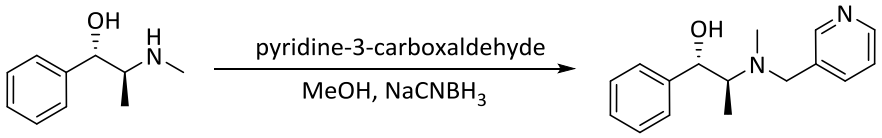
75 **76**

Product **76** was prepared according to VI 2.1.3 using compound **75** (0.79 g, 2.00 mmol) and lithium bis(trifluoromethane)sulfonimide (0.63 g, 2.20 mmol) to yield the product as yellow liquid.

Analytical data was in accordance with literature.[86]

Yield	1.02 g (86%) yellow liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.48 (d, J = 5.87 Hz, 1H, *H*-pyridine), 7.89-7.82 (m, 2H, *H*-pyridine), 7.71 (dd, J_1 = 7.53 Hz, J_2 = 6.36 Hz, 1H, *H*-arom), 7.30-7.26 (m, 5H, *H*-arom), 4.62 (d, J = 7.43 Hz, 1H, C*H*-OH), 4.28 (t, J = 7.63 Hz, 2H, CH-N arom), 3.79/3.77 (2d, J = 15.85 Hz, 2H, CH_2-N), 2.92-2.88 (m, 1H, H-NCH_3), 2.67 (brs, 1H, OH), 2.14 (s, 3H, CH_2-CH_2-CH_2), 1.77 (q, J = 7.83 Hz, 1H, CH_2-CH_2-CH_2), 1.29 (sext, J = 7.83 Hz, 2H, CH_2-CH_2-CH_2), 1.17 (d, J = 6.65, 3H, CH_3-CH_2-CH_2), 0.93 (t, J = 7.34 Hz, 3H, CH_3-CH)
$T_{5\%\ onset}$	251 °C
ν_{max}/cm^{-1}	3534 (OH), 2960 (NH), 1350 (C=C), 1330 (C-H), 690 (C-H-arom)

VI 3.1.16 (1*S*,2*S*)-2-[Methyl(pyridin-3-ylmethyl)amino]-1-phenyl-propan-1-ol 78



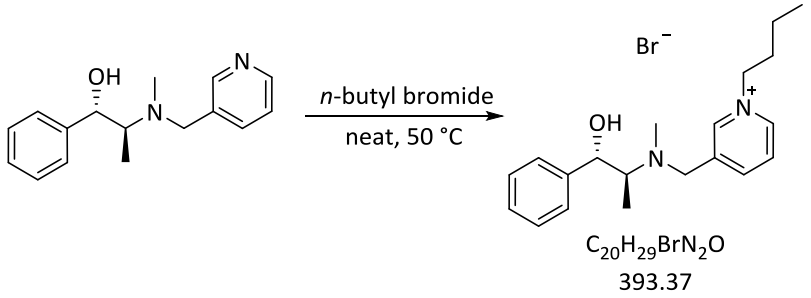
$C_{16}H_{20}N_2O$
256.35

77 **78**

Synthesized according to procedure VI 3.1.13 from (1*S*,2*S*)-pseudoephedrine **77** (4.13 g, 25 mmol), molecular sieve 4 Å (10 g) in 100 mL anhydrous MeOH, freshly distilled pyridine-3-carboxaldehyde (2.68 g, 25 mmol) and acetic acid (9.00 g, 150 mmol) to yield **78** as colorless liquid.

Yield	5.52 g (86%) colorless liquid
^{1}H-NMR (400 MHz, $CDCl_3$)	δ_H = 8.45-8.36 (m, 1H, *H*-pyridine), 7.65 (td, J_1 = 1.81 Hz, J_2 = 7.63 Hz, 1H, *H*-pyridine), 7.25-7.20 (m, 6H, *H*-arom), 4.87 (brs, 1H, OH), 4.26 (d, J = 9.83 Hz, 1H, C*H*-OH), 3.69 (d, J = 13.12 Hz, 1H, CH_2-NCH_3), 3.44 (d, J = 13.29 Hz, 1H, CH_2-NCH_3), 2.62-2.58 (m, 1H, C*H*-N), 2.16 (s, 3H, N-CH_3), 0.74 (d, J= 6.71 Hz, 3H, CH_3-CH)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ_C = 150.3 (d, *C*-arom), 149.0 (d, *C*-arom), 141.6 (s, *C*-arom), 136.5 (d, *C*-arom), 134.0 (s, *C*-arom), 128.3 (d, *C*-arom), 127.8 (d, *C*-arom), 127.3 (d, *C*-arom), 123.6 (d, *C*-arom), 74.8 (d, *C*-OH), 65.1 (d, N-*C*H), 55.5 (q, N-*C*H_3), 35.7 (t, *C*H_2), 7.4 (q, *C*H_3)
Specific Rotation	α_D^{20} = +108.23 (*c* 0.91, CH_2Cl_2)
$T_{5\%\ onset}$	215 °C
ν_{max}/cm^{-1}	3370 (O-H), 1576 (C-C), 1451 (C=C), 1480 (C-H), 1025.38 (NH-CH_3), 756 (C-H-arom)
Elemental analysis	calculated: w-% C: 74.97, w-% H: 7.86 calculated: 0.01xH_2O: w-% C: 74.44, w-% H: 7.89 measured: w-% C: 74.58, w-% H: 7.38

VI 3.1.17 1-Butyl-3-[[[(1*S*,2*S*)-1-hydroxy-1-phenylprop-2-yl]methylamino]methyl]pyridinium bromide 79

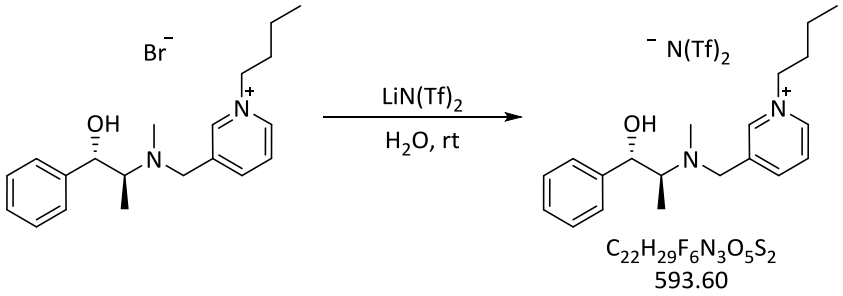


78 **79**

Preparation from **78** (1.13 g, 4.40 mmol) according to procedure VI 3 with *n*-butyl bromide (0.47 ml, 4.40 mmol) and gave **79** as viscous brown oil.

Yield	1.67 g (97%) brown oil
^{1}H-NMR (400 MHz, $CDCl_3$)	δ_H = 9.68 (s, 1H, *H*-pyridine), 9.22 (d, J = 5.94 Hz, 1H, *H*-pyridine), 8.34 (d, J = 7.85 Hz, 1H, *H*-pyridine), 7.96 (t, J = 6.98 Hz, 1H, *H*-pyridine), 7.20 (s, 5H, *H*-arom), 4.83-4.78 (m, 3H, OH, C*H*$_2$-N arom), 4.34 (d, J = 9.39 Hz, 1H, C*H*-OH), 3.97 (d, J = 14.88 Hz, 1H, C*H*$_2$-NCH_3), 3.76 (d, J = 14.77 Hz, 1H, C*H*$_2$-NCH_3), 2.80-2.77 (m, 1H, CH-OH), 2.22 (s, 3H, N-CH_3), 1.86-1.82 (m, 2H, CH_2-C*H*$_2$-CH_2), 1.28-1.20 (m, 2H, CH_2-CH_2-C*H*$_2$), 0.83 (t, J = 7.28 Hz, 3H, C*H*$_3$-CH_2-CH_2), 0.71 (d, J = 6.64 Hz, 3H, C*H*$_3$-CH)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ_C = 145.1 (d, *C*-arom), 144.7 (s, *C*-arom), 143.5 (d, *C*-arom), 141.8 (s, *C*-arom), 140.8 (d, *C*-arom), 128.2 (2d, *C*-arom), 127.9 (d, *C*-arom), 127.8 (d, *C*-arom), 127.2 (d, *C*-arom), 74.9 (d, *C*-OH), 65.3 (d, N-*C*H), 61.3 (t, *C*H_2-CH_2-CH_2), 54.5 (q, N-*C*H_3), 36.4 (t, *C*H_2), 33.7 (t, CH_2-*C*H_2-CH_2), 19.2 (t, CH_2-CH_2-*C*H_2), 13.5 (q, *C*H_3-CH_2-CH_2), 7.4 (q, *C*H_3)
Specific Rotation	α_D^{20} = +63.52 (*c* 1.22, CH_2Cl_2)
$T_{5\%\ onset}$	221 °C
ν_{max}/cm^{-1}	3315 (O-H), 1632 (C-C), 1500 (C-C), 1453 (C=C), 1038.69 (NH-CH_3), 702 (C-H-arom)
Elemental analysis	calculated: w-% C: 61.07, w-% H: 7.43 calculated: 0.5xH_2O: w-% C: 59.57, w-% H: 7.52 measured: w-% C: 59.29, w-% H: 7.15

VI 3.1.18 1-Butyl-3-[[[(1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]methyl-amino]methyl]pyridinium bis(trifluoromethane)sulfonimide 80



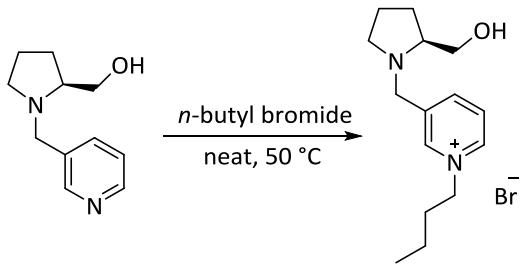
$C_{22}H_{29}F_6N_3O_5S_2$
593.60

79 **80**

Product **80** was prepared according to VI 2.1.3 using compound **79** (1.00 g, 2.54 mmol) and lithium bis(trifluoromethane)sulfonimide (0.80 g, 2.79 mmol) to yield the product as yellow oil.

Yield	1.45 g (96%) yellow oil
^{1}H-NMR (400 MHz, $CDCl_3$)	δ_H = 8.72 (s, 1H, *H*-pyridine), 8.58 (d, J = 6.00 Hz, 1H, *H*-pyridine), 8.36 (d, J = 8.01 Hz, 1H, *H*-pyridine), 7.89-7.85 (m, 1H, *H*-pyridine), 7.25 (s, 5H, *H*-arom), 4.50 (t, J = 7.59 Hz, OH, C*H*$_2$-N-arom), 4.33 (d, J = 9.59 Hz, 1H, C*H*-OH), 3.94 (d, J = 15.05 Hz, 1H, C*H*$_2$-NCH_3), 3.71 (d, J = 15.13 Hz, 1H, C*H*$_2$-NCH_3), 2.78-2.73 (m, 1H, C*H*-OH), 2.23 (s, 3H, N-C*H*$_3$), 1.90-1.85 (m, 2H, CH_2-C*H*$_2$-CH_2), 0.89 (t, J = 7.26 Hz, 3H, C*H*$_3$-CH_2-CH_2), 0.77 (d, J = 6.64 Hz, 3H, C*H*$_3$-CH)
^{13}C-NMR (100 MHz, $CDCl_3$)	δ_C = 145.3 (d, *C*-arom), 143.8 (d, *C*-arom), 142.9 (s, *C*-arom), 141.6 (d, *C*-arom), 141.3 (d, *C*-arom), 128.4 (s, *C*-arom), 128.2 (d, *C*-arom), 128.1 (d, *C*-arom), 127.3 (d, *C*-arom), 119.6 (q, J = 324.62 Hz, *C*F_3), 75.0 (d, *C*-OH), 65.6 (d, N-*C*H), 62.2 (t, *C*H_2-CH_2-CH_2), 54.3 (q, N-*C*H_3), 36.1 (t, *C*H_2), 33.3 (t, CH_2-*C*H_2-CH_2), 19.2 (t, CH_2-CH_2-*C*H_2), 13.2 (q, *C*H_3-CH_2-CH_2), 8.0 (q, *C*H_3)
Specific Rotation	α_D^{20} = +17.80 (*c* 0.88, CH_2Cl_2)
$T_{5\%\ onset}$	250 °C
ν_{max}/cm^{-1}	2961 (O-H), 1504 (C-C), 1456 (C=C), 1348 (C-H), 1178 (C-F_3), 1132 (S=O), 1052 (NH-CH_3), 788 (C-H-arom)
Elemental analysis	calculated: w-% C: 44.51, w-% H: 4.92 calculated: 0.9xH_2O: w-% C: 44.33, w-% H: 5.09 measured: w-% C: 43.17, w-% H: 4.71

VI 3.1.19 1-Butyl-3-[[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]pyridinium bromide 82



81 **82**

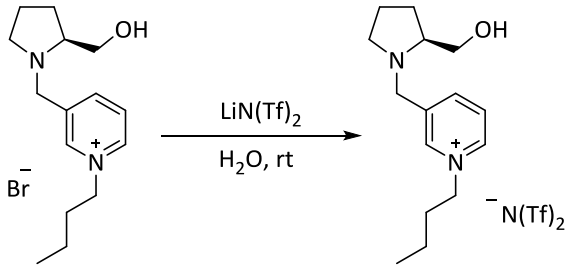
Preparation from **81**[xvi] (0.58 g, 3.00 mmol) according to procedure VI 3 with *n*-butylbromide (0.32 ml, 3.00 mmol) and gave **82** as viscous brown oil.

Analytical data was in accordance with literature.[86]

[xvi] Compound **81** was synthesized according to literature and available in our lab.[164]

Yield	0.98 g (99%) brown oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 9.64 (s, 1H, *H*-pyridine), 9.24 (d, J = 5.87 Hz, 1H, *H*-pyridine), 8.41 (d, J = 7.83 Hz, 1H, *H*-pyridine), 8.00 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, *H*-pyridine), 4.85 (m, 2H, C*H*-N arom), 4.42/3.72 (2d, J = 14.86 Hz, 2H, CH_2-N), 4.10 (brs, 1H, O*H*), 3.50 (m, 2H, CH_2-OH), 2.95-2.52 (m, 2H, CH_2-N-pyrrolidine, C*H*-N-pyrrolidine), 2.35-2.21 (m, 1H, CH_2-N pyrrolidine), 2.14-1.48 (m, 6H, CH_2-CH_2-CH_2, 2 CH_2-CH_2), 1.35 (sext, J = 7.75 Hz, 2H, CH_2-CH_2-CH_2), 0.91 (t, J = 7.24 Hz, 3H, CH_3-CH_2-CH_2)
$T_{5\%\ onset}$	279 °C
ν_{max}/cm^{-1}	3535 (O-H), 2879 (N-C), 1636(C-C), 1329 (C=C), 1052 (NH-CH_3)

VI 3.1.20 1-Butyl-3-[[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]-pyridinium bis(trifluoromethane)sulfonimide 83



$C_{17}H_{25}F_6N_3O_5S_2$
529.52

82 **83**

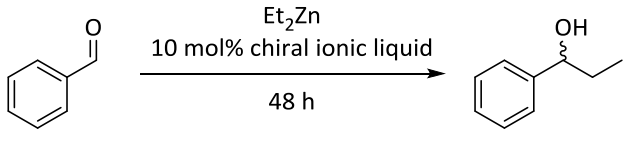
Product **83** was prepared according to VI 2.1.3 using compound **82** (2.22 g, 6.76 mmol) and lithium bis(trifluoromethane)sulfonimide (2.13 g, 7.44 mmol) to yield the product as yellow oil.

Analytical data was in accordance with literature.[86]

Yield	3.24 g (91%) yellow oil
^{1}H-NMR (200 MHz, d_6-DMSO)	δ_H = 9.04 (s, 1H, *H*-pyridine), 8.97 (d, J = 5.87 Hz, 1H, *H*-pyridine), 8.53 (d, J = 7.83 Hz, 1H, *H*-pyridine), 8.08 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, *H*-pyridine), 4.82-4.52 (m, 3H, C*H*-N arom, O*H*), 4.27/3.66 (2d, J = 14.48 Hz/ J = 14.67, 2H, CH_2-N), 3.42 (brs, 2H, CH_2-OH), 2.94-2.41 (m, 2H, CH_2-N-pyrrolidine, C*H*-N-pyrrolidine),2.27 (m, 1H, CH_2-N-pyrrolidine), 1.91 (m, 3H, CH_2-CH_2-CH_2, CH_2-CH_2), 1.75-1.42 (m, 3H, 2 CH_2-CH_2), 1.30 (sext, J = 7.75 Hz, 2H, CH_2-CH_2-CH_2), 0.92 (t, J = 7.34 Hz, 3H, CH_3-CH_2-CH_2)
$T_{5\%\ onset}$	280 °C

ν_{max}/cm^{-1} 3551 (O-H), 2880 (N-C), 1636(C-C), 1346 (C=C), 1132 (S=O), 1178 (C-F_3), 1052 (NH-CH_3)

VI 3.1.21 General Procedure for the Enantioselective Alkylation of Benzaldehyde



$C_9H_{12}O$
136.19

84 **85**

The chiral ionic liquid (0.10 mmol) was dissolved in 2 ml of anhydrous solvent under a dry argon atmosphere and cooled to 0 °C. A solution of diethylzinc (1.0 M in *n*-hexane, 2.20 mmol) was added slowly at 0 °C. After the reaction was stirred for 30 minutes, freshly distilled benzaldehyde **84** (0.1 g, 1.00 mmol) was added dropwise *via* microsyringe at 0 °C, the reaction was slowly warmed to room temperature and stirred for 48 hours at this temperature. The mixture was carefully hydrolyzed with 1 M HCl and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with a small amount of brine, dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (30 g silica, PE:EtO_2= 5:1) to yield 1-phenyl-1-propanol **85**as colorless liquid.

Data are in accordance with literature.[164]

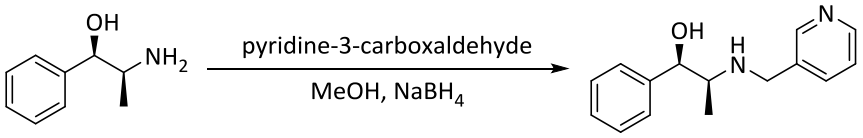
^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.28 -7.18 (m, 5H, *H*-arom), 4.52 (t, J = 6.58 Hz, 1H, C*H*-OH), 1.85 (brs, 1H, O*H*), 1.80-1.60 (m, 2H, CH_2-CH_3), 0.84 (t, J = 7.43 Hz, 3H, CH_3)

For recycling experiments the crude reaction mixture was hydrolyzed with 1 M HCl and extracted three times with *n*-hexane. The combined *n*-hexane layers were dried with anhydrous Na_2SO_4, filtered and concentrated to yield **85** as colorless liquid.

The aqueous layers were washed with CH_2Cl_2 and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The obtained chiral ionic liquid was dried under reduced pressure (0.01 mbar) and used for a consecutive run.

VI 4 Amino Alcohol-Derived Chiral Ionic Liquids in Transfer Hydrogenation

VI 4.1.1 (1*R*,2*S*)-1-Phenyl-2-((pyridin-3-ylmethyl)amino)propan-1-ol 87



$C_{15}H_{18}N_2O$
242.32

86 **87**

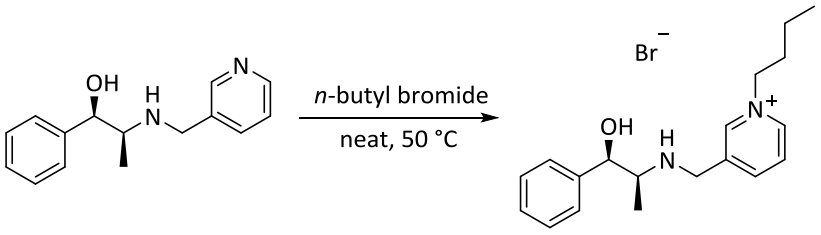
Preparation from (1*R*,2*S*)-norephedrine **86** (0.50 g, 3.31 mmol) according to procedure VI 3.1.1 with pyridine-3-carboxaldehyde (0.31 ml, 3.31 mmol), 1.50 g 3Å activated molecular sieve and sodium borohydride (0.14 g, 3.64 mmol) to give **87** as colorless crystals after purification *via* MPLC (CH_2Cl_2:MeOH= 6:1).

Analytical data was in accordance with literature.[164]

Yield 0.64 g (80%) colorless crystals

^{1}H-NMR (200 MHz, MeOH) δ_H= 8.46-8.40 (m, 2H, *H*-pyridine), 7.78-7.73 (m, 1H, *H*-pyridine), 7.41-7.25 (m, 5H, *H*-arom), 4.70 (d, J = 5.00 Hz, C*H*-OH), 3.82 (dd, J_1= 5.28 Hz, J_2= 32.50 Hz, 2H, CH_2-NH), 2.92-2.79 (m, 1H, C*H*-CH_3), 1.04 (d, J= 6.46, 3H, CH_3)

VI 4.1.2 1-Butyl-3-((((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)amino)methyl)pyridin-1-ium bromide 88



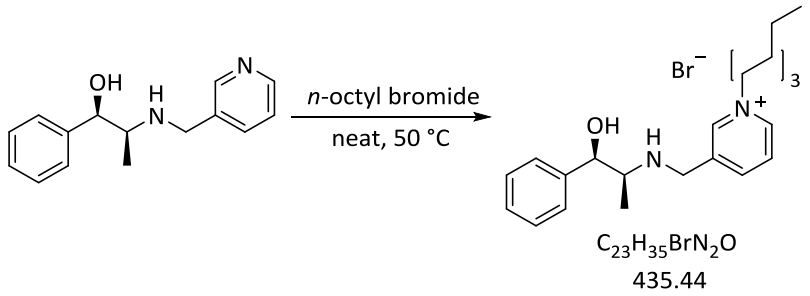
$C_{19}H_{27}BrN_2O$
379.34

87 **88**

Preparation from **87** (1.14 g, 4.71 mmol) according to procedure VI 3 with *n*-butyl bromide (0.51 ml, 4.71 mmol) and gave **88** as viscous brown oil. The product was purified by preparative HPLC using MeOH/H_2O=50:50 to yield the product as light yellow oil.

Yield	0.79 g (54%) yellow oil
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.92 (s, 1H, *H*-pyridine), 8.85 (d, J = 6.00 Hz, 1H, *H*-pyridine), 8.46 (d, J = 8.05 Hz, 1H, *H*-pyridine), 8.03-7.96 (m, 1H, *H*-pyridine), 7.40-7.25 (m, 5H, *H*-arom), 4.72 (d, J = 4.80 Hz, C*H*-OH), 4.60 (t, J = 7.54 Hz, 2H, CH_2-N), 4.08 (dd, J_1= 6.60 Hz, J_2= 37.28 Hz, 2H, CH_2-NH), 2.98-2.86 (m, 1H, C*H*-CH_3), 2.07-1.91 (m, 2H, CH_2-CH_2-N), 1.42 (sext, J = 7.44 Hz, 2H, CH_2-CH_2-CH_2-N), 1.08-0.98 (m, 6H, CH_3, CH_3-CH_2-CH_2-CH_2-N)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 143.4 (2d, *C*-arom), 142.5 (d, *C*-arom), 141.3 (d, *C*-arom), 141.2 (s, *C*-arom), 126.6 (s, *C*-arom), 126.5 (2d, *C*-arom), 126.0 (d, *C*-arom), 124.9 (2d, *C*-arom), 73.4 (d, *C*H-OH), 60.0 (t, *C*H_2-NH), 57.2 (d, *C*H-CH_3), 45.4 (t, CH_2-N^+), 31.6 (t, CH_2-*C*H_2-CH_2-CH_3), 17.6 (t, CH_2-CH_2-*C*H_2-CH_3), 12.2 (q, CH_2-CH_2-CH_2-*C*H_3), 11.0 (q, CH-*C*H_3)
Specific Rotation	α_D^{20} = +3.52 (c 0.79, MeOH)
$T_{5\%\ onset}$	213 °C
ν_{max}/cm^{-1}	3276 (O-H), 1633 (C-C), 1593 (C-C), 1449 (C=C), 1116 (NH-CH_3), 702 (C-H arom)
Elemental analysis	calculated: w-% C: 60.16, w-% H: 7.17, w-% N: 7.38 calculated: 0.69xH_2O: w-% C: 58.25, w-% H: 7.30, w-% N: 7.15 measured: w-% C: 58.27, w-% H: 6.99, w-% N: 7.38

VI 4.1.3 3-((((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)amino)methyl)-1-octylpyridin-1-ium bromide 89



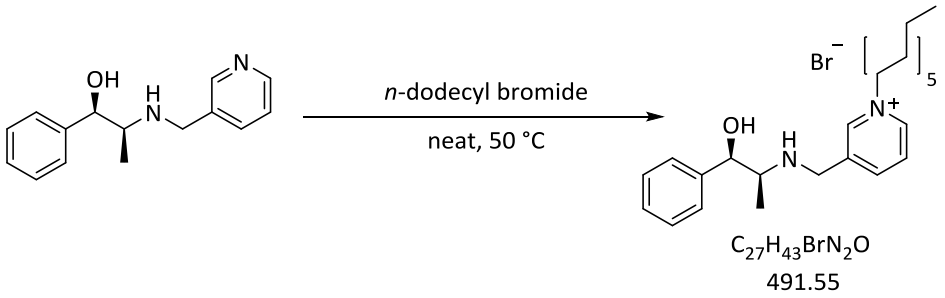
$C_{23}H_{35}BrN_2O$
435.44

87 **89**

Preparation from **87** (0.46 g, 1.89 mmol) according to procedure VI 3 with *n*-octyl bromide (0.33 ml, 1.89 mmol) and gave **89** as viscous brown oil. The product was purified by preparative HPLC using MeOH/H_2O=50:50 to yield the product as light yellow oil.

Yield	0.32 g (45%) yellow oil
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.94 (s, 1H, *H*-pyridine), 8.86 (d, J = 5.98 Hz, 1H, *H*- pyridine), 8.48 (d, J = 8.05 Hz, 1H, *H*- pyridine), 8.03-7.96 (m, 1H, *H*- pyridine), 7.40-7.25 (m, 5H, H-arom), 4.89 (d, J = 4.89 Hz, 1H, C*H*-OH), 4.59 (t, J = 7.54 Hz, 2H, CH_2-N), 4.09 (dd, J_1 = 6.10 Hz, J_2 = 36.82 Hz, 2H, CH_2-NH), 3.00-2.88 (m, 1H, C*H*-CH_3), 2.04-2.01 (m, 2H, CH_2-CH_2-N), 1.38-1.30 (m, 10H, CH_2-CH_2-CH_2-CH_2-CH_2-N), 1.06 (d, J = 6.60 Hz, 3H, CH_3), 0.93-0.86 (m, 3H, CH_3-alkyl-N)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 148.6 (2d, *C*-arom), 147.7 (d, *C*-arom), 146.5 (d, *C*-arom), 141.4 (s, *C*-arom), 134.5 (s, *C*-arom), 129.6 (2d, *C*-arom), 129.0 (d, *C*-arom), 127.0 (2d, *C*-arom), 71.5 (d, *C*H-OH), 63.6 (t, *C*H_2-NH), 61.6 (d, *C*H-CH_3), 43.3 (t, CH_2-N^+), 33.9 (t, $(CH_2)_{10}$-*C*H_2), 32.4 (t, $(CH_2)_9$-*C*H_2), 30.2/30.1 (2t, $(CH_2)_{8/7}$-*C*H_2), 27.7 (t, $(CH_2)_6$-*C*H_2), 20.5 (t, $(CH_2)_5$-*C*H_2), 20.1 (t, $(CH_2)_4$-*C*H_2), 15.6 (t, $(CH_2)_3$-*C*H_2), 14.4 (q, $(CH_2)_{12}$-*C*H_3), 10.1 (q, CH-*C*H_3)
Specific Rotation	α_D^{20} = +6.75 (c 0.77, MeOH)
$T_{5\%\ onset}$	200 °C
ν_{max}/cm^{-1}	3294 (N-H), 2925 (O-H), 1632 (C-C), 1535 (C-C), 1498 (C=C), 1197 (NH-CH_3), 702 (C-H arom.)
Elemental analysis	calculated: w-% C: 64.13, w-% H: 8.30, w-% N: 6.23 calculated: 4.71xH_2O: w-% C: 53.95, w-% H: 8.76, w-% N: 5.24 measured: w-% C: 53.97, w-% H: 8.53, w-% N: 4.97

VI 4.1.4 1-Dodecyl-3-((((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)amino)methyl)pyridin-1-ium bromide 90

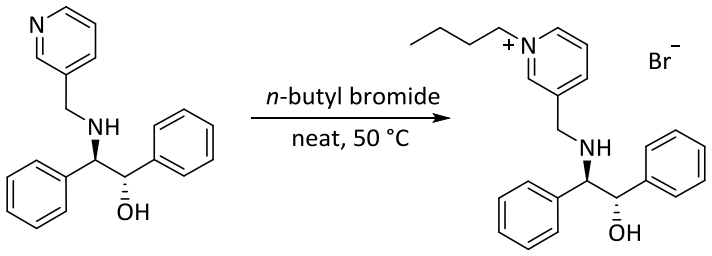


87 **90**

Preparation from **87** (1.14 g, 4.70 mmol) according to procedure VI 3 with *n*-dodecyl bromide (1.13 ml, 4.70 mmol) and gave **90** as viscous brown oil. The product was purified by preparative HPLC using MeOH/H_2O=50:50 to yield product as light yellow liquid.

Yield	1.05 g (59%) yellow liquid
^{1}H-NMR (400 MHz, MeOD)	δ_H = 8.89 (s, 1H, *H*-pyridine), 8.84 (d, J = 6.06 Hz, 1H, *H*-pyridine), 8.45 (d, J = 8.15 Hz, 1H, *H*-pyridine), 8.02-7.95 (m, 1H, *H*-pyridine), 7.40-7.25 (m, 5H, H-arom.), 4.69 (d, J = 4.89 Hz, C*H*-OH), 4.58 (t, J = 7.53 Hz, 2H, CH_2-N), 4.05 (dd, J_1 = 6.90 Hz, J_2 = 37.66 Hz, 2H, CH_2-NH), 2.94-2.81 (m, 1H, C*H*-CH_3), 2.04-1.97 (m, 2H, CH_2-CH_2-N), 1.38-1.30 (m, 18H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-N), 1.06 (d, J = 6.65 Hz, 3H, CH_3), 0.93-0.87 (m, 3H, CH_3-alkyl-N)
^{13}C-NMR (100 MHz, MeOD)	δ_C = 147.0 (2d, *C*-arom), 146.1 (d, *C*-arom), 144.9 (d, *C*-arom), 140.2 (s, *C*-arom), 128.2 (2d, *C*-arom), 128.0 (s, *C*-arom), 127.5 (d, *C*-arom), 125.7 (2d, *C*-arom), 70.4 (d, *C*H-OH), 62.2 (t, *C*H_2-NH), 62.1 (d, *C*H-CH_3), 52.2 (t, CH_2-N^+), 45.5 (2t, $(CH_2)_{11}$-*C*H_2), 31.5 (t, $(CH_2)_9$-*C*H_2), 31.2 (t, $(CH_2)_8$-*C*H_2), 28.8/28.7 (2t, $(CH_2)_{7/6}$-*C*H_2), 25.9 (t, $(CH_2)_5$-*C*H_2), 22.3 (t, $(CH_2)_4$-*C*H_2), 13.0 (t, $(CH_2)_3$-*C*H_2), 9.08 (t, $(CH_2)_2$-*C*H_2), 7.8 (q, $(CH_2)_{12}$-*C*H_3), 6.3 (q, CH-*C*H_3)
Specific Rotation	α_D^{20} = +0.58 (c 0.97, MeOH)
$T_{5\%\ onset}$	225 °C
ν_{max}/cm^{-1}	3305 (N-H), 2922 (O-H), 1632 (C-C), 1634 (C-C), 1498 (C=C), 1198 (NH-CH_3), 702 (C-H-arom)
Elemental analysis	calculated: w-% C: 65.97, w-% H: 8.82, w-% N: 5.70 calculated: 7.20xH_2O: w-% C: 52.20, w-% H: 9.31, w-% N: 4.51 measured: w-% C: 52.04, w-% H: 7.87, w-% N: 5.76

VI 4.1.5 1-Butyl-3-((((1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl)amino)methyl)pyridin-1-ium bromide 91



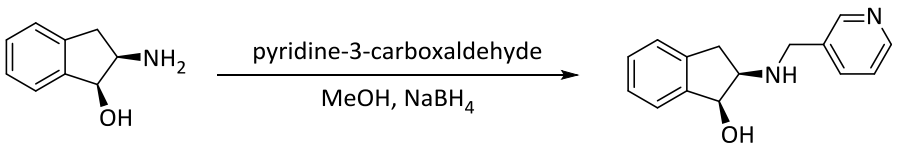
$C_{24}H_{29}BrN_2O$
441.41

52 **91**

Preparation from **52** (0.40 g, 1.31 mmol) according to procedure VI 3 with *n*-butyl bromide (0.14 ml, 1.31 mmol) and gave **91** as viscous yellow oil. The product was purified by preparative HPLC using MeOH/H_2O=80:20 to yield the product as light yellow liquid

Yield	0.32 g (64%) yellow liquid
^{1}H-NMR (200 MHz, MeOD)	δ_H= 9.33 (s, 1H, *H*-pyridine), 9.06 (d, J = 5.76 Hz, 1H, *H*-pyridine), 8.11 (d, J = 7.89 Hz, 1H, *H*-pyridine), 7.86-7.79 (m, 1H, *H*-pyridine), 7.17-7.06 (m, 5H, H-arom), 5.09 (d, J = 3.91 Hz, C*H*-OH), 4.74 (t, J = 7.25 Hz, 2H, CH_2-N), 3.97 (d, J = 4.00 Hz, C*H*-NH), 3.86 (s, 2H, CH_2-NH), 2.91 (brs, 1H, N*H*) 2.98-2.86 (m, 1H, C*H*-CH_3), 2.00-1.85 (m, 2H, CH_2-CH_2-N), 1.40-1.29 (m, 2H, CH_2-CH_2-CH_2-N), 0.92 (t, J = 7.33 Hz, 3H, CH_3-CH_2-CH_2-CH_2-N)
^{13}C-NMR (50 MHz, MeOD)	δ_C= 146.5 (d, *C*-arom), 144.4 (d, *C*-arom), 143.5 (s, *C*-arom), 140.9 (d, *C*-arom), 130.0 (s, *C*-arom), 129.2 (s, *C*-arom), 129.0 (d, *C*-arom), 128.8 (d, *C*-arom), 128.7 (d, *C*-arom), 128.3 (d, *C*-arom), 78.3 (d, *C*H-OH), 69.9 (d, *C*H-N), 62.8 (t, *C*H_2-CH_2-CH_2), 55.7 (t, *C*H_2), 34.4 (t, CH_2-*C*H_2-CH_2), 20.5 (t, CH_2-CH_2-*C*H_2), 13.8 (q, *C*H_3-CH_2-CH_2)
Specific Rotation	α_D^{20} = +9.66 (c 1.02, MeOH)
$T_{5\%\ onset}$	218 °C
ν_{max}/cm^{-1}	3250 (N-H), 2707 (O-H), 1598 (C-C), 1357 (C=C), 1191 (NH-CH_3), 702 (C-H-arom)
Elemental analysis	calculated: w-% C: 65.31, w-% H: 6.62, w-% N: 6.35 calculated: 2.62xH_2O: w-% C: 61.25, w-% H: 6.91, w-% N: 5.95 measured: w-% C: 61.29, w-% H: 7.07, w-% N: 5.81

VI 4.1.6 (1*S*,2*R*)-2-((Pyridin-3-ylmethyl)amino)-2,3-dihydro-1*H*-inden-1-ol 93



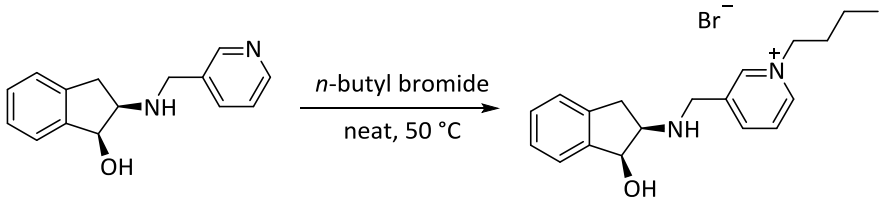
$C_{15}H_{16}N_2O$
240.31

92 **93**

Preparation from (1*S*,2*R*)-aminoindanol **92** (0.51 g, 3.41 mmol) according to procedure VI 3.1.1 with pyridine-3-carboxaldehyde (0.32 ml, 3.41 mmol), 2.00 g 3Å activated molecular sieve and sodium borohydride (0.13 g, 3.41 mmol) to give **93** as colorless crystals after MPLC (CH_2Cl_2:MeOH= 6:1).

Yield	0.48 g (59%) colorless crystals
Mp	90-93 °C
^{1}H-NMR (200 MHz, MeOD)	δ_H = 8.64 (d, J = 2.00 Hz, 1H, *H*-pyridine), 8.55 (dd, J_1 = 1.59 Hz, J_2 = 4.81 Hz, 1H, *H*-pyridine), 7.78 (td, J_1 = 1.84 Hz, J_2 = 7.45 Hz, 1H, *H*-pyridine), 7.34-7.25 (m, 5H, H-arom), 4.48-4-42 (m, 1H, C*H*-NH), 4.14 (d, J = 5.28 Hz, C*H*-OH), 4.04 (s, 2H, CH_2-NH), 3.15-2.92 (m, 2H, CH_2-indol), 2.85 (brs, 1H, N*H*)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 149.6 (d, *C*-pyridine), 148.8 (d, *C*-pyridine), 142.0 (s, *C*-arom), 140.9 (s, *C*-pyridine), 136.0 (d, *C*-pyridine), 135.2 (s, *C*-arom), 128.2 (*C*-pyridine), 126.8 (d, *C*-arom), 125.7 (d, *C*-arom), 123.9 (d, *C*-arom), 123.6 (d, *C*-arom), 71.0 (d, *C*H-OH), 65.3 (d, *C*H-NH), 49.8 (t, *C*H_2-NH), 39.7 (t, *C*H_2-indanol)
Specific Rotation	α_D^{20} = -9.84 (c 0.89, MeOH)
$T_{5\%\ onset}$	255 °C
ν_{max}/cm^{-1}	3300 (N-H), 2916 (O-H), 1737 (C-C), 1456 (C=C), 729 (C-H-arom)
Elemental analysis	calculated: w-% C: 74.97, w-% H: 6.71, w-% N: 11.66 measured: w-% C: 75.00, w-% H: 6.55, w-% N: 11.66

VI 4.1.7 1-Butyl-3-((((1*S*,2*R*)-1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)amino)methyl)pyridin-1-ium bromide 94



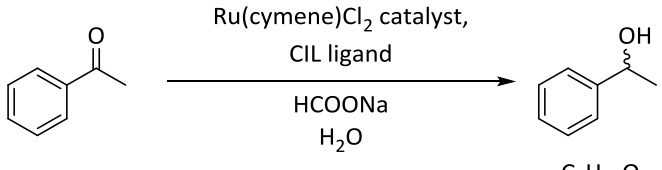
$C_{19}H_{25}BrN_2O$
377.33

93 **94**

Preparation from **93** (0.81 g, 3.35 mmol) according to procedure VI 3 with *n*-butyl bromide (0.36 ml, 3.35 mmol) and gave **94** as viscous brown oil.

Yield	0.78 g (61%) brown oil
^{1}H-NMR (200 MHz, MeOD)	δ_H = 9.17 (s, 1H, 8.64, *H*-pyridine), 8.94 (d, J = 6.06 Hz, 1H, *H*-pyridine), 8.70 (d, J = 8.03 Hz, 1H, *H*-pyridine), 8.11-8.08 (m, 1H, *H*-pyridine), 7.53-7.25 (m, 5H, *H*-arom), 4.70-4.63 (m, 3H, CH_2-N$^+$, CH_{2a}-NH), 4.38-4.30 (m, 3H, C*H*-OH, CH_{2b}-NH, C*H*-NH), 3.10-2.92 (m, 2H, CH_2-indanol), 2.03 (p, J = 7.58 Hz, 2H, CH_2-CH_2-CH_2-CH_3), 1.50-1.38 (m, 2H, CH_2-CH_2-CH_2-CH_3), 1.02 (t, J = 7.23 Hz, 3H, CH_2-CH_2-CH_2-CH_3)
^{13}C-NMR (50 MHz, MeOD)	δ_C = 149.6 (d, *C*-pyridine), 148.8 (d, *C*-pyridine), 142.0 (s, *C*-arom), 140.9 (s, *C*-pyridine), 136.0 (d, *C*-pyridine), 135.2 (s, *C*-arom), 129.4 (*C*-pyridine), 128.9 (d, *C*-arom), 127.8 (d, *C*-arom), 126.4 (d, *C*-arom), 126.0 (d, *C*-arom), 72.8 (d, *C*H-OH), 66.8 (d, *C*H-NH), 62.9 (t, *C*H_2-N$^+$), 40.5 (t, *C*H_2-NH), 34.4 (t, *C*H_2-indanol), 20.5 (t, CH_2-*C*H_2-CH_3), 13.8 (q, *C*H_3)
Specific Rotation	α_D^{20} = -2.04 (c 0.47, MeOH)
$T_{5\%\ onset}$	231 °C
ν_{max}/cm^{-1}	3264 (N-H), 2929 (O-H), 1637 (C-C), 1634 (C-C), 1456 (C=C), 729 (C-H-arom)
Elemental analysis	calculated: w-% C: 60.48, w-% H: 6.68, w-% N: 7.42 calculated: 1.47xH_2O= w-% C: 56.54, w-% H: 6.97, w-% N: 6.94 measured: w-% C: 56.48, w-% H: 6.45, w-% N: 6.90

VI 4.1.8 General Procedure for the Enantioselective Transferhydrogenation of Acetophenone: Application of Amino Alcohol Chiral Ionic Liquids



95 **96**

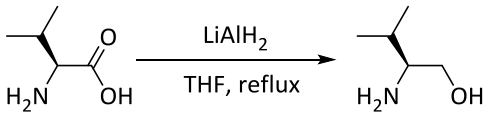
The chiral ionic liquids (0.02 mmol) and the Ru-catalyst (0.01 mmol) were weighted in a predried schlenk flask using a glove box and dissolved in 4 ml water which was freeze-dried prior to use. The active catalyst complex was stirred at 40 °C for 30 minutes before ketone **95** (2 mmol) and sodium formiate (10.00 mmol) were added under inert atmosphere. The reaction mixture was stirred under the given conditions for 48 hours. After completed reaction the mixture was extracted with ether, dried over Na_2SO_4 and filtered over a short patch to silica to remove excess ruthenium particles and concentrated to yield the product **96** as colorless liquid. No further purification was necessary and the product was analysed via ^{1}H NMR, GC and HPLC.

Analytical data was in accordance with literature.[208]

^{1}H-NMR (200 MHz, MeOD) δ_H = 7.50-7.18 (m, 5H, *H*-arom), 4.83 (q, J = 6.45 Hz, 1H, C*H*-OH), 1.74 (brs, 1H, OH), 1.42 (d, J = 6.45 Hz, CH_3-CH)

VI 5 Synthesis of Aza-bisoxazoline-Containing Chiral Ionic Liquids

VI 5.1.1 (*S*)-2-Amino-3-methylbutan-1-ol 61



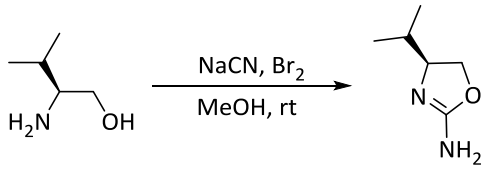
$C_5H_{13}NO$
103.16
61

Product **59** was prepared according to VI 2.3.1 using L-valine (10.00 g, 85.50 mmol) and $LiAlH_4$ (10.00 g, 255.00 mmol) to yield the product as colorless oil.

Analytical data was in accordance with literature.[209]

Yield	7.63 g (87%) colorless oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 3.57 (dd, J_1 = 3.94 Hz, J_2 = 10.53 Hz, 1H, CH_{2a}-OH), 3.23 (dd, J_1 = 8.79 Hz, J_2 = 10.45 Hz, 1H, CH_{2b}-OH), 2.54-2-44 (m, 1H, CH-NH_2), 1.93 (brs, 2H, NH_2), 1.51 (sext, J = 6.72 Hz, 1H, CH-2CH_3), 0.85 (dd, J_1 = 2.57 Hz, J_2 = 6.80 Hz, 6H, 2CH_3)

VI 5.1.2 (*S*)-4-Isopropyl-4,5-dihydrooxazol-2-amine 97



$C_6H_{12}N_2O$
128.18

61 **97**

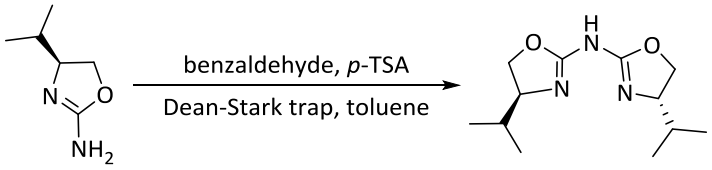
Bromine (13.49 g, 84.37 mmol) was added dropwise to 80 ml anhydrous MeOH at 0 °C before sodium cyanide (4.13 g, 84.37 mmol) was added in small portions over 45 min *via* a dosing screw. After the sodium cyanide was dissolved completely compound **62** (7.10 g 68.90 mmol) was added to the solution and the reaction mixture was stirred at rt for 1 hour until GC-MS indicated full conversion to the desired product. The reaction mixture was quenched with 30 ml conc. NH_3 (25%) in H_2O followed by the removal of MeOH under reduced pressure. The residue was dissolved in 30 ml aqueous NaOH (20%) and extracted three times by EtOAc. The combined organic layers were dried and the solvent was removed

under reduced pressure to yield product **97** as colorless crystals. The product was used for the next step without further purification.

Analytical data was in accordance with literature.[210]

Yield	8.27 g (84%) colorless crystals
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 4.82 (brs, 2H, NH_2), 4.25 (t, J = 8.39 Hz, 1H, CH_{2a}-OH), 3.92 (t, J = 7.63 Hz, 1H, CH_{2a}-OH), 3.71 (m, 1H, CH-N), 1.62 (sept, J = 6.72 Hz, 1H, CH-2CH_3), 0.87 (dd, J_1 = 6.71 Hz, J_2 = 16.80 Hz, 6H, 2CH_3)

VI 5.1.3 (*S*)-Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amine 98



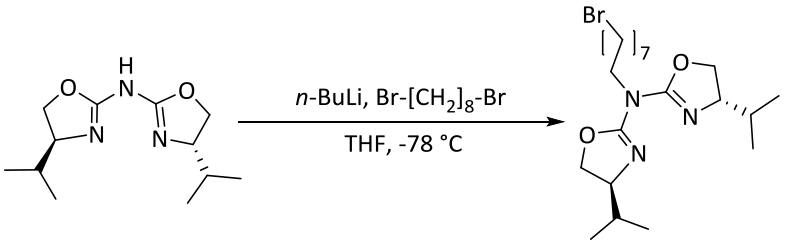
97 **98**

Compound **97** (2.85 g, 22.30 mmol), freshly distilled benzaldehyde (4.73 g, 44.6 mmol) and *p*-toluenesulfonic acid (0.19g, 1.12 mmol) were refluxed in 250 ml toluene on a Dean-Stark apparatus overnight. After complete reaction the solvent was removed under reduced pressure and the residue was either purified by MPLC (PE:EtOAc=50:50) or dissolved in 2N HCl in EtO_2 to produce the hydrochloride of the product, which was further extracted with CH_2Cl_2 and release with 2N NaOH. After drying of the combined organic layers and removal of the solvent under reduced pressure the product **98** could be isolated as yellow oil.

Analytical data was in accordance with literature.[210]

Yield	1.40 g (50%) yellow oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 4.37 (t, J = 8.73 Hz, 2H, CH_{2a}-OH), 4.04 (t, J = 7.80 Hz, 2H, CH_{2b}-OH), 3.85-3.73 (m, 2H, CH-N), 1.71 (sext, J = 7.80, 2H, CH-2CH_3), 0.93 (dd, J_1 = 6.70 Hz, J_2 = 16.11 Hz, 12H, 4CH_3)

VI 5.1.4 (*S*)-*N*-(8-Bromooctyl)-4-isopropyl-*N*-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-amine 101



$C_{20}H_{36}BrN_3O_2$
430.42

98 **101**

Compound **98** (0.51 g, 2.09 mmol) was dissolved in 30 ml anhydrous THF under argon atmosphere in a 50 ml flame-dried Schlenk flask and cooled to -78 °C. The reaction mixture was stirred for 10 min before *n*-BuLi (2.15 mmol) in *n*-hexane was slowly added *via* cannula and the reaction mixture was stirred at this temperature for 30 min. The cold bath was removed and the flask was warmed slowly to rt.

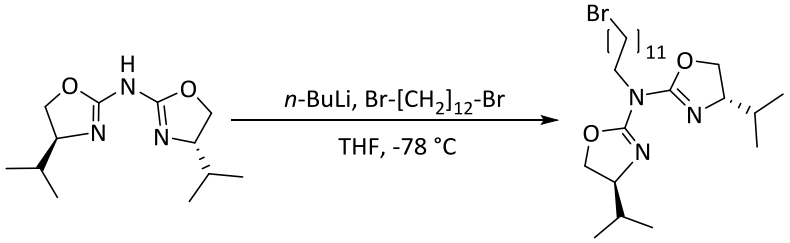
A solution of 1,8-dibromooctane (1.42 g, 5.23 mmol) in 170 ml anhydrous THF was meanwhile prepared and cooled to 0 °C. The solution of deprotonated amine was added dropwise to the dibromooctane solution under argon atmosphere *via* a transfer cannula and stirred at ambient temperature under inert atmosphere for three days until NMR showed complete conversion of the starting material.

The reaction mixture was quenched with satured NH_4Cl solution and extracted with Et_2O. The pooled organic layers were dried and the solvent was removed under reduced pressure. For purification the crude product was dissolved in EtOAc and filtered over a short a pad of silica using following solvents in the given order: PE, PE:EtOAc=1:1, EtOAc, CH_3CN. The product was isolated in the CH_3CN fraction, yielding the pure product **101** as light yellow oil.

Since the product showed high reactivity towards self-attack to polymerize it was immediately used for the next step.

Yield	0.42 g (46%) light yellow oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 4.24 (t, J = 8.73 Hz, 2H, CH_{2a}-O), 3.99 (t, J = 7.45 Hz, 2H, CH_{2b}-O), 3.80 - 3.64 (m, 4H, CH_2-N, 2C*H*-N), 3.28 (t, J = 6.84 Hz, 2H, CH_2-Br), 1.76-1.56 (m, 6H, 2C*H*-CH_3, CH_2-CH_2-N, CH_2-CH_2-Br), 1.30-1.14 (m, 8H, CH_2-CH_2- CH_2-CH_2-CH_2-CH_2-N), 0.79 (dd, J_1 = 16.31 Hz, J_2 = 6.62 Hz, 12H, 4CH_3)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 157.2 (s, N-*C*-O), 71.0 (t, *C*-O), 69.8 (d, *C*H-N), 50.0 (t, *C*H_2-N), 34.0 (t, C-Br), 32.9 (d, *C*H-CH_3), 29.1-26.4 (6t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-N), 18.7/17.7 (q, 2CH_3)
Specific Rotation	α_D^{20} = -16.40 (c 1.47, MeOH)

VI 5.1.5 (*S*)-*N*-(12-Bromododecyl)-4-isopropyl-*N*-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-amine 102



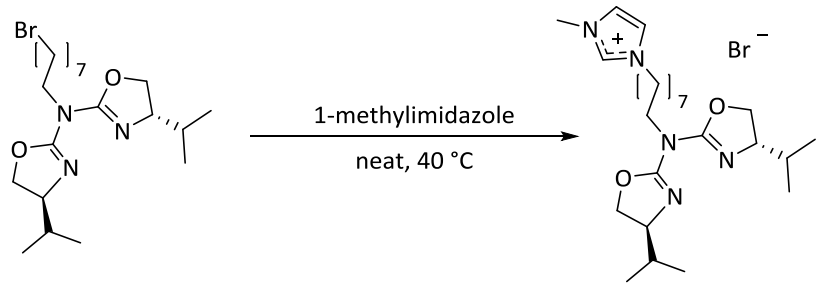
$C_{24}H_{44}BrN_3O_2$
486.53

98 **102**

Product **102** was prepared according to VI 5.1.4 using compound **98** (0.37 g, 1.75 mmol), *n*-BuLi (1.25 ml, 1.80 mmol) and 1,12-dibromododecane (2.87 g, 8.75 mmol) to yield the product as colorless oil.

Yield	0.21 g (28%) colorless oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 4.28 (t, J = 8.73 Hz, 2H, CH_{2a}-O), 4.04 (t, J = 7.48 Hz, 2H, CH_{2b}-O), 3.85-3.65 (m, 4H, CH_2-N, 2CH-N), 3.34 (t, J = 6.85 Hz, 2H, CH_2-Br), 1.81-1.57 (m, 6H, 2CH-CH_3, CH_2-CH_2-N, CH_2-CH_2-Br), 1.56-1.19 (m, 16H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-N), 0.84 (dd, J_1 = 16.36 Hz, J_2 = 6.69 Hz, 12H, 4CH_3)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 157.2 (s, N-*C*-O), 71.0 (t, *C*-O), 69.7 (d, *C*H-N), 50.1 (t, *C*H_2-N), 34.1 (t, C-Br), 32.8 (d, *C*H-CH_3), 29.5-26.5 (10t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-CH_2-N), 18.7/17.7 (q, 2CH_3)
Specific Rotation	α_D^{20} = -24.6 (c 1.90, EtOAc)

VI 5.1.6 1-(8-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)octyl)-3-methyl-1*H*-imidazol-3-ium bromide 103



101

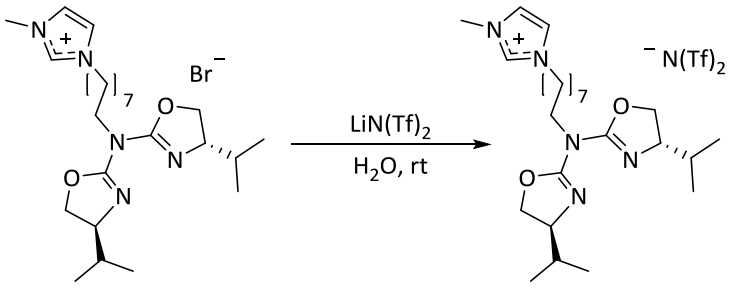
$C_{24}H_{42}BrN_5O_2$
512.53
103

Product **103** was prepared according to VI 2.1.2 using compound **101** (96 mg, 0.22 mmol) and 1-methyimidazole (17.5 µl, 0.22 mmol) to yield the product as colorless oil. The product was immediately used for the next step.

Yield 114 mg (99%) colorless oil

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 10.68 (s, 1H, *H*-imidazole), 7.30 (s, 1H, *H*-imidazole), 7.23 (s, 1H, *H*-imidazole), 4.24-4.41 (m, 4H, 2C*H*-N, CH_2-N-imidazole), 4.12 (s, 3H, CH_3-N-imidazole), 4.11 (t, 4H, CH_2-O), 3.71-3.93 (m, 4H, 2C*H*-N, CH_2-N), 1.58-2.00 (m, 6H, 2C*H*-CH_3, CH_2-CH_2-N, CH_2-CH_2-Br), 1.20-1.43 (m, 8H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-N), 0.89 (dd, J_1 = 16.41 Hz, J_2 = 6.75 Hz 12H, 4CH_3)

VI 5.1.7 1-(8-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)octyl)-3-methyl-1*H*-imidazol-3-ium bis(trifluoromethane)sulfonimide 104



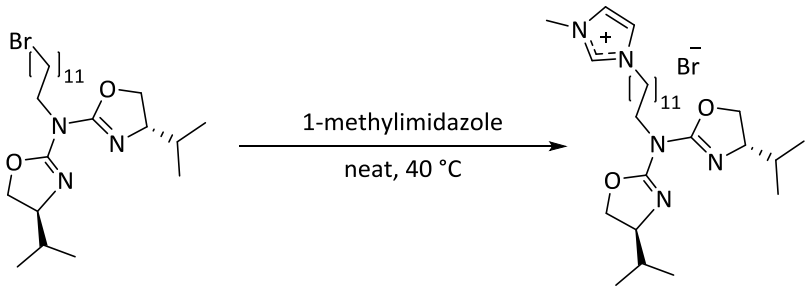
103 → **104**

$C_{26}H_{42}F_6N_6O_6S_2$
712.77

Product **104** was prepared according to VI 2.1.2 using compound **103** (114 mg, 0.22 mmol) and lithium bis(trifluoromethane)sulfonamide (69 mg, 0.24 mmol) to yield the product as colorless liquid.

Yield	148 mg (95%) colourless crystals
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.79 (s, 1H, *H*-imidazole), 7.30 (s, 1H, *H*-imidazole), 7.28 (s, 1H, *H*-imidazole), 4.42-4.38 (m, 2H, C*H*$_2$-N-imidazole), 4.11-4.09 (m, 4H, C*H*$_2$-O), 3.94 (s, 3H, CH_3-N-imidazole), 3.93-3.71 (m, 4H, 2C*H*-N, C*H*$_2$-N), 1.93-1.56 (m, 6H, 2C*H*-CH_3, C*H*$_2$-CH_2-N, C*H*$_2$-CH_2-imidazol), 1.20-1.40 (m, 8H, C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH_2-CH_2-N), 0.89 (dd, J_1 = 16.45 Hz, J_2 = 6.72 Hz, 12H, 4C*H*$_3$)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 157.2 (s, N-*C*-O), 123.5 (d, *C*-imidazole), 122.2 (d, *C*-imidazole), 119.7 (q, J = 301.41 Hz, *C*F_3), 71.1 (t, *C*H_2-O), 69.7 (d, *C*H-N), 50.1 (t, *C*H_2-N), 49.8 (t, CH_2-N-imidazole), 36.4 (q, CH_3-imidazole), 32.8 (d, *C*H-CH_3), 30.4-26.3 (5t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-CH_2-N), 18.6/17.6 (q, 2CH_3)
Specific Rotation	α_D^{20} = -11.86 (c 1.48, EtOAc)
$T_{5\%\ onset}$	260 °C
TLC-MS	positiv: *m/z* = 240.3 (Fragment V+H$^+$); negativ: *m/z* = 279.8 (NTf_2^-), 579.6 (2 NTf_2^- + Na^+)

VI 5.1.8 1-(12-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)dodecyl)-3-methyl-1*H*-imidazol-3-ium bromide 105



102 **105**

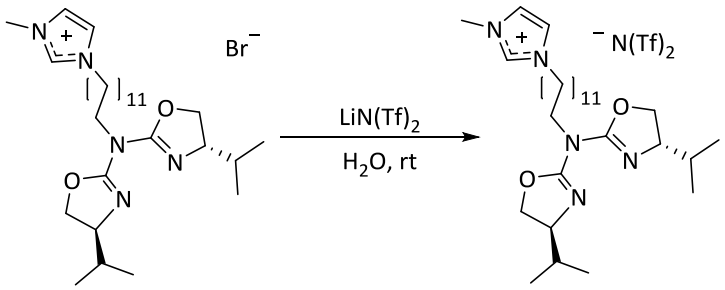
$C_{28}H_{50}BrN_5O_2$
568.63

Product **105** was prepared according to VI 2.1.2 using compound **102** (82 mg, 0.17 mmol) and 1-methyimidazole (13.6 µl, 0.17 mmol) to yield the product as yellow oil. The product was immediately used for the next step.

Yield 93 mg (96%) yellow oil

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 10.61 (s, 1H, *H*-imidazole), 7.35 (s, 1H, *H*-imidazole), 7.25 (s, 1H, *H*-imidazole), 4.24-4.40 (m, 4H, 2C*H*-N, CH_2-N-imidazole), 4.12 (s, 3H, CH_3-N-imidazole), 4.10 (t, 4H, CH_2-O), 3.70-3.93 (m, 4H, 2C*H*-N, CH_2-N), 1.58-1.98 (m, 6H, 2C*H*-CH_3, CH_2-CH_2-N, CH_2-CH_2-Br), 1.15-1.40 (m, 16H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2 -CH_2-CH_2-N), 0.89 (dd, J_1 = 16.41 Hz, J_2 = 6.75 Hz, 12H, 4CH_3)

VI 5.1.9 1-(12-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)dodecyl)-3-methyl-1*H*-imidazol-3-ium bis(trifluoromethane)sulfonimide 106



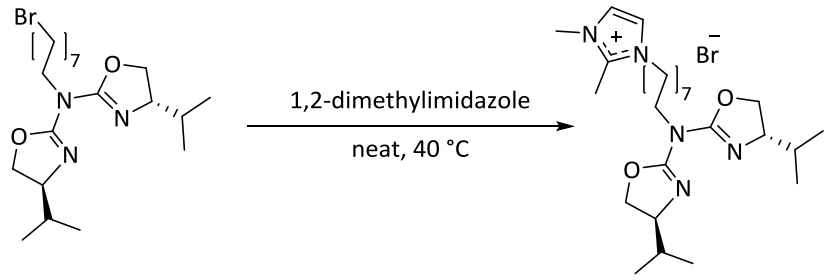
$C_{30}H_{50}F_6N_6O_6S_2$
768.87

105 **106**

Product **106** was prepared according to VI 2.1.2 using compound **105** (93 mg, 0.17 mmol) and lithium bis(trifluoromethane)sulfonimide (52 mg, 0.18 mmol) to yield the product as colorless liquid.

Yield	148 mg (95%) colourless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 8.89 (s, 1H, *H*-imidazole), 7.30-7.21 (m, 2H, *H*-imidazole), 4.45-4.31 (m, 2H, C*H*$_2$-N-imidazole), 4.18-4.12 (m, 4H, C*H*$_2$-O), 3.96 (s, 3H, CH_3-N-imidazole), 3.65-3.98 (m, 4H, 2C*H*-N, C*H*$_2$-N), 1.54-1.97 (m, 6H, 2C*H*-CH_3, C*H*$_2$-CH_2-N, C*H*$_2$-CH_2-imidazol), 1.13-1.36 (m, 16H, C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH_2-CH_2-N), 0.89 (dd, J_1 = 16.44 Hz, J_2 = 6.75 Hz, 12H, 4C*H*$_3$)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 156.2 (s, N-*C*-O), 122.6 (d, *C*-imidazole), 121.1 (d, *C*-imidazole), 119.8 (q, J = 301.45 Hz, *C*F_3), 70.2 (t, *C*H_2-O), 68.6 (d, *C*H-N), 59.4 (t, *C*H_2-N), 49.2 (t, CH_2-N-imidazole), 35.4 (q, CH_3-imidazole), 31.8 (d, *C*H-CH_3), 32.9-25.3 (10t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-N), 17.7/16.7 (q, 2CH_3)
Specific Rotation	α_D^{20} = -15.32 (c 1.09, EtOAc)
$T_{5\%\ onset}$	227 °C
TLC-MS	positiv: *m/z* = 296.4 (Fragment V+H$^+$); negativ: *m/z* = 279.8 (NTf_2^-), 579.6 (2 NTf_2^- + Na^+)

VI 5.1.10 1-(8-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)octyl)-2,3-dimethyl-1*H*-imidazol-3-ium bromide 107



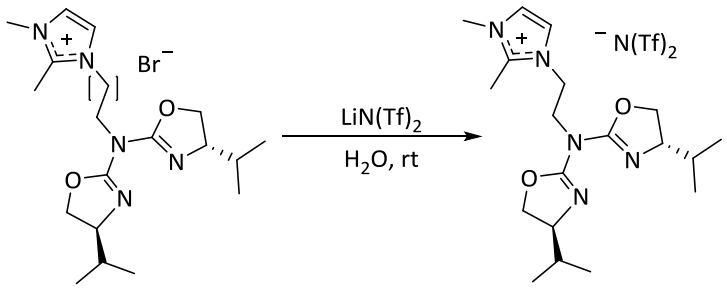
$C_{25}H_{44}BrN_5O_2$
526.55

101 **107**

Product **107** was prepared according to VI 2.1.6 using compound **101** (121 mg, 0.25 mmol) and 1,2-dimethyimidazole (24 mg, 0.25 mmol) to yield the product as yellow oil. The product was immediately used for the next step.

Yield	144 mg (99%) yellow oil
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 7.63 (s, 1H, *H*-imidazole), 7.35 (s, 1H, *H*-imidazole), 4.33-4.15 (m, 4H, 2C*H*-N, CH_2-N-imidazole), 4.10 (t, 4H, CH_2-O), 4.00 (s, 3H, CH_3-N-imidazole), 3.70-3.91 (m, 4H, 2C*H*-N, CH_2-N), 2.79 (s, 3H, CH_3-imidazole), 1.55-1.89 (m, 6H, 2C*H*-CH_3, CH_2-CH_2-N, CH_2-CH_2-Br), 1.20-1.43 (m, 8H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-N), 0.89 (dd, J_1 = 16.41 Hz, J_2 = 6.75 Hz, 12H, 4CH_3)

VI 5.1.11 1-(8-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)octyl)-2,3-dimethyl-1*H*-imidazol-3-ium bis(trifluoromethane)sulfonimide 108



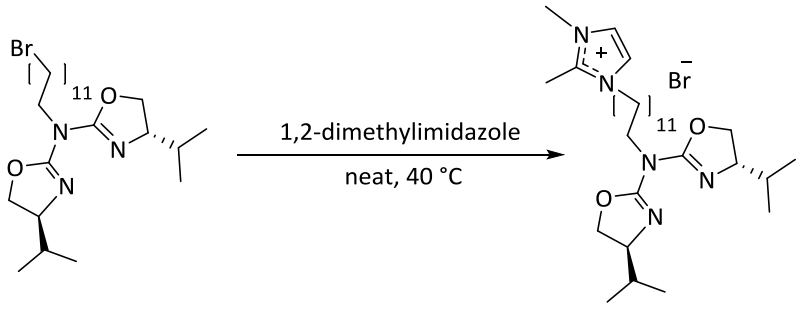
107

$C_{27}H_{44}F_6N_6O_6S_2$
726.79
108

Product **108** was prepared according to VI 2.1.2 using compound **107** (120 mg, 0.23 mmol) and lithium bis(trifluoromethane)sulfonimide (72 mg, 0.25 mmol) to yield the product as colorless liquid.

Yield	157 mg (98%) colourless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 7.16-7.09 (m, 2H, *H*-imidazole), 4.30 (t, J = 8.74 Hz, 2H, CH_2-N-imidazole), 4.04 (t, J = 7.55 Hz, 2H, CH_{2a}-O), 3.97 (t, J = 8.67 Hz, 2H, CH_{2b}-O), 3.73 (s, 3H, CH_3-N-imidazole), 3.69-3.92 (m, 4H, 2C*H*-N, CH_2-N), 2.58 (s, 3H, CH_3-imidazole), 1.54-1.87 (m, 6H, 2C*H*-CH_3, CH_2-CH_2-N, CH_2-CH_2-imidazol), 1.19 – 1.39 (m, 8H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-N), 0.88 (dd, J_1 = 15.67 Hz, J_2 = 6.70 Hz, 12H, 4CH_3)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 157.2 (s, N-*C*-O), 143.6 (s, *C*-imidazole), 122.6 (d, *C*-imidazole), 119.9 (q, J = 301.53 Hz, *C*F_3), 71.1 (t, *C*H_2-O), 69.7 (d, *C*H-N), 49.9 (t, *C*H_2-N), 48.8 (t, CH_2-N-imidazole), 35.3 (q, CH_3-imidazole), 32.8 (d, *C*H-CH_3), 29.5-26.1 (5t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-N), 18.6/17.6 (q, 2CH_3), 9.6 (q, CH_3-imidazole)
Specific Rotation	α_D^{20} = -15.92 (c 1.38, EtOAc)
$T_{5\%\ onset}$	273 °C
TLC-MS	positiv: *m/z* = 240.3 (Fragment V+H^+); negativ: *m/z* = 279.8 (NTf_2^-), 579.6 (2 NTf_2^- + Na^+)

VI 5.1.12 1-(12-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)dodecyl)-2,3-dimethyl-1*H*-imidazol-3-ium bromide 109



$C_{29}H_{52}BrN_5O_2$
582.66

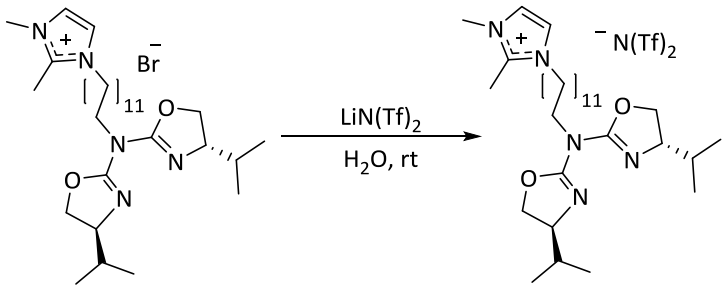
102 **109**

Product **109** was prepared according to VI 2.1.6 using compound **102** (87 mg, 0.19 mmol) and 1,2-dimethyimidazole (18 mg, 0.19 mmol) to yield the product as yellow oil. The product was immediately used for the next step.

Yield 107 mg (98%) yellow oil

^{1}H-NMR (200 MHz, $CDCl_3$) δ_H = 7.63 (s, 1H, *H*-imidazole), 7.35 (s, 1H, *H*-imidazole), 4.33-4.15 (m, 4H, 2C*H*-N, CH_2-N-imidazole), 4.10 (t, 4H, C*H*$_2$-O), 4.02 (s, 3H, CH_3-N-imidazole), 3.70-3.93 (m, 4H, 2C*H*-N, C*H*$_2$-N), 2.78 (s, 3H, CH_3-imidazole), 1.58-1.91 (m, 6H, 2C*H*-CH_3, C*H*$_2$-CH_2-N, C*H*$_2$-CH_2-Br), 1.17-1.40 (m, 16H, C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH_2-CH_2-N), 0.89 (dd, J_1 = 16.53 Hz, J_2 = 6.89 Hz, 12H, 4C*H*$_3$)

VI 5.1.13 1-(12-(Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)amino)dodecyl)-2,3-dimethyl-1*H*-imidazol-3-ium bis(trifluoromethane)sulfonimide 110



$C_{31}H_{52}F_6N_6O_6S_2$
782.90

109 **110**

Product **109** was prepared according to VI 2.1.2 using compound **108** (142 mg, 0.25 mmol) and lithium bis(trifluoromethane)sulfonimide (77 mg, 0.27 mmol) to yield the product as colorless liquid.

Yield	185 mg (97%) colorless liquid
^{1}H-NMR (200 MHz, $CDCl_3$)	δ_H = 7.21-7.15 (m, 2H, *H*-imidazole), 4.28 (t, J = 8.61 Hz, 2H, C*H*$_2$-N-imidazole), 4.17-3.94 (m, 4H, 2C*H*-N, C*H*$_2$-N), 3.87-3.65 (m, 4H, C*H*$_2$-O), 3.79 (s, 3H, CH_3-N-imidazole), 2.58 (s, 3H, CH_3-imidazole), 1.52-1.89 (m, 6H, 2C*H*-CH_3, C*H*$_2$-CH_2-N, C*H*$_2$-CH_2-imidazol), 1.14-1.38 (m, 16H, C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH_2-CH_2-N), 0.83 (dd, J_1 = 15.90 Hz, J_2 = 6.77 Hz, 12H, 4C*H*$_3$)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ_C = 157.2 (s, N-*C*-O), 143.6 (s, *C*-imidazole), 122.6 (d, *C*-imidazole), 120.0 (q, J = 301.61 Hz, *C*F_3), 71.0 (t, *C*H_2-O), 69.7 (d, *C*H-N), 50.0 (t, *C*H_2-N), 48.8 (t, CH_2-N-imidazole), 35.3 (q, CH_3-imidazole), 32.8 (d, *C*H-CH_3), 29.7-26.7 (5t, *C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-*C*H_2-CH_2-N), 18.6/17.7 (q, 2CH_3), 9.6 (q, CH_3-imidazole)
Specific Rotation	α_D^{20} = -12.30 (c 1.85, EtOAc)
$T_{5\%\ onset}$	216 °C
TLC-MS	positiv: *m/z* = 296.4 (Fragment V+H$^+$); negativ: *m/z* = 279.8 (NTf_2^-), 579.6 (2 NTf_2^- + Na^+)

VI 6 Ionic liquids in Gas Chromatography

VI 6.1 Preparation of Ionic liquid-coated Gas Chromatography Columns

VI 6.1.1 Pretreatment of Capillary Column

A saturated solution of sodium chloride in MeOH (HPLC grade) and 2ml were added dropwise to 4 ml of anhydrous CH_2Cl_2. The suspension was sonoficated for 15 minutes and stored at 0 °C for one hour until the bigger particles sedimented.

The supernatant solution was that added to a pressurizable flask and 5.50 ml of the suspension was pumped through the column using nitrogen pressure with a rate of 1 drop/s.

The column was that tightly closed and stored at rt for 12 hours, followed by evacuating the column at 1 mbar for 24 hours.

VI 6.1.2 Coating of Capillary Column

A solution of 0.4 wt% to 4 wt% IL in anhydrous CH_2Cl_2 (5.50 ml) were placed in a pressurizable flask and pumped through the pretreated column using nitrogen pressure with a rate of 1 drop/s. The column was stored at rt for 24 hours followed by evacuating the column at 1 mbar for 24 hours.

Afterwards the column was dried in a GC oven at 50 °C with open end at a helium flow rate of 1 ml/min for 12 hours. The conditioning of the capillary column was performed using following temperature program: isothermal 40 °C for 60 minutes, temperature ramp of 0.5 °C/min to 150 °C and isothermal at 150 °C for 360 minutes at a flow of 1.5 ml/min and a split ration of 10:1.

The analytes used for evaluation of the column were prepared with a concentration of 0.01% in diethylether (HPLC grade).

VII Appendix

VII 1 List of abbreviations

A^-	anion
AAIL	amino acid ionic liquid
AcOH	acetic acid
BINOL	[1,1'-binaphthalene]-2,2'-diol
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Bn	benzyl
BSA	bis(trimethylsilyl)acetamide
C^+	cation
Cbz	carboxybenzyl
CE	capillary electrophoresis
CD	circular dichroism
CIL	chiral ionic liquid
CMC	critical micell concentration
DABCO	triethylendiamine
DAIB	*exo*-(dimethylamino)isoborneol
DCC	*N*,*N*'-dicyclohexylcarbodiimid
DMAP	4-(dimethylamino)-pyridin
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
eq	molar equivalent
FCC	flash column chromatography
GC	gas chromatography
HOBt	1-hydroxybenzotriazol
HPLC	high pressure liquid chromatography
IL	ionic liquid
i-PrOH	*iso*-propanol
KOAc	potassium acetate
$Li(NTf)_2$	lithium bis(trifluoromethane)sulfonimide
MeOH	methanol
m.p.	melting point
m.w.	molecular weight
MPLC	medium pressure liquid chromatography
NMO	*N*-methylmorpholin-*N*-oxid
PE	petrolether
on	over night
p-TSA	*p*-toluenesulfonic acid
ref	reference
rt	room temperature, 25 °C
TCA	trichloroacetic acid
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

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VII 3 Curriculum Vitae – Maria Vasiloiu

Personal Details

Date of Birth: September 9th 1986 in Bukarest/ Rumania

Nationality: Austrian

Family Status: Unmarried

Education

1992/9 – 1996/7 Elementary school in Ostermiething and Braunau am Inn

1996/9 – 2004/5 Grammar school with focus on chemistry and biology

2004/10 – 2008/4 Bachelor studies of Technical Chemistry at Vienna University of Technology

2008/10 – 2010/5 Master studies of Synthetic Chemistry at the Institute of Applied Synthetic Chemistry – Diploma examination with distinction

Master thesis: Basic Chiral Ionic Liquids - A New Strategy of Acid-Free Organocatalysis

Since Sept. 2010 Ph.D research in the group of Prof. Gärtner under the supervision of Katharina Bica - Institute of Applied Synthetic Chemistry - Vienna University of Technology

Working Experience and Internships

2001/8 Internship at LAROVA in Berlin (Laboratory for enzymatic biochemistry)

2006/6 Internship at ISOVOLTA Graz (www.isovolta.at)

2006/8 Internship at laboratory for water trace analysis Dr. Gerhard Watschinger

each Oct. 2006-2009 Participation at VIENNALE International Film Festival Vienna

2007/8 Internship at BOREALIS in Vienna (www.borealisgroup.com)

2008/8, 2008/9 Internship at DSM – Fine Chemicals (www.dsm.com) in Linz

2009/4 Trainer at „Töchtertag TU Wien“

2009/7 Trainer at TechNIKE Summer - Workshop „Seife und CO“, organized by fForte WIT- Women in Technology

Since 2010 University Assistant at the Institute of Applied Synthetic Chemistry

Publications and conference contributions

Publications

Iron-catalyzed Michael addition. Chloroferrate ionic liquids as efficient catalysts under microwave conditions

Vasiloiu, M.; Gaertner, P.; Bica, K. *Science China: Chemistry* **2012**, 55, 1614-1619.

Basic chiral ionic liquids: A novel strategy for acid-free organocatalysis

Vasiloiu, M.; Rainer, D.; Gaertner, P.; Reichel, C.; Schroeder, C.; Bica, K. *Catalysis Today* **2013**, 200, 80-86.

Coordinating chiral ionic liquids

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Active pharmaceutical ingredients based on salicylate ionic liquids: insights into the evaluation of pharmaceutical profiles

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Automated evaluation of pharmaceutically active ionic liquids´(eco)toxicity through the inhibition of human carboxylesterase and Vibrio fischeri

Costa S., Dela Justina V., Bica K., Vasiloiu M., Pinto P., Saraiva M. *Journal of Hazardous Materials* **2014**, 265,133-141.

Poster

Basic Chiral Ionic Liquids - A New Strategy for Acid-Free Organocatalysis

M. Vasiloiu, K. Bica, P. Gärtner:
Poster: EUCHEM 2010 Conference on Molten Salts and Ionic Liquids, Bamberg, D; March 2010; in: "*Book of Abstracts*", (2010), S. 345.

Chiral ionic liquids: From recognition to chiral separation

M. Vasiloiu, P. Gärtner, K. Bica
Poster: 4th Congress on Ionic Liquids, Washington DC, USA; June 2011.

Chiral ionic liquids: Design, synthesis and application in asymmetric synthesis

M. Vasiloiu, P. Gärtner, K. Bica
Poster: EUCHEM 2012 Conference on Molten Salts and Ionic Liquids, Celtic Manor, Newport, Wales; UK; August 2012.

Design of chiral ionic liquids: Structural investigation towards chiral recognition

M. Vasiloiu, P. Gärtner, K. Bica
Poster: 5th Congress on Ionic Liquids, Algarve, Portugal; May 2013.