DISSERTATION

IONIC LIQUIDS IN ASYMMETRIC SYNTHESIS:

SYNTHESIS OF COORDINATING AND ORGANOCATALYTIC IONIC LIQUIDS AND THEIR APPLICATION IN ASYMMETRIC C-C BOND FORMING REACTIONS

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FÜR ALLE, DIE AN MICH GEGLAUBT HABEN

„Damit das Mögliche entsteht,
muss immer wieder
das Unmögliche versucht werden“
Herrmann Hesse

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DEUTSCHE KURZFASSUNG

Ziel der Arbeit war die Synthese neuer chiraler ionischer Flüssigkeiten sowie deren Anwendung als Katalysatoren in asymmetrischen C-C-Knüpfungsreaktionen.

Die Synthese von aminoalkoholfunktionalisierten chiralen ionischen Flüssigkeiten (CIL) erfolgte durch ein etabliertes Protokoll ausgehend von chiralen *L*-Aminosäuren und Ephedrin. Eine erfolgreiche Anwendung dieser CILs in der asymmetrischen Henry Reaktion wird berichtet. Es konnten gute Ausbeuten und Selektivitäten erzielt werden. Zusätzlich wird der Einsatz der aminoalkoholfunktionalisierten CILs in der asymmetrischen Cyclopropanierung von Styrol untersucht.

Weiters wird die Synthese von verschiedenen chiralen ionischen Flüssigkeiten ausgehend von *L*-Prolinderivaten vorgestellt. Diese organokatalytisch aktiven ionischen Flüssigkeiten beinhalten ein chirales sekundäres Amin zur Aktivierung von Carbonylen über Imin-Enaminbildung. Ein Einsatz dieser CILs als Organokatalysatoren in asymmetrischen Alkylierungsreaktionen wird vorgestellt.

SHORT ABSTRACT

Task of this thesis was the synthesis of novel chiral ionic liquids as well as their application in asymmetric C-C bond forming reactions.

Synthesis of amino alcohol functionalised chiral ionic liquids was carried out according to a well established protocol starting from chiral pool derived *L*-amino acids and ephedrine. The successful application of these CILs in asymmetric Henry reaction is reported. Good yields and enantioselectivities could be obtained. Additionally the usage of the amino alcohol functionalised ionic liquids in asymmetric cyclopropanation of styrene is examined.

Furthermore synthesis of various chiral ionic liquids starting from *L*-proline is presented. These organocatalytic active ionic liquids contain a chiral secondary amine for imine-enamine activation of carbonyls. The application of organocatalytic ionic liquids in asymmetric alkylation reactions is reported.

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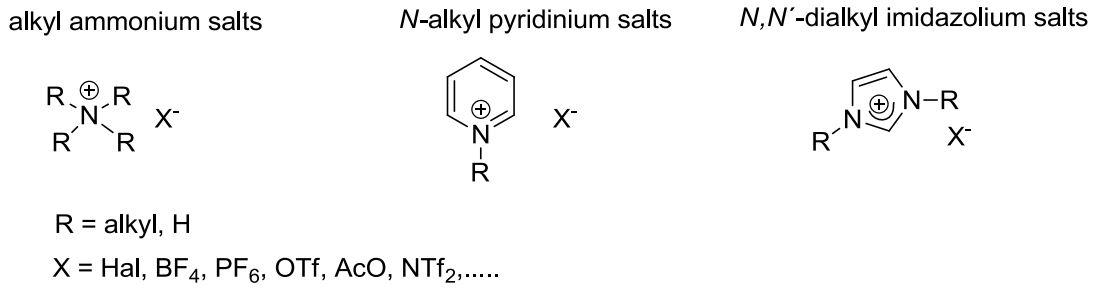
1 Introduction

1.1 Ionic liquids – facts and challenges

In 1914 a room temperature liquid salt was described for the first time.[1] The scientist Paul Walden synthesised the odourless and colourless liquid ethyl ammonium nitrate. Although this salt is believed to be the earliest reported example of a room-temperature ionic liquid (IL), it took until the early nineties, that academic and industrial research focused on this special class of low melting organic salts. The growing awareness of the outstanding and sometimes peculiar properties that ILs possess resulted in a comet-like boost in IL research and an almost exponential increase of publications. So far more than 1500 different ionic liquids have been reported and an almost unlimited number of ionic liquids would theoretically be possible by the choice of different ions.

Ionic liquids are defined as liquids that consist almost exclusively of ions. According to the current definition, ionic liquids have melting points or glass-transition temperatures below 100 °C. In particular ILs with a melting point around or below room temperature are classified as "room-temperature ionic liquids". Importantly, the properties of ILs can be fine tuned by changing the cation and anion counterparts.[2] The common classes of ILs comprise alkyl ammonium salts, *N*-alkyl pyridinium salts and *N,N´*-dialkyl imidazolium salts, whereat alkyl means any organic moiety (Scheme 1).[3]

[1] Walden, P. *Bull. Acad. Imper. Sci. (St Petersburg)* **1914**, 1800.
[2] Patil, M.L.; Sasai, H. *The Chemical Record*, **2008**, *8*, 98; Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed*. **2000**, *39*, 3772.
[3] Baudequin, C. ; Baudoux, J. ; Levillain, J. ; Cahard, D. ; Gaumont, A. ; Plaquevent, J. *Tetrahedron Asymmetry.* **2003**, *14*, 3081.



Scheme 1: Common classes of ionic liquids

The combination of the constantly growing number of possible cations and anions provides the possibility to create tailor-made ILs with different physical and chemical properties, well defined and perfectly adapted to certain applications.

As a consequence of those unique properties, the potential of ILs for synthesis was early recognised and they have rapidly found a place as valuable substitutes for volatile solvents due to their physical properties such as a negligible vapour pressure, high thermal stability, nonflammability and low volatility.[4] Ionic liquids turned out to be attractive novel type solvents in terms of environmentally benign chemistry according to the Montreal protocol.[5] In the last decades a wide range of organic reactions has been successfully performed in ILs as replacement for conventional solvents and the BASIL™ process for the production of the generic photo initiator precursor alkoxyphenylphosphine as first industrial process involving ILs was announced in March 2003.[6]

Interesting applications of ionic liquids can not only be found in synthesis but also in other different areas: To name but a few, they were used in the storage of hazardous gases, as electrolytes or as stationary phases in chromatography. Further material applications such as lubricants, thermometers or even active pharmaceutical ingredients and antimicrobial agents should be mentioned.[7] Even the potential of ILs as catalysts in organic synthesis was early recognised and up to now ionic liquids have been successfully applied in a variety of chemical

[4] Freemantle, M. *Chem. Eng. News*, 1998, *76*, 32; Wilkes, J.S. *Green Chem.*, **2002**, *4*, 73.
[5] Sheldon, R. A. *Chem. Commun.* **2001**, 2399. Gordon, C. M. *Appl. Catal. A.* **2001**, *222*, 101. Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today*, **2002**, *2654*, 1.
[6] Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, **2003**.
[7] Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed*. **2000**, *39*, 3772.

transformations.[8] Biphasic catalysis in or with ionic liquids cannot only improve reactivity but allows immobilising, activating and recycling of catalysts.[9]

As ionic liquids possess a polymer-like behaviour and show a high degree of organisation, a significant transfer of chirality can be expected with chiral species of ILs.[10] The specific properties of ILs combined with the comparable simple synthesis and the possibility for recyclation suggest that chiral ionic liquids (CILs) could outperform classical chiral solvents in asymmetric synthesis. The use of chiral ionic liquids is not only limited to the application as solvent but also possible for catalyst design or as chiral ligand itself.

The first attempt of using CILs in asymmetric synthesis was reported by Howarth et al., who prepared the cation chiral IL *N,N´*-bis[(*2S*)-2-methylbutyl] imidazolium bromide.[11] However, they were not successful in obtaining stereoselectivity. It took several years after the first CIL was published that the first chiral induction by a CIL was reported[12] and some more years that an enantioselective synthesis with an enantiomeric excess >90% received with a CIL was published.[13] Nevertheless, even this field is growing rapidly and nowadays CILs do not only function as solvents to induce chirality but also as catalysts in asymmetric reactions. Combining the advantages of recyclability of ILs and chiral induction, CILs could go one step further than chiral ligands when applied as catalysts in organic reactions.

1.2 Ionic liquids in green chemistry

In our days, one of chemists´ main fields of interest is the avoidance of toxic and environmentally unfriendly reagents and organic solvents. Solvents are often responsible for the majority of waste in syntheses and processes and due to their

[8] Qiao, K.; Deng, Y. *J. Mol. Catal. A: Chem*. **2001**, *171*, 81-84. Deng, Y.; Shi, F.; Beng, J.; Qiao, K. *J. Mol. Catal. A: Chem*. **2001**, *165*, 33. Valkenberg, M.H.; de Castro, C.; Hölderich, W.F. *Appl. Catal. A: Gen*. **2001**, *215*, 185.
[9] Ressmann, A. *Diploma Thesis, Vienna University of Technology*, 2011.
[10] Antonietty, M.; Kuang, D.; Smarsly, B.; Zhou, Y. *Angew. Chem.; Int. Ed*. **2004**, *43*, 4988. Dupont, J. *J. Braz. Chem. Soc.* **2004**, *15*, 341.
[11] Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, D. *Tetrahedron Lett*. **1997**, *38*, 3097.
[12] Earle, M.J.; McCormac, P.B.; Seddon, K.R. *Green Chem*. **1999**, *1*, 23.
[13] For a review: Bica, K.; Gaertner, P. *Eur. J. Org. Chem*. **2008**, 3235.

volatility and solubility had contributed to pollution of air and water. The principle of green chemistry tries to overcome these problems. More than 20 years ago the term "green chemistry" was mentioned for the first time, coining a new, vital part of chemistry disciplines.[14, 15] An important aspect of green chemistry is design, including novelty, planning and systematic conception.[16] It covers topics such as new solvents and reaction media as well as catalysis and biocatalysis. The concept of green chemistry strives to achieve sustainability at the molecular level, going beyond research in laboratories and its philosophy has already been applied in all industry sectors as well as in education, environment and the general public. In 1998 Paul Anastas and John Warner introduced the twelve principles of green chemistry as a guide towards cleaner processes and to reduce hazards across all life-cycle stages.[17]

[14] Collins, T.J. in *Green Chemistry*, *Macmillan Encyclopedia of Chemistry* **1997**, *2*, 691.
[15] Afonso, C.A.M.; Grespo, J.G. *Green Seperation Processes;* Wiley-VCH Verlag GmbH &Co. KGaA: Weinheim, 2005; pp 1-17, 229.
[16] Anastas, P.; Eghbali, N. *Chem. Soc. Rev*. **2010**, *39*, 301.
[17] Anastas, P.T:; Warner, J.C. *Green Chemistry, Theory and Practice*, Oxford University Press, New York, **1998**. Poliakoff, M.; Licence, P. *Nature*, **2007**, *450*, 810.

1. prevention
2. atom economy
3. less hazardous chemical synthesis
4. designing safer chemicals
5. safer solvents and auxiliaries
6. design for energy efficiency
7. use of renewable feed stocks
8. reduce derivatives
9. catalysis
10. design for degradation
11. real time analysis for pollution prevention
12. inherent safer chemistry for accident prevention

Figure 1: The twelve principles of green chemistry

Due to some of their special properties like an insignificant vapour pressure, the inflammability and the comparable high thermal stability up to 400 °C, ionic liquids can cover some of the green chemistry aspects. The structural variability of ionic liquids is not only able to design tailor made ILs for certain applications but also provides substances that have a low risk for environment and health. There is a good chance to synthesise sustainable ionic liquids with an excellent risk profile for a defined technical application.[18] Together with water or supercritical fluids, ILs are examples for green answers to avoid conventional toxic or flammable solvents.[19]

In the last years green chemistry in and with ionic liquids has received a lot of attention and spectrum of applications reached actually organic chemistry.[20, 21]

[18] Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev*. **2007**, *107*, 2183.
[19] Breslow, R. *Green Chem*., **1998**, 225; Anastas, P.; Eghbali, N. *Chem. Soc. Rev*. **2010**, *39*, 301.
[20] Sandhu, S.; Sandhu, J.S. *Green Chemistry Letters and Reviews*, **2011**, *4*, 311. Welton, T. *Green Chemistry*, **2011**, *13*, 225.
[21] Earle, J.M.; Seddon, K.R. *Pure and applied chemistry*, **2000**, *72*, 1391.

- A classical reaction, promoted by Lewis acidic ionic liquids for example is the Friedel-Crafts reaction, which worked efficiently in chloroaluminated ILs.[22]
- Neutral ionic liquids have been found to be excellent solvents for Diels Alder reactions, giving an enhancement of reaction rates in comparison to classical organic solvents.[12]
- The recent progress of ionic liquids is also shown in Michael addition, using non polluting catalysts and replacing volatile organic solvents.[23]

To demonstrate relevant distinctions between ILs and conventional solvents on the one hand and to accentuate some green properties of ionic liquids, Table 1 gives a brief visual comparison of typical values of organic solvents and ionic liquids.[9]

Table 1: Comparison of organic solvents with ionic liquids

property	organic solvents	ionic liquids
number	>1000	>1 000 000
vapour pressure	obeys Clausius-Clapeyron	negligible vapour
flammability	usually flammable	usually nonflammable
Viscosity [cP]	0.2-100	22-40 000
Density [g cm^{-3}]	0.6-1.7	0.8-3.3
refractive index	1.3-1.6	1.5-2.2
solvation	weakly solvating	strongly solvating
cost	cheap	between 2 and 100 fold
tuneability	limited range of solvents	unlimited "designer solvents"
recyclability	green imperative	economic imperative

[22] Boon, J.A.; Levisky, J.A.; Pflug, J.L.; Wilkes, J.S. *J. Org. Chem*. **1986**, *51*, 480.
[23] Sandhu, S.; Sandhu, J.S. *Green Chemistry Letters and Reviews*, **2011**, *4*, 311.

catalytic ability	rare	common and tuneable
chirality	rare	common and tuneable

However, it should be noted that the use of the term "green solvent" for ionic liquids has been repeatedly challenged due to recent toxicity, degradation and ecotoxicity studies.[24] A comparative risk analysis of ILs and conventional solvents is reasonable. In addition, many common cations are generated from non renewable resources. Especially the most commonly used imidazolium based ILs are synthesised from imidazoles and alkyl halides which are both obtained from petroleum feedstock. To improve this issue, renewable resources for ionic liquids are desired[25] and many CILs have used α-amino acids, available at low cost and good enantiomeric purity as starting materials in their synthesis.[25] Furthermore organic solvents or toxic starting materials are often used for the synthesis of ILs.

For all these reasons a responsible handling of the term "green solvents" is necessary when dealing with ionic liquids.[26]

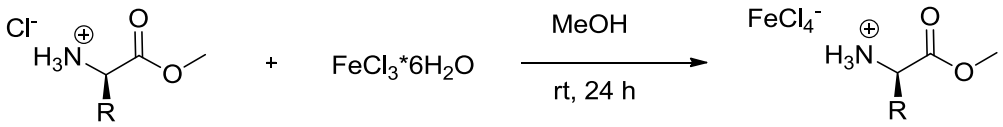
1.3 Iron containing ionic liquids

Due to the search for cheap, non-toxic and air-stable catalysts, a major challenge in current organic synthesis, the scope for iron-catalysed chemistry was constantly growing in the last decade.[27] Iron is one of the most inexpensive and non-pollutant metals on earth and the low toxicity inherent to many iron compounds makes them ideally suited as catalysts. Considering the trends towards green and sustainable catalysis, the positive environmental aspects of chloroferrate ionic liquids should boost research in this field and new applications in synthesis are still to be expected in the future.[28]

[24] Pinkert , A.; Marsh, K.N.; Pang, S.; Staiger, M.P. *Chem. Rev.* **2009**, *109, 6715.* Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev*. **2007**, *107*, 2183.
[25] Payagala, T.; Armstrong, D.W. *Chirality*, **2012**, *24*, 17.
[26] Freemantle, M. *An Introduction to Ionic Liquids*; The Royal Society of Chemistry:Cambridge, 2010; pp 1-99.
[27] For a review: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.*, **2004,** *104,* 6217.
[28] Bica, K.; Leder, S.; Gaertner, P. *Curr. Org. Synth*. **2011**, *8*, 824.

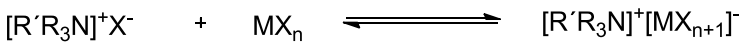
The pioneering work of Osteryoung and Wilkes on Lewis acidic ILs was a major breakthrough on this area.[29] Today a variety of metal-containing ILs composed of an imidazolium, ammonium, pyridinium or phosphonium core together with a large number of transition metal halides has been described and applications of these ILs have entered the field of organic synthesis.[22, 30]

Although most chloroferrate ILs are based on traditional alkyl imidazolium or ammonium cations, they provide the possibility of including chirality in the cation and design chiral metal containing ILs.[13, 31] Starting from cheap and commercially available camphene, our group reported an early example of a dual-functional chiral and iron containing IL.[32] An extensive selection of amino acid-derived chloroferrate chiral ILs was recently published by Warner and co-workers.[33] These magnetic chiral ILs (Scheme 2) could be obtained in a simple reaction between amino acid methyl ester hydrochlorides and iron(III) chloride and showed a strong response to a magnetic field.



Scheme 2: Synthesis of magnetic chiral ionic liquids

Paramagnetic properties were confirmed using SQUID measurements. Steady-state fluorescence spectroscopy was further used to prove the chiral recognition abilities, using racemic 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as analyte.



Scheme 3: General formation of Lewis acidic ILs

[29] Chum, H.L.; Koch, V.R.; Miller, L.L.; Osteryoung, R.A. *J. Am. Chem. Soc*. **1975**, *97*, 3264; Wilkes, J.S.; Levisky, J.A.; Wilson, R.A.; Hussey, C.L. *Inorg. Chem*., **1982**, *21*, 1263.

[30] Valkenberg, M.H.; deCastro, C.; Hölderich, W.F. *Appl. Catal. A:General.*, **2001**, *215*, 185.

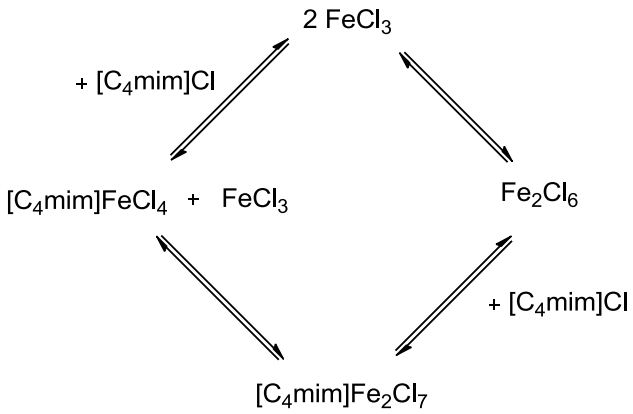
[31] For reviews: Prechtl, M.H.G.; Scholten, J.D.; Neto, B.A.D.; Dupont, J. *Curr. Org. Chem.*, **2009**, *13*, 1259; Bica, K.; Gaertner, P. *Eur. J. Org. Chem*., **2008**, *19*, 3235.

[32] Bica, K.; Gmeiner, G.; Reichelt, C.; Lendl, B.; Gaertner, P. *Synthesis*, **2007**, *9*, 1333.

[33] Li, M.; De Rooy, S.L.; Bwambok, D.K.; El-Zahab, B.; DiTusa, J.F.; Warner, I.M.. *Chem. Commun*., **2009**, *45*, 6922.

As for any chlorometalate species, care has to be taken in considering the stoichiometric ratio of organic halide and Lewis acid, since several species are often present in equilibrium, depending on the ratio [cation]X/MX_n.[34]

Mössbauer spectroscopy revealed that the addition of $FeCl_3$ to [C_4mim]Cl results in a complex equilibrium of [C_4mim]$FeCl_4$, [C_4mim]Fe_2Cl_7, [C_4mim]Cl, $FeCl_3$ and Fe_2Cl_6 that is determined by the molar ratios of the quaternary ammonium salt and the Lewis acid (Scheme 4). In any case, Raman scattering and mass spectroscopic investigations proved $FeCl_4$ as a dominating anion species; however, when $FeCl_3$ is in excess, Fe_2Cl_7 is formed as a second anion and increases with the addition of excess $FeCl_3$.



Scheme 4: Equilibrium of iron containing ILs

These results were further confirmed with *ab initio* calculations. Optimised structures revealed tetrahedral or distorted tetrahedral geometry of all chloroferrate anions. Single-crystal structures of the tetrachloroferrateIL [C_4mim]$_2FeCl_4$ ($\chi(FeCl_3)$ = 0.33) also confirmed tetrahedral symmetry of $FeCl_4$.[35]

[34] Tait, S.; Osteryoung, R.A. *Inorg. Chem.*, **1984**, *23*, 4352.
[35] Zhong, C.; Sasaki, T.; Jimbo-Kobayashi, A.; Fujiwara, E.; Kobayashi, A.; Tada, M.; Iwasawa, Y. *Bull. Chem. Soc. Jpn.*, **2007**, *80*, 2365. Kölle, P.; Dronskowski, *Inorg. Chem.*, **2004**, *43*, 2803.

1.4 Asymmetric synthesis

Nearly all living structures are made from chiral molecules – well known examples are sugars and amino acids. Every naturally occurring amino acid, building block for peptides and proteins is existing as one enantiomer only and has the *L*-configuration which in most cases is equal to *(S)*-configuration. As a consequence all living systems are chiral environments, requiring chiral drugs and pharmaceuticals. In synthesis of drug molecules, making the right enantiomer can be a matter of life or death.[36] People suffering from Parkinson's disease are treated with the chiral amino acid (3-(3,4-dihydroxyphenyl)alanine, dopa. While (*S*)-dopa is effective in restoring nerve function, the (*R*)-enantiomer is not only ineffective, it is, in fact, quite toxic. The drug - and many others - must be marketed as a single enantiomer. Indeed, nine of the top ten drug sales in 2003 were chiral compounds and six are sold on the market as single enantiomers (Table 2). It is therefore comprehensible that efficient strategies for the selective production of single enantiomers are constantly investigated.[37]

Table 2: Top ten drugs sold in 2003, sales figures from IMS Health[38]

brand	global sales 2003 [$ billion]	active ingredient	form of active ingredient	therapeutic effect
Lipitor	10.3	atorvastatin	single enantiomer	lipid lowering agent
Zocor	6.1	simvastatin	single enantiomer	lipid lowering agent
Zyprexa	4.8	olanzapine	achiral	psychotropic agent
Norvasc	4.5	amlodipine	racemate	calcium channel blocker
Procrit	4.0	epoetin a	protein	stimulant of blood cell production
Prevacid	4.0	lansoprazole	racemate	inhibitor of gastric acid secration
Nexium	3.8	esomeprazole	single enantiomer	inhibitor of gastric acid secretion

[36] ClaydenPlavix, J.; Greeves, N:; Warren, S.; Wothers, P. *Organic Chemistry*, **2001**, Oxford University Press, ISBN 978-0-19-850346-0.
[37] Bica, K. *PhD Thesis*, Vienna University of Technology**, 2007**.
[38] Rouhi, A. M. *Chem. Eng. News,* **2004**, *82*, 47.

Plavix	3.7	clopidogrel	single enantiomer	inhibitor of platelet aggregation
Advair	3.7	salmeterol	racemate	b_2-adrenergic bronchodilator
		fluticasone	single enantiomer	anti-inflammatory agent
Zoloft	3.4	sertraline	single enantiomer	selective serotonin reuptake inhibitor

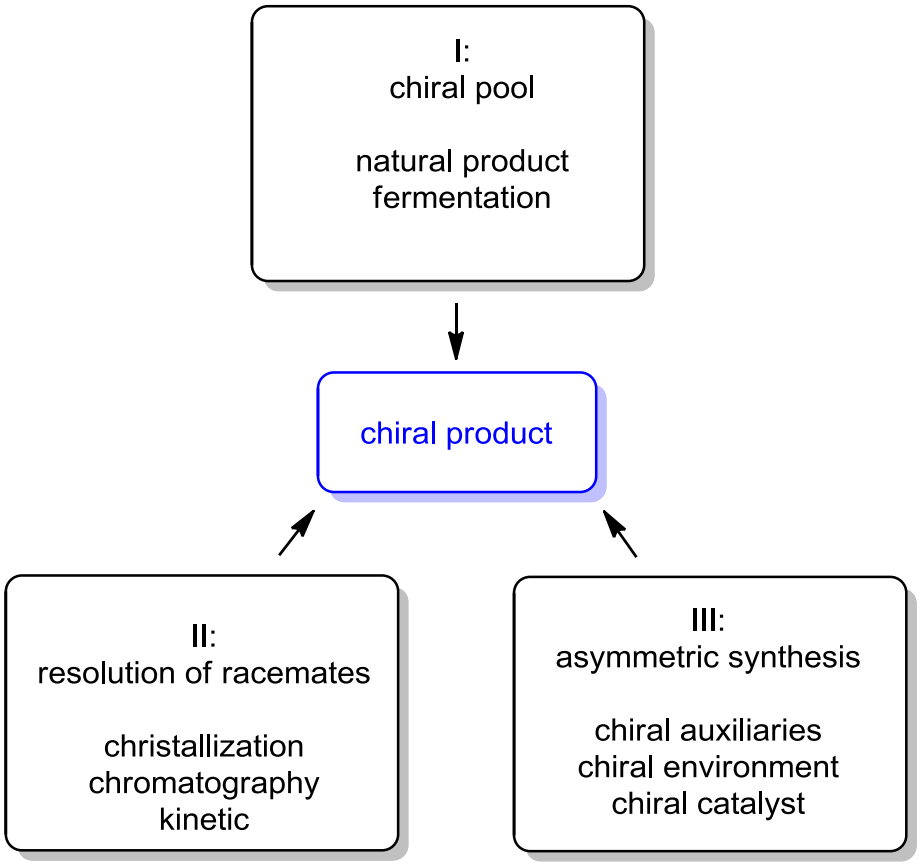


Figure 2: Strategies to synthesise a chiral product

The synthesis of chiral compounds has become an important role in life sciences and the construction of organic compounds containing one or more chiral centres utilising chiral starting materials is certainly one of the most exciting and spectacular chapters of organic chemistry. Figure 2 shows three possible ways, a chiral compound can be synthesised.

In general, when a new stereogenic centre is formed during a reaction, a racemic mixture is obtained because the transition states leading to the two enantiomers are equal in energy.[36] What chemists need to overcome this issue is an enantiomerically

pure molecule or environment that will be present during the reaction and will interact with the transition state in a way, controlling the formation of the new stereogenic centre.[36] Chiral catalysts, reagents or auxiliaries can be used to transform the two enantiomeric transition states into diastereomeric ones with unequal energies. The lower transition state will be favoured and an excess of one enantiomer will be generated during the formation of the new stereo centre.

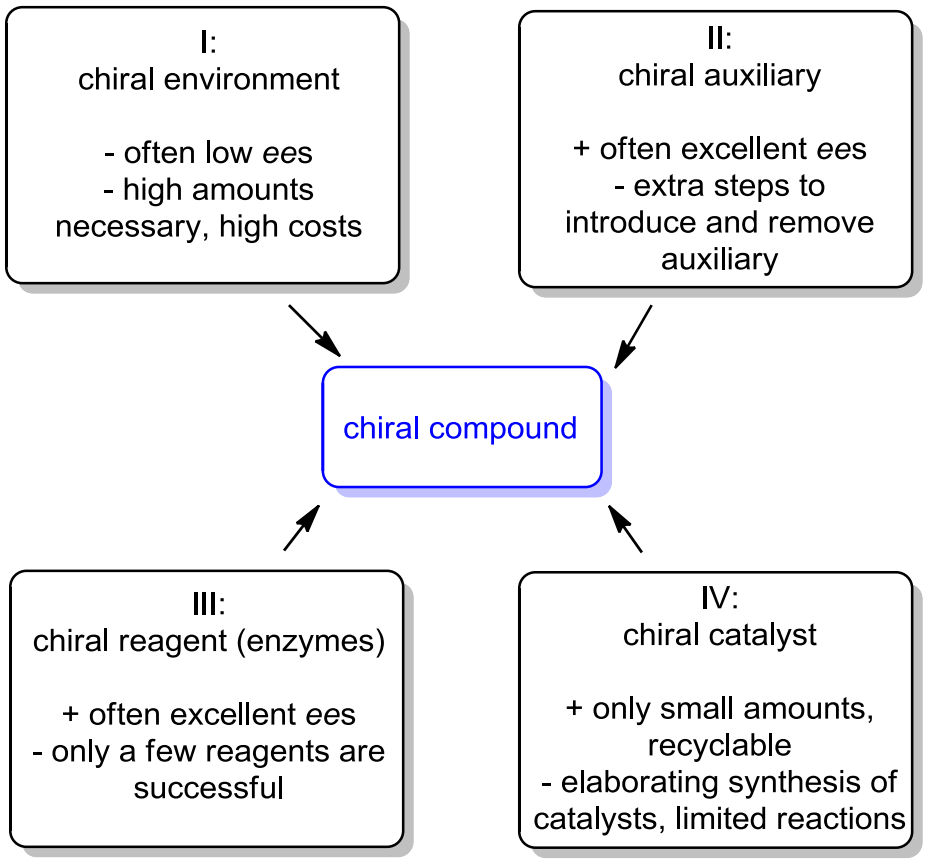


Figure 3: Methods for asymmetric synthesis

Asymmetric synthesis means the ability to control the three dimensional structure of the molecular architecture. Over the past three decades it has revolutionised chemistry and has been an important topic of research for chemists in both industrial laboratories and the academic world.[39] A summary of the methods of the field asymmetric synthesis and their advantages is shown in Figure 3. The importance of this area of chemistry was underlined by the granting of the Nobel Prize in chemistry

[39] Dalko, P.I. *Chimia*, **2007**, *61*, 213.

in 2001 to Dr. Knowles, Prof. Noyori and Prof. Sharpless for their contributions in enantioselective synthesis.[40]

Among the various ways of creating enantiomerically enriched products, catalytical methods where chemical transformations are controlled by a substoichiometric amount of a chiral compound are considered to be the most appealing. The current trend in asymmetric catalysis focuses on low catalyst loading and/or recyclation.

Chiral catalyst synthesis often requires starting material derived from the chiral pool – a collection of cheap, readily available pure natural products, from which pieces containing the required chiral centres can be incorporated into the target structure.[36]

1.4.1 Asymmetric C-C bond forming reactions as examples

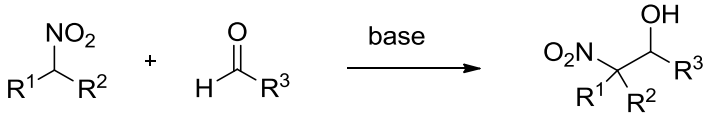
Because of the continuing imperative to improve drug efficacy, the pharmaceutical industry has a rising demand for chiral intermediates and research reagents. Many new synthetic methods as sources of chiral building blocks including a great variety of catalytic reactions have been developed which facilitate the production of complex chiral drug candidates for clinical trials. These man-made chiral building blocks can be utilised for the elaboration of more complex synthons to be used for the final synthetic target and must, therefore, be multifunctional.

Synthesis of homochiral compounds from non-chiral starting materials is discussed in the following chapters. Special attention was turned towards the synthesis of chiral building blocks *via* asymmetric C-C bond forming reactions.

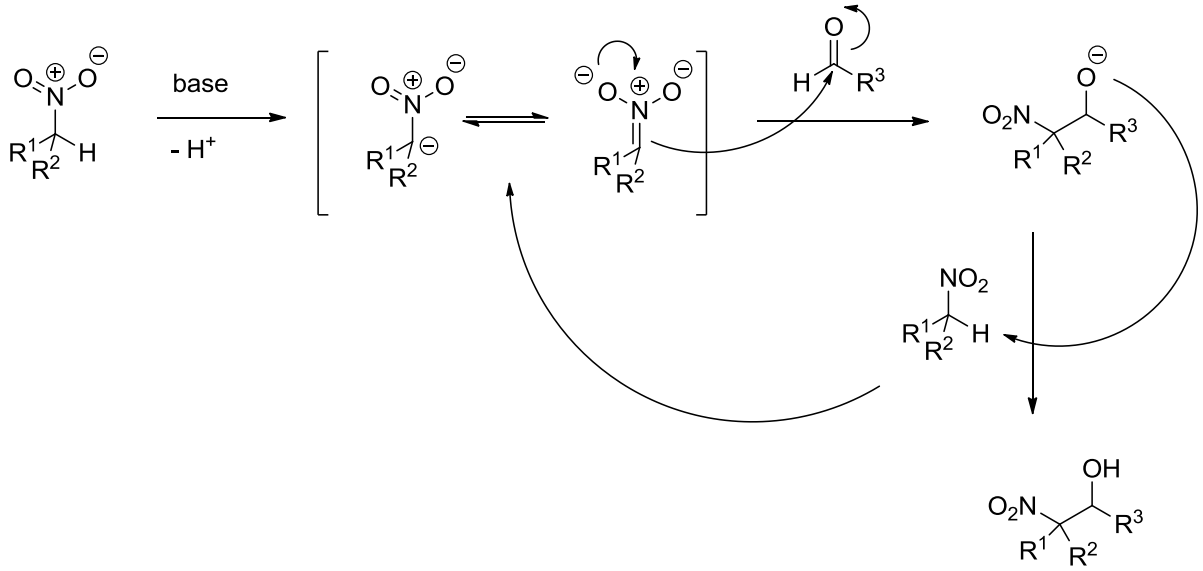
[40] The Nobel Prize in Chemistry 2001". Nobelprize.org. 4 Nov 2012; Bräse, S.; Lauterwasser, F.; Ziegert, R.E. *Adv. Synth. Catal*. **2003**, *345*, 869.

1.4.1.1 Asymmetric Henry reaction

The nucleophilic addition of nitro alkane to carbonyl groups is known as the Henry reaction (Scheme 5 and Scheme 6).[41] The resulting α-hydroxy nitro compounds are useful precursors for the synthesis of biologically significant chiral building blocks due to the chemical versatility of the nitro group.[42, 43]



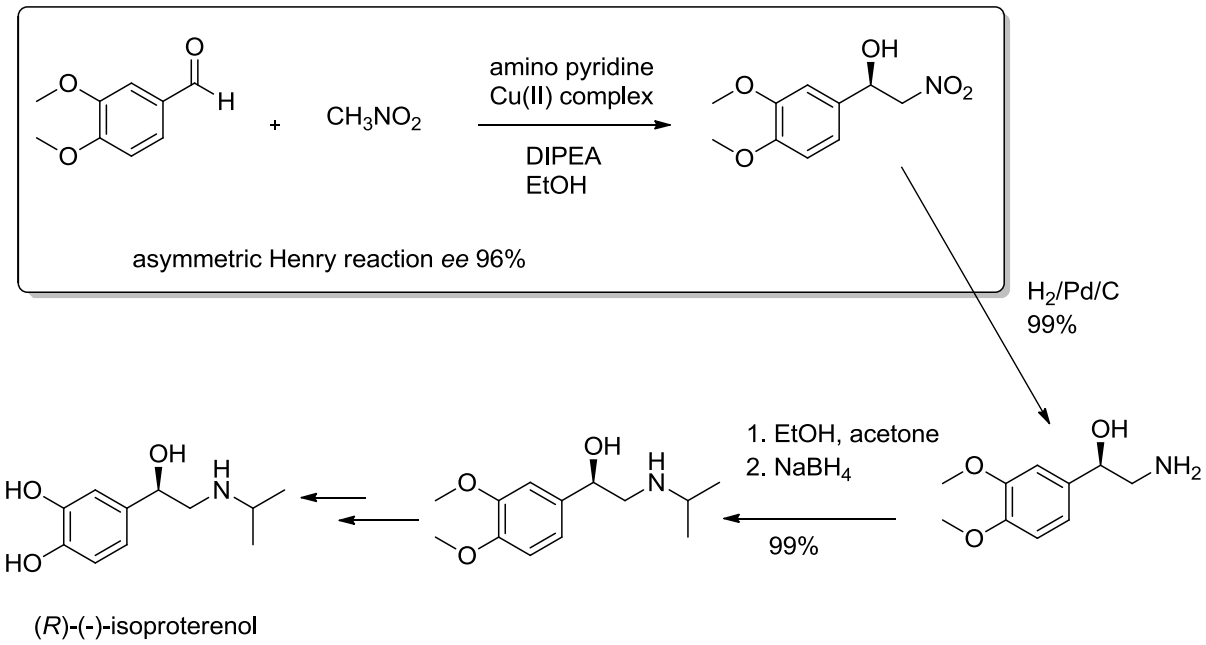
Scheme 5: Henry reaction



Scheme 6: Mechanism of Henry reaction

For example, 2-nitro-1-arylalkanols are key intermediates for the synthesis of adrenergic drugs.[44] Furthermore the class III antiarrythmic drug sotalol and the adrenoreceptor isoproterenol could be successfully synthesised in enantiomerically pure form (Scheme 7).[45]

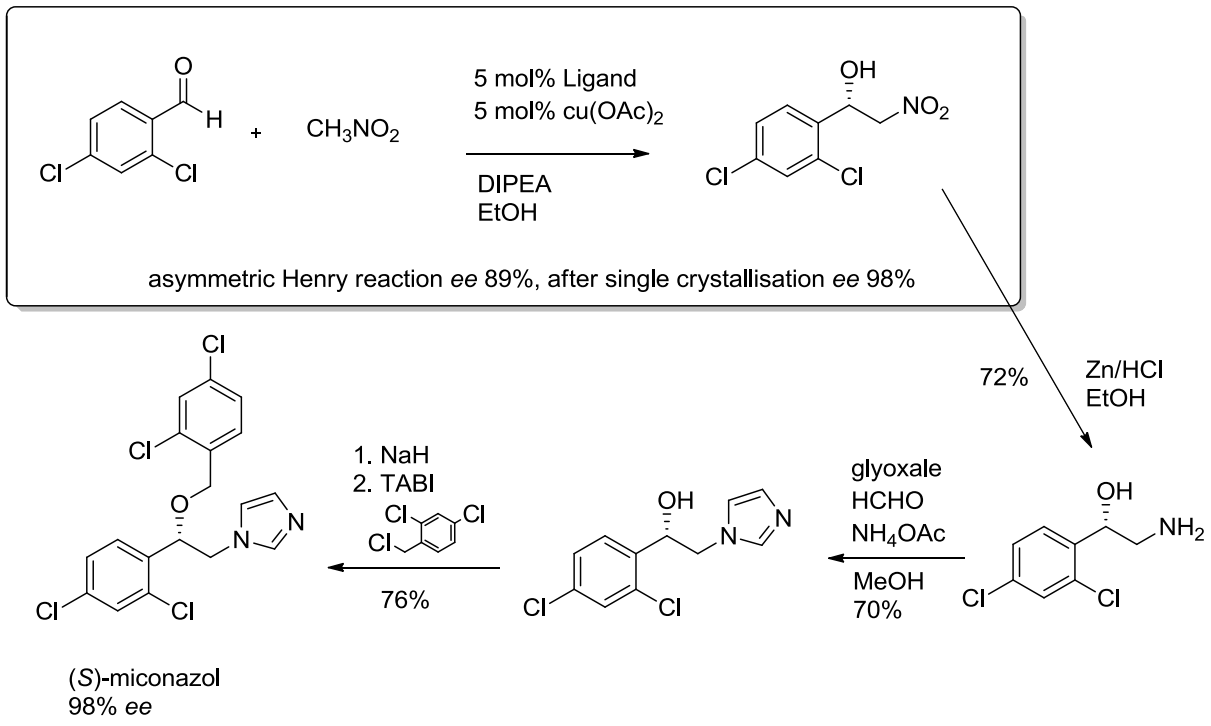
[41] Henry, L.: *Formation synthétique d'alcools nitrés*. Compt. Rend. Hebd. *Séances Acad. Sci*. 120, **1895**, 1265.
[42] Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2006**, *17*, 2046. Bandini, M.; Benaglia, M.; sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org.Lett*. **2007**, *9*, 2151.
[43] Constable, E.C.; Zhang, G.; Housecroft, C.E.; Neuburger, M.; Schaffner, S.; Woggon, W. *New J. Chem*. **2009**, *33*, 1064. Selvakumar, S.; Sivasankaran, D.; Singh, V.K. *Org. Biomol. Chem*. **2009**, *7*, 3156.
[44] Reddy, B.V.S.; Reddy, S.M.; Manisha, S.; Madan, C. *Tetrahedron Asymmetry*, **2011**, *22*, 530.
[45] Blay, G.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2010**, *21*, 578.



Scheme 7: Synthesis of (*R*)-(-)-isoprotenereol according to Blay

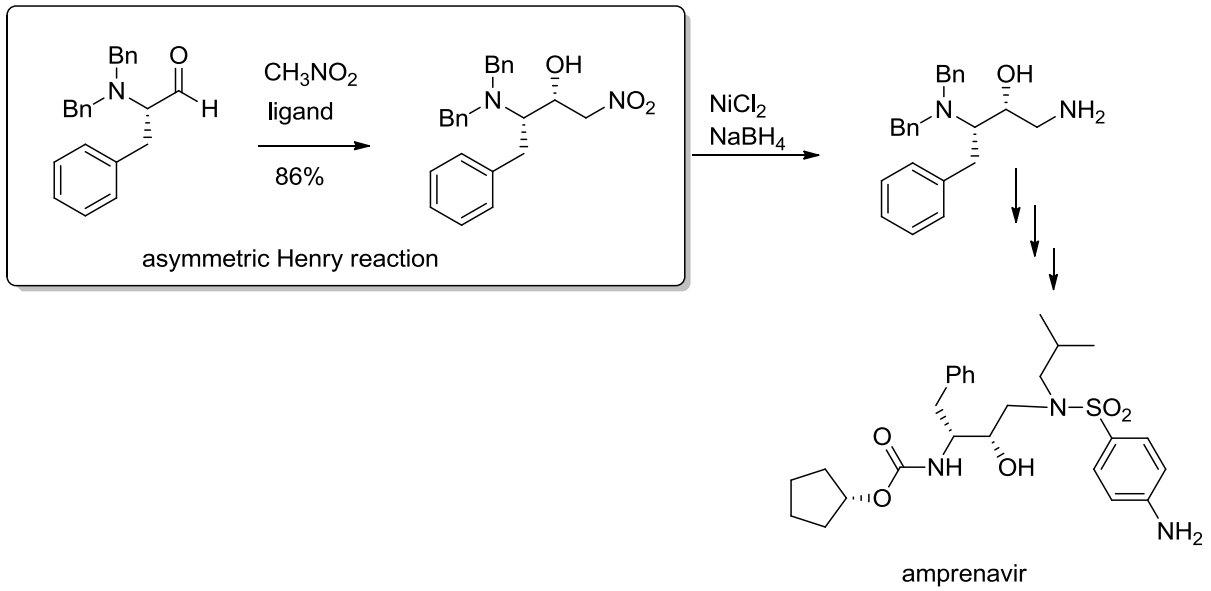
In both examples, the chiral centre was introduced *via* an asymmetric Henry reaction starting from suitable aromatic aldehydes. Another application of asymmetric Henry reaction is the synthesis of (*S*)-1-(2,4-dichlorophenyl)-2-nitroethanol with 98% *ee* as a precursor in the enantioselective synthesis of the antifungal agent (*S*)-miconazol (Scheme 8).[46]

[46] Blay, G.; Domingo, L.R.; Hernandez-Olmos, V.; Pedro, J.R. *Chem. Eur. J.*. **2008**, *14*, 4725.



Scheme 8: Enantioselective synthesis of (*S*)-miconazol

A new strategy for the stereo controlled synthesis of the HIV protease inhibitor amprenavir reported by Corey involved the diastereoselective nitroaldol reaction of the (*S*)-aldehyde, shown in Scheme 9.[47]



Scheme 9: Synthesis of amprenavir

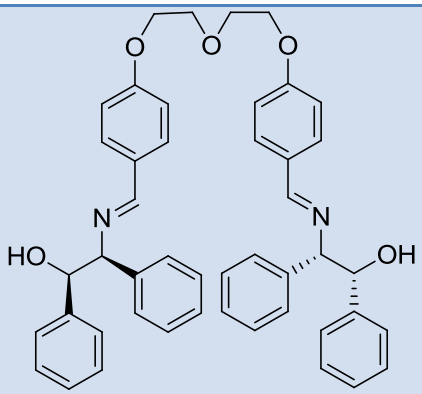
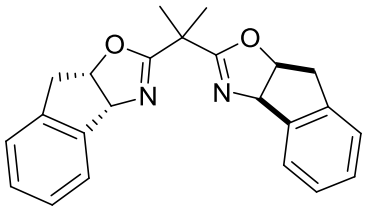
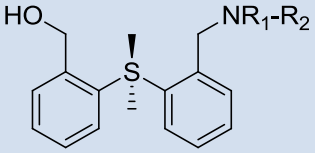
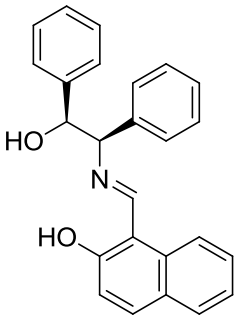
[47] Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed. Engl*. **1999**,*38*, 1931.

Asymmetric Henry reaction usually is performed in the presence of metal complexes with various chiral ligands coordinating to the metal centre and introducing chirality to the product (Table 3, entry 7).[48] Since Shibasaki presented a BINOL-derived heterometallic complex in his pioneering work,[49] various types of catalytic systems have been studied up to date.[50] Especially Lewis acidic metal salts in combination with moderately basic ligands proved to be very successful in asymmetric Henry reaction. They facilitate the deprotonation of the nitro alkane as a prelude to the aldol addition process (Table 3, entry 2).[51, 52] The most outstanding achievements have been obtained with copper complexes.[46] Chiral amino alcohol based ligands were described as catalysts allowing the Henry reaction in good yields and high enantiomeric excesses[53] and were used to study the effect of the quantities of metal salt as well as the effect of additionally added base in Henry reaction[54] at a wide scope of substrates.[55] Even a great variety of solvents for Henry reaction is reported. Aprotic solvents like CH_2Cl_2, THF or AcCN were used,[42, 56] although alcohols are reported to be most suitable solvents for this kind of reaction.[48, 53, 64] While EtOH proved to be the optimal solvent in the work of Evans,[51] Ginotra and Guo used *i*-PrOH in their labs.[58]

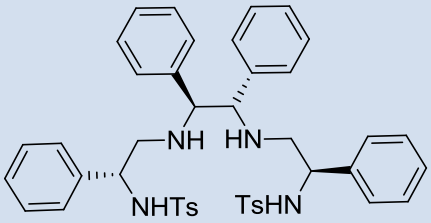
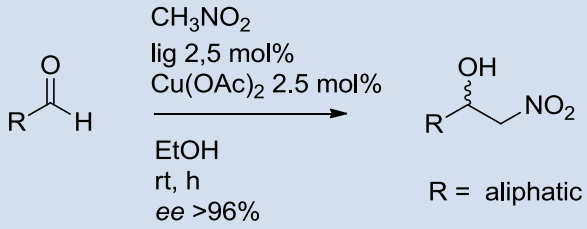
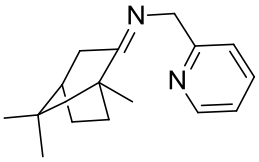
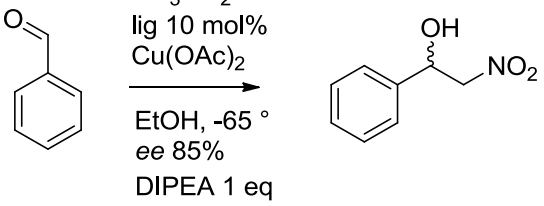
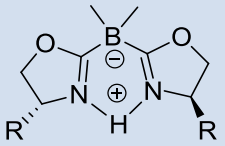
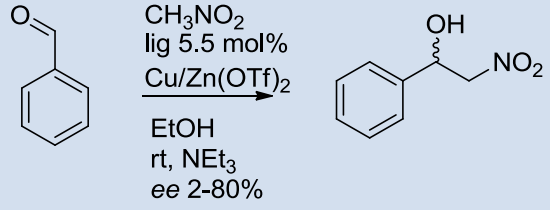
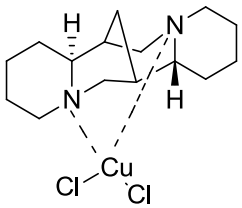
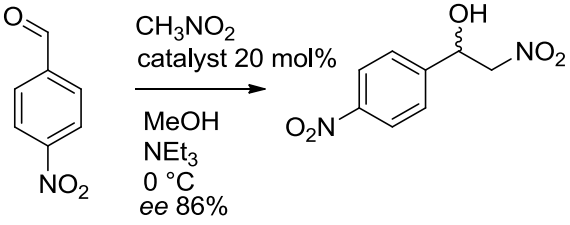
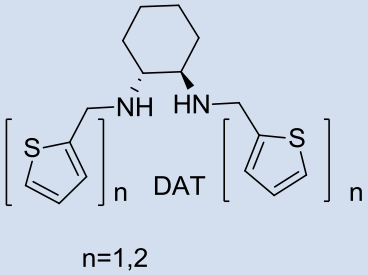
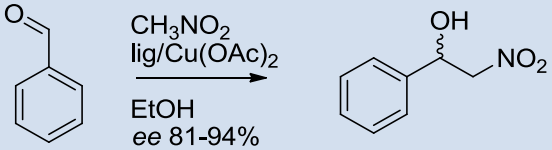
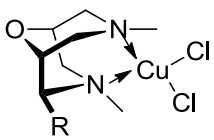
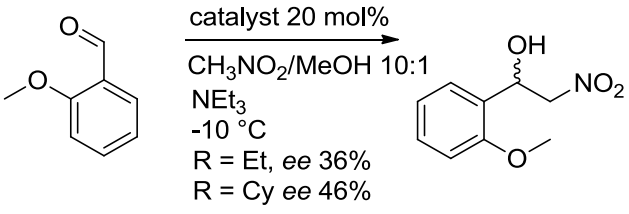
An excerpt of relevant papers published until now gives an overview on the enormous scope of ligands and conditions in asymmetric Henry reaction.

[48] Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem*. **2008**, 4591.
[49] Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. Arai, T.; Yamada, Y.M.A.; Yamamoto, N.; Sasai, H.; Shibasaki M. *Chem. Eur. J*. **1996**, *2*, 1368.
[50] Guo, J.; Mao, J. *Chirality*. **2009**, *21*,619. Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2006**, *17*, 2046. Trost, B.M.; Yeh, V.S.C. *Angew.Chem.Int.Ed*. **2002**, *41*, 861. Colak M.; Demirel N. *Tetrahedron:Asymmetry*. **2008**, *19*, 635. Ginotra, S.K.; Singh, V.K. *Org.Biomol.Chem*. **2007**, *5*, 3932. Blay, G.; Hernadez-Olmos, V.; Pedro, J.R. *Tetrahedron:asymmetry*. **2010**, *21*, 578.
[51] Evans, D.A.; Seidl, D.; Rueping, M.; Lam, H.W.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc*. **2003**, *125*, 12692.
[52] Selvakumar, S.; Sivasankaran, D.; Singh, V.K. *Org.Biomol.Chem*. **2009**, *7*, 3156.
[53] Gan, C.; Lai, G.;, Zhang, Z.; Wang, Z.; Zhou, M. *Tetrahedron:Asymmetry*. **2006**, *17*, 725. Lai, G.; Wang, S.; Wang, Z. *Tetrahedron:Asymmetry*. **2008**, 19, 1813. Steurer, M.; Bolm, C. *J.Org.Chem*. **2010**, *75*, 3301.
[54] Palomo, C.; Oiarbide, M.; Laso, A. *Angew.Chem.Int.Ed*. **2005**, *44*, 3881.
[55] Christensen, C.; Juhl, C.; Jorgensen, K.A. *Chem.Commun*. **2001**, 2222.
[56] Colak, M.; Aral, T.; Rueping M.; Hosgören H.; Demirel N. *Tetrahedron:Asymmetry*. **2007**, *18*, 1129.

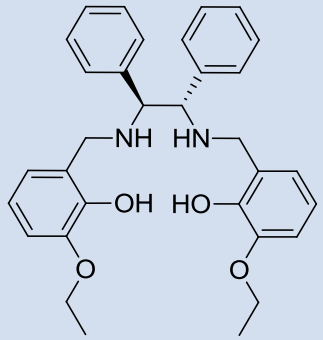
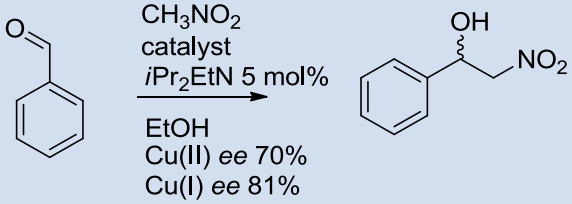
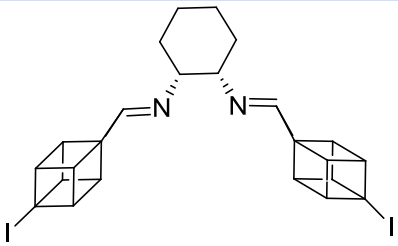
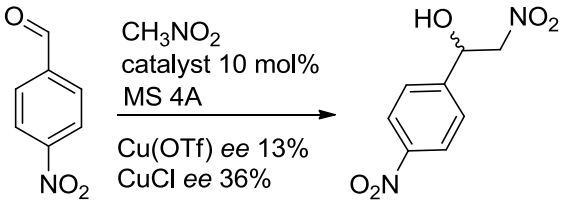
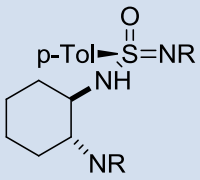
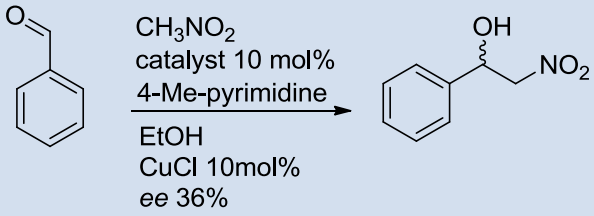
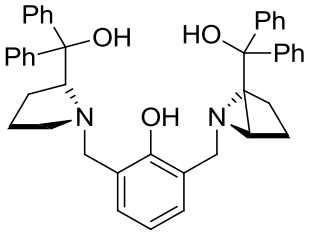
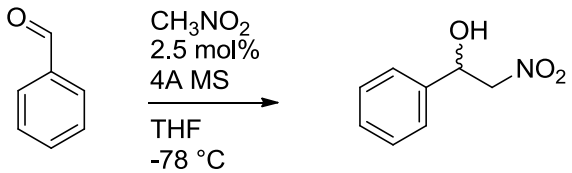
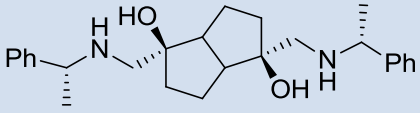
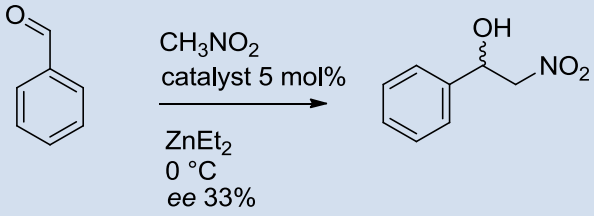
Table 3: Enantioselective Henry reaction – a literature survey

entry	chiral catalyst	reaction	Lit
1		CH_3NO_2, lig 10 mol%, $Cu/Zn(OTf)_2$, EtOH, rt, 40 h, $Cu(OTf)_2$ *ee* 44%, $Zn(OTf)_2$ *ee* 8%	57
2		CH_3NO_2, lig 5.5 mol%, $Cu(OAc)_2$, EtOH, *ee* 81%; *i*-PrOH, *ee* 86-97%	51, 58
3		CH_3NO_2, lig 5 mol%, $Cu(OAc)_2$, EtOH, *ee* 85-98%	59
4		CH_3NO_2, lig 10 mol%, $Cu(OAc)_2H_2O$, EtOH, *ee* 77%	60

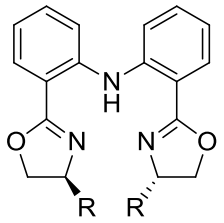
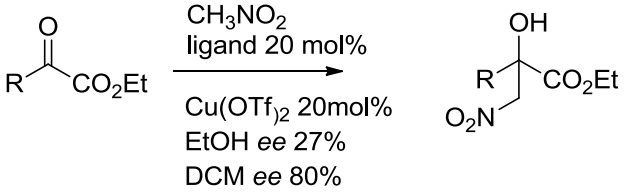
[57] Colak, M.; Aral, T.; Rueping M.; Hosgören H.; Demirel N. *Tetrahedron:Asymmetry*. **2007**, *18*, 1129. Colak M.; Demirel N. *Tetrahedron:Asymmetry*. **2008**, *19*, 635.
[58] Ginotra, S.K.; Singh, V.K. *Org.Biomol.Chem*. **2007**, *5*, 3932.
[59] Rachwalsky, M.; Lesniak, S.;Sznajder E.; Kielbasinski P. *Tetrahedron:Asymmetry*. **2009**, *20*, 1547.
[60] Guo, J.; Mao, J. *Chirality*. **2009**, *21*,619.

entry	chiral catalyst	reaction	Lit
5			61
6			62
7			48
8			63
9			64
10			65

[61] Jin , W.; Li, X; Huang, Y.; Wu, F.; Wan, B. *Chem.Eur.J.* **2010**, *16*, 8259.
[62] Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2006**, *17*, 2046. Blay, G.; Domingo, L.R.; Hernandez-Olmos, V.; Pedro, J.R. *Chem. Eur. J*. **2008**, *14*, 4725.
[63] Maheswaran, H.; Prasanth, K.L.; Krishna, G.G.; Ravikumar, K.; Sridhar, B.; Kantam, M.L. *Chem.Commun*. **2006**, 4066.
[64] Bandini, M.; Picinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem.Commun*. **2007**, 616.
[65] Breuning, M.; Hein, D.; Steiner, M.; Gessner, V.H.; Strohmann, C. *Chem.Eur.J*. **2009**, *9*, 12764.

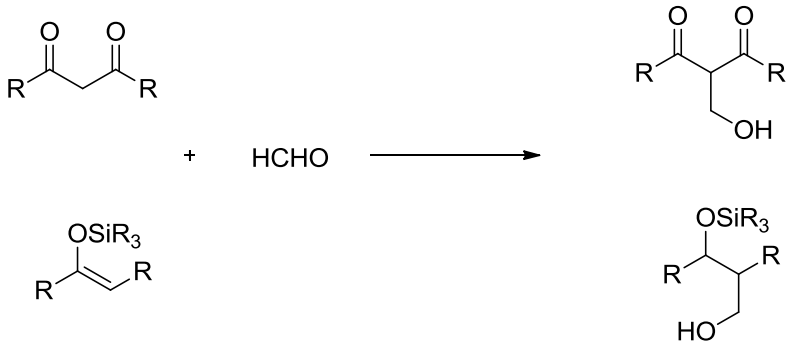
entry	chiral catalyst	reaction	Lit
11			42
12			66
13			67
14			68
15			69

[66] Ingansbe, M.L.; Denis, J.D.; Gleason, J.L.; Savage, G.P.; Priefer, R. *Synthesis*. **2010**, *1*, 98.
[67] Steurer, M.; Bolm, C. *J.Org.Chem*. **2010**, *75*, 3301.
[68] Trost, B.M.; Yeh, V.S.C. *Angew.Chem.Int.Ed*. **2002**, *41*, 861.
[69] Zhong, Y.; Tian, P.; Lin, G. *Tetrahedron:Asymmetry*. **2004**, *15*, 771.

entry	chiral catalyst	reaction	Lit
16			70

1.4.1.2 Asymmetric hydroxymethylation

Hydroxymethylations of enolates of 1,3 dicarbonyl compounds with formaldehyde, an important C_1 electrophile in organic chemistry, provide an efficient method to introduce a CH_2OH group at the α-position of carbonyls and has broad applications in organic synthesis.[71]



Scheme 10: Reaction scheme of hydroxymethylation

Many biologically active compounds contain a β–hydroxymethyl carbonyl unit as structural motif.[72] For example, the hydroxymethylated oxo ester methyl 1-(hydroxymethyl)-2-oxocyclopentanecarboxylate has been described as an intermediate for anti-HIV drugs.[73] While many C_1 homologisation reactions are limited by the use of gaseous formaldehyde, solid para formaldehyde or trioxane, which has to be depolymerised before use, an aqueous formaldehyde solution is

[70] Lu, S.; Du, D.; Zhang, S.; Xu, J. *Tetrahedron:Asymmetry*. **2004**, *15*, 3433.
[71] Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 12236.
[72] Shiraga, Y.; Okano, K.; Akira, T.; Fukaya, C.; Yokoyama, K.; Tanaka, S.; Fukui, H.; Tabata, M. *Tetrahedron*, **1988**, *44*, 4703-4711. Chan, T.H.; Schwerdtfeger, A.E. *J. Org. Chem.*, **1991**, *56*, 3294.
[73] Kumamoto, H.; Haraguchi, K.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G.E.; Cheng, Y.-C.; Kato, K. *Nucleosides Nucleotides Nucleic Acids*, **2005**, *24*, 73.

therefore preferable. Even from a "green" point of view, the development of organic reactions in water is currently a topic of great interest.[74]

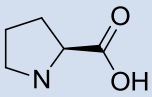
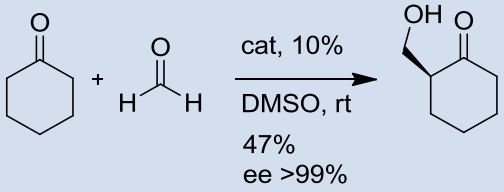
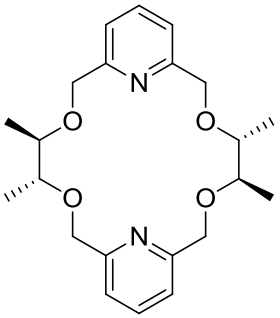
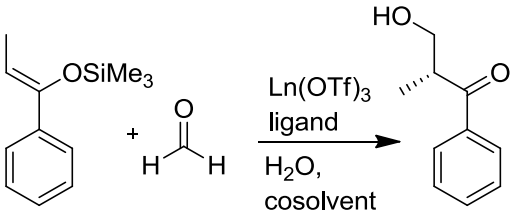
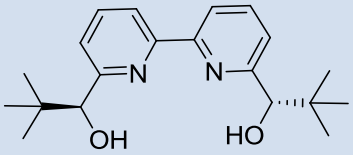
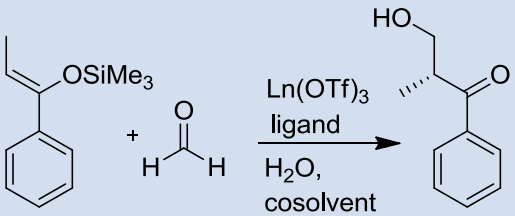
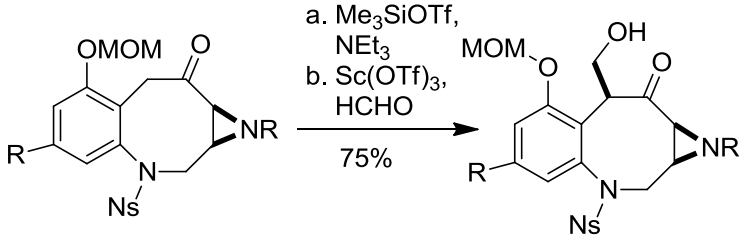
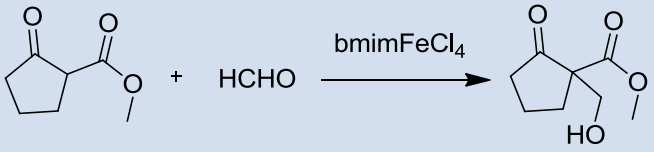
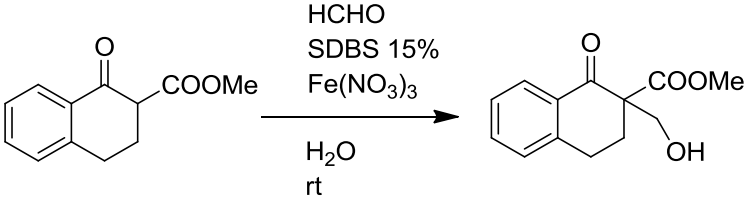
A successful application of water as solvent in combination with transition metal catalysis was reported by the group of Gaertner (Table 4, entry 5).[75] Using the iron containing ionic liquid [C_4mim]$FeCl_4$, hydroxymethylation reactions of β-keto esters could be directly performed in aqueous formaldehyde solution without addition of co-solvents and surfactants. The metal containing ionic liquid did act as catalyst under mild conditions and facilitated recyclation. Another iron catalysed hydroxymethylation in water was reported by Ogawa (Table 4, entry 6).[74] A combination of sodium dodecyl benzene sulfonate SDBS as surfactant and $Fe(NO_3)_3$*9 H_2O yielded 90% hydroxymethylated dicarbonyl compounds.

Although several groups have developed successful enantioselective aldol reactions, there are few reports on the asymmetric hydroxymethylation of carbonyl compounds using formaldehyde as the electrophile. An example where formaldehyde was used in the asymmetric Mukaiyama aldol reaction as efficient method to introduce a C_1 functional group constructing a new stereo centre was reported by Kobayashi (Table 4, entry 3).[71]

A direct organocatalytic approach of an asymmetric α-hydroxymethylation of ketones and aldehydes with formaldehyde has been developed by Cordova´s group (Table 4, entry 1).[76] The combination of a chiral crown ether and $Ln(OTf)_3$ was also investigated in asymmetric hydroxymethylations of silicon enolates, giving moderate *ee* values (Table 4, entry 2).[77] A detailed overview of relevant papers published until now, including achiral versions of this useful reaction, gives an impression on ligands and conditions.

[74] Ogawa, C.; Kobayashi, S. *Chemistry Lett*. **2007**, *36*, 56.
[75] Bica, K.; Gaertner, P. 2008, *Eur. J. Org. Chem*. **2008**, 3453.
[76] Casas, J.; Sunden, H.; Cordova, A. *Tetrahedron Lett*. **2004**, *45*, 6117.
[77] Manabe, K.; Ishikawa, S.; Hamada, T.; Kobayashi, S. *Tetrahedron*, **2003**, *59*, 10439.

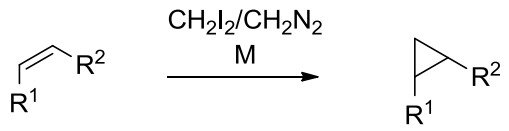
Table 4: Achiral and enantioselective hydroxymethylation – a literature survey

entry	chiral catalyst	reaction	lit
1			76
2			77
3			71
4	-		78
5	-		75
6	-		74

[78] Namiki, H.; Chamberland, S.; Gubler, D.A.; Williams, R.M. *Org. Lett*. **2007**, *9*, 5341.

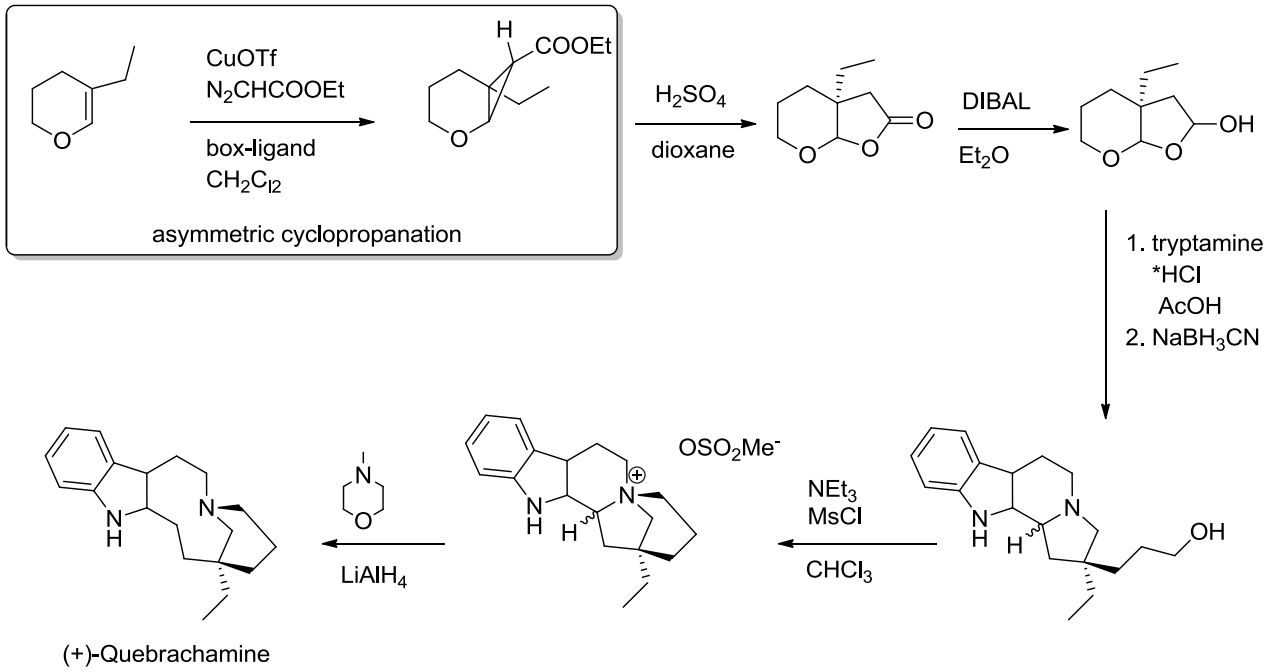
1.4.1.3 Asymmetric cyclopropanation

As common substructures of biologically active substances, highly strained three membered rings such as oxirane and cyclopropane are important building blocks in synthesis of natural compounds.[79] Important biological properties of the cyclopropane subunit found in many active ingredients has led to the development of several methods for cyclopropanation reactions, including the metal catalysed reactions of diazo compounds with olefins (Scheme 11).[80]



Scheme 11: Cyclopropanation; M = metal

Additionally, great effort has been directed towards methodologies for their asymmetric synthesis.[81] As example, a key step in the total synthesis of the natural product (+)-quebrachamine was the enantioselective Cu(I) catalysed cyclopropanation of a cyclic enol ether (Scheme 12).[82]



[79] Honma, M.; Takeda, H.; Takano, M.; Nakada, M. *Synlett*, **2009**, *11*,1695.
[80] Guo-Qiang Lin, Yue-Ming Li, Albert S.C. Chan. *Principles and Applications of Asymmetric Synthesis*, **2001**, John Wiley & Sons, Inc. ISBNs: 0-471-40027-0 (Hardback); 0-471-22042-6 (Electronic).
[81] Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Adv. Synth. Catal*. **2001**, *343*, 79.
[82] Temme, O.; Taj, S.A.; Andersson, P.G. *J. Org. Chem*. **1998**, *63*, 6007.

Scheme 12: Synthesis of (+)-quebrachamine

Other examples for cyclopropanes in active compounds are 1-aminocyclopropane-1-carboxylic acid as the general precursor of a plant hormone, coronatine as a strong elictor of stress response in plants or the insecticides pyrethroids, shown in Figure 4.[83]

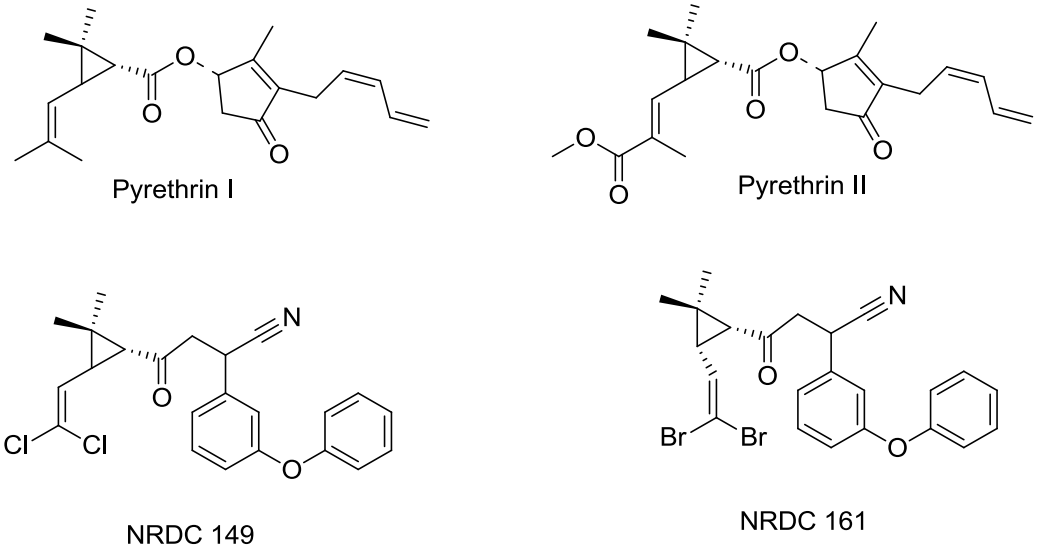
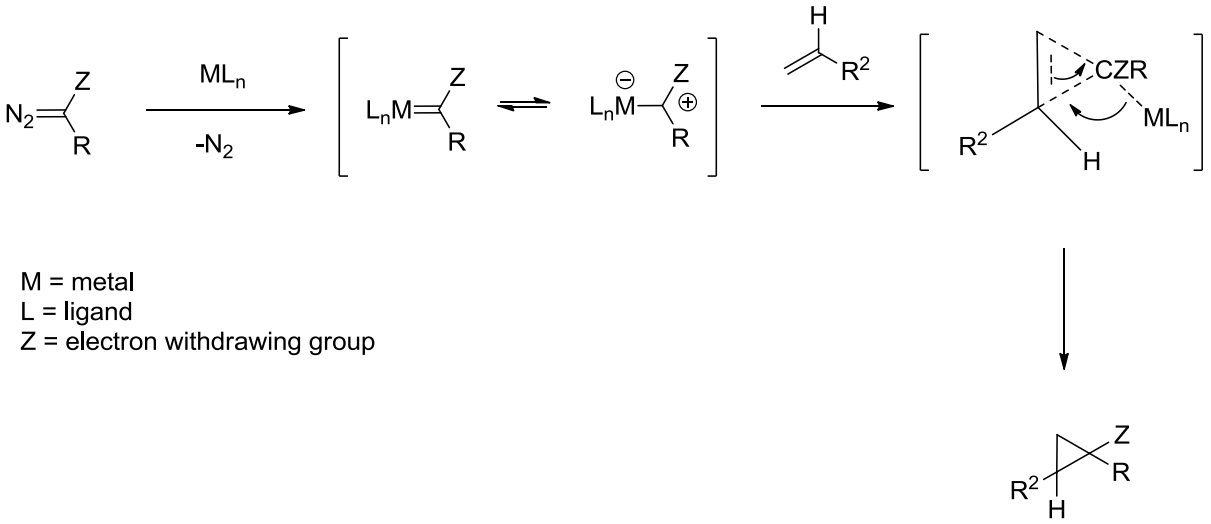


Figure 4: Natural and synthetic pyrethroids

The most common catalytic method of obtaining cyclopropanes involves transfer of a carbene moiety to olefinic double bonds. Cycloaddition of carbenoid structures to π-bonds is still the most practical way to synthesise cyclopropanes (Scheme 13).[84]

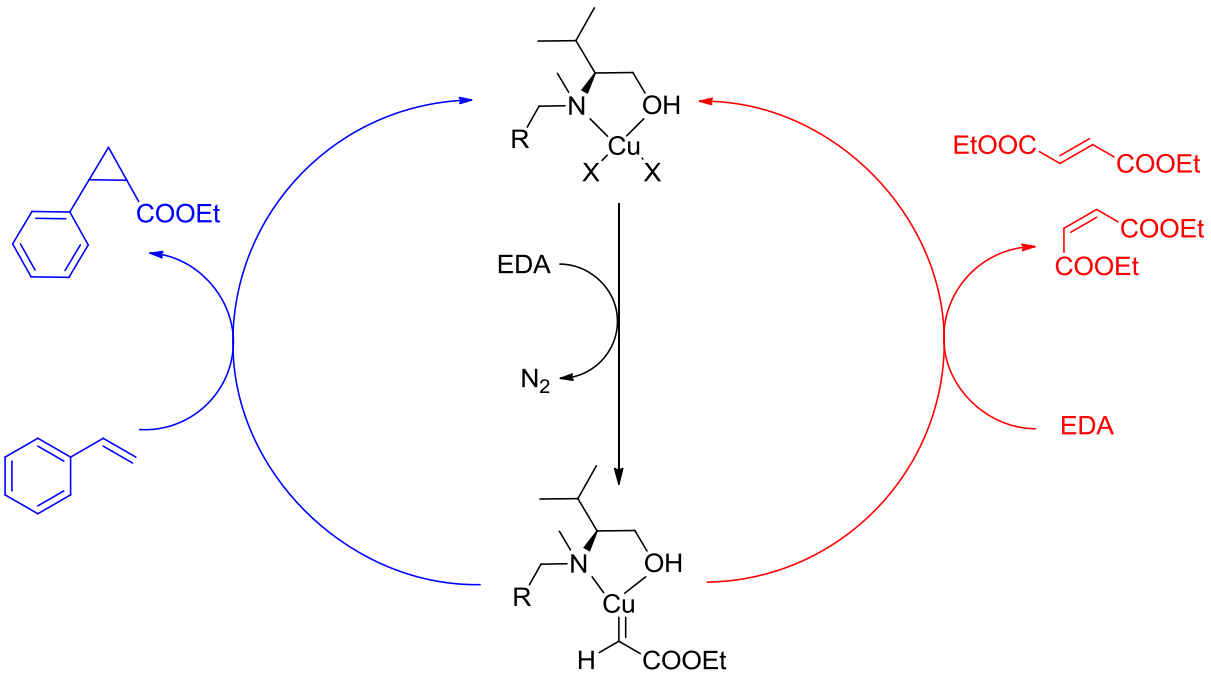
[83] Wessjohann, L.A.; Brandt, W.; Thiemann, T. *Chem. Rev*. **2003**, *103*, 1625; Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature* **1973**, *244*, 456.
[84] Rosenberg, M.L.; Krivokapic, A.; Tilset, M. *Org. Lett*. **2009**, *11*, 547.



Scheme 13: Mechanism of cyclopropanation reaction

A common side reaction is formation of dimers explained by a general mechanistic scheme of copper catalysed cyclopropanation similar to that proposed by Perez[85] or Kwong[86] (Scheme 14). The copper carbene intermediate, the active catalytic species, can not only react with the olefin. Two reactions are possible: with an olefin (here styrene) to form cyclopropanes or with another equivalent of ethyl diazoacetate (EDA) to form diethyl fumarate and maleinate as by-products.

[85] Diaz-Requejo, M.M.; Belderrain, T.R.; Nicasio, M.C.; Prieto, F.; Perez, P.J. *Organometallics*, **1999**, *18*, 2601.
[86] Lee, W-S.; Yeung, C-T.; Sham, K-C.; Wong, W-T.; Kwong, H-L. *Polyhedron*, **2011**, *30*, 178.



Scheme 14: Mechanistic scheme of copper catalysed cyclopropanation reaction with ethyl diazoacetate and styrene

In cyclopropanation reaction two new stereogenic centres are formed leading to two diastereomeric products. *Cis-trans* selectivity is an important stereochemical issue of this recation.[81] Among others the control of *cis-trans* selectivity is dependent from the bulkiness of employed diazo compound[87] and additionally is done by ligand design.

One of the first metal catalysed asymmetric cyclopropanations between an alkene and a diazo ester was reported by Nozaki and Noyori in 1965.[88, 89] They used a chiral Schiff base copper complex as catalyst in the reaction. Further studies have led to a variety of interesting regio- and stereo-selective examples.[82] Many excellent catalysts for cyclopropanation reactions have been developed up to date.[90, 91] However, most of them are *trans* selective. Satisfactoring examples of high *cis* selectivity and

[87] Caballero, A.; Sabater, M.; Morilla, E.; Nicasio, M.C.; Belderrain, T.R.; Diaz-Requejo, M.M.; Perez, P.J. *Inorganica Chimica Acta*, **2009**, *362*, 4599
[88] Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron Lett*. **1965**, 2563.
[89] Llewellyn, D.B.; Adamson, D.; Arndtsen, B.A. *Org. Lett*. **2000**, *2*, 4165.
[90] Fritschi, H.; Leutenegger, U.; Pfalz, A. *Angew. Chem. Int. Ed*. **1986**, *25*, 1005; Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *26*, 6005.
[91] Khanbabaee, K.; Basceken, S.; Flörke, U. *Tetrahedron Asym*. **2006**, *17*, 2804; Wu, X.Y.; Shen, Y.Y.; Ma, B.; Zhou, Q.L.; Chan, A.S.C. *J. Mol. Catal. A: Chemical*. **2000**, *157*, 59.

enantioselectivity are rare: Niimi demonstrated that the ligand design of a Co(II)-salen complex enables both *cis* and *trans* selective cyclopropanation.[81]

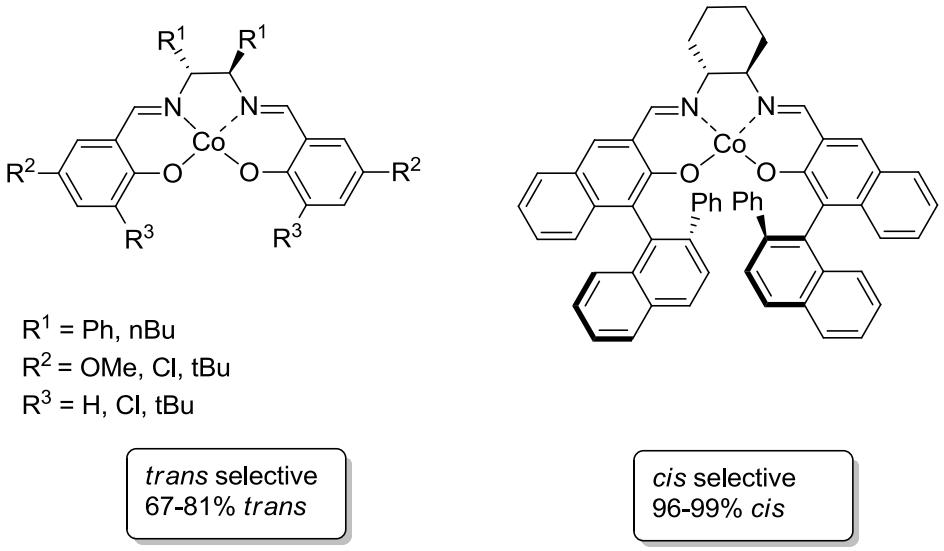


Figure 5: Co-salen complexes for selective cyclopropanation

Highly *cis*-selective cyclopropanations with ethyl diazoacetate using a novel Rh(I) catalyst with a chelating iminocarbene ligand were recently reported by Rosenberg.[84]

Apart from the metals mentioned above copper in its oxidation states I and II is one of the most common used transition metals for enantioselective cyclopropanation reactions.[92] Burke studied the use of Cu(I) and a Cu(II) precatalyst reduced *in situ* to Cu(I) and their performance in asymmetric cyclopropanations using arylid-box and isbut-box ligands.[93] As the group obtained slightly lower *ee* values than usually known with box ligands, they also examined the effect of the counter ion and the bite angle of the complexes on reaction selectivity (Table 5, entry 11).[94] Larger bite angles in their box-Cu-complexes should allow the carbenoid carbon of the intermediate to move slightly away from the source of asymmetric induction, which was postulated to be the reason for this observation.

[92] Garcia, J.I.; Lopez-Sanchez, B.; Mayoral, J.A.; Pires, E.; Villalba, I. *Journal of Catalysis*, **2008**, *258*, 378; Llewellyn, D.B.; Adamson, D.; Arndtsen, B.A. *Org. Lett.* **2000**, *2*, 4165

[93] Burke, A.J.; da Palma Carreiro, E.; Chercheja, S.; Moura, N.M.M.; Prates Ramalho, J.P.; Rodridues, A.I.; dos Santos, C.I.M. *J. Org. Met. Chem.* **2007**, *692*, 4863

[94] Evans, D.A.; Woerpel, K.A.; Hinman, M.M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

Another example of chiral box ligands in metal catalysed asymmetric cyclopropanation was reported by Evans in 1991.[94] The effect of ligand structure on reaction enantioselectivity was evaluated with a ligand-Cu(OTf) complex formed *in situ*. Chelucci reported a general trend: the introduction of an alkyl group onto the carbon adjacent to the heterocyclic ring of phenanthroline derived ligands displayed a positive effect on enantioselectivity of cyclopropanation reactions.[95] The *ee*s for both *trans* and *cis* isomers increased substantially when the hydrogen of the ligand was substituted by a methyl group. Increasing the steric bulk from methyl to benzyl led to a further improvement of *ee* values (see Figure 6).

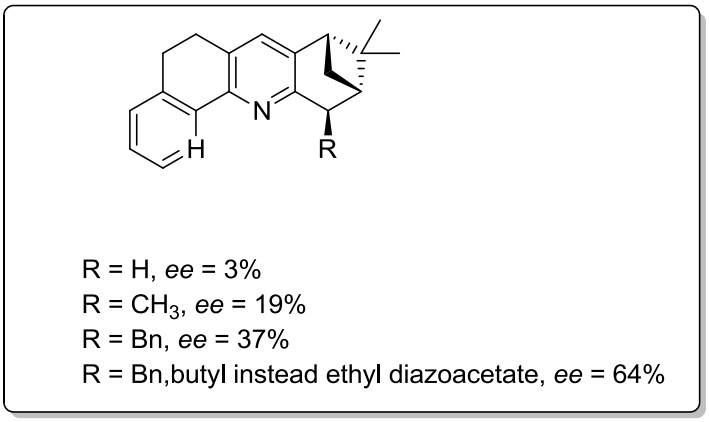


Figure 6: Effect of substituents of catalysts on enantioselectivity of cyclopropanations

Bouet reported a ranging of *ee* values from 0 to 65% with different C_2-symmetric bipyridyl ligands, also indicating that enantioselectivity was highly influenced by the nature of the ligands.[96] Garcia showed the advantages of aza-box-Cu-catalysts immobilized on laponite and demonstrated an influence of the clay surface on the stereochemical course of the reaction (Table 5, entry 10).[97] Under heterogeneous conditions higher *ee* values than under homogeneous were obtained, indicating that support effects can be beneficial to the stereoselectivity of the reaction. An attractive polymeric support for catalysts is methoxypolyethylene glycol, because it is soluble in many organic solvents and can be precipitated with diethyl ether (Table 5, entry

[95] Chelucci G.; Gladiali, S.; Sanna, M.G.; Brunner, H. *Tetrahedron Asymmetry*, **2000**, *11*, 3419
[96] Bouet, A.; Heller, B.; Papamicael, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, *5*, 1397
[97] Garcia, J.I.; Lopez-Sanchez, B.; Mayoral, J.A.; Pires, E.; Villalba, I. *Journal of Catalysis*, **2008**, *258*, 378.

2).[98] Another literature example showed improved yield and enantioselectivity of the reaction of styrene with phenyl diazoacetate by introduction of a pendant oxazoline (Table 5, entry 5).[99]

In general, especially C_2 symmetric chiral complexes are excellent catalysts for cyclopropanations.[100] C_2 symmetric bis-(ephedrine)-Cu(II) complexes and their behaviour in the reaction of styrene with diazoacetate were examined by Gao (Table 5, entry 7).[101] The authors presented *ee* values up to 89% while C_1 symmetric terpyridine ligands gave *ee* values <80%.[102] Disappointing results with Schiff base Cu(II) complexes as catalysts in cyclopropanation reactions (Table 5, entry 1)[103] clearly demonstrate, that there is still demand of novel, both regio- and enantioselective catalysts for this useful type of reaction and fine tuning of ligands to improve catalytic properties is inevitable.

The group of Vaultier compared $[C_2mim][NTf_2]$, $[C_2mim][BF_4]$ and $[C8_3NMe][NTf_2]$ with classical organic solvents in the asymmetric cyclopropanation of styrene and ethyl diazoacetate[104] and studied the role of the IL anion and catalyst recovery. Main problems arose from the equilibrium between complexed and free ligand. Free ligand was extracted during product extraction and the remaining free copper precursor caused a reduction in enantioselectivity in the next reaction cycle. Additionally Vaultier was able to demonstrate that aza-box ligands in cyclopropanation carried out in ionic liquids have clear advantages over box ligands due to the electron donating properties of the aza-bridge. This increased stability of the complex and improved the reusability of the chiral catalyst solution.

Furthermore, stabilisation and successful recovery of gold catalysts in the cyclopropanation of alkenes within various different imidazolium ILs was reported

[98] Glos, M, Reiser, O. *Org. Lett*. **2000**, *2*, 2045.
[99] Xu, Z.H.; Zhu, S.N.; Sun, X.L.; Tang,Y.; Dai, L.X. *Chem. Commun*. **2007**, 1960.
[100] Pfaltz, A. *Acta Chim. Scand*. **1996**, *50*, 189; Gao, J.; Zhong, S.H. *J. Mol. Catal. A: Chemical*, **2003**, *191*, 23.
[101] Gao, J.; Zhong, S.H. *J. Mol. Catal. A: Chemical*, **2003**, *191*, 23.
[102] Yeung, C.T.; Lee, W.S.; Tsang, C.S.; Yiu, S.M.; Wong, W.T.; Wong, W.Y.; Kwong, H.L. *Polyhedron*, **2010**, *29*, 1497.
[103] Iglesias, A.L.; Aguirre, G.; Somanathan, R.; Parra-Hake, M. *Polyhedron*, **2004**, *23*, 3051.
[104] Fraile, J.M.; Garcia, J.I.; Herrerias, C.I.; Mayoral, J.A.; Carrie, D.; Vaultier, M. *Tetrahedron Asymmetry*, **2001**, *12*, 1891.

recently.[105] The performance of ionic liquids as catalysts itself would be interesting. To the best of our knowledge, there are no examples of ILs as catalysts in cyclopropanation reactions found in literature up to date.

The following table gives an overview of up to now reported catalysts and reaction conditions of asymmetric cyclopropanations.

Table 5: Enantioselective cyclopropanation – a literature survey

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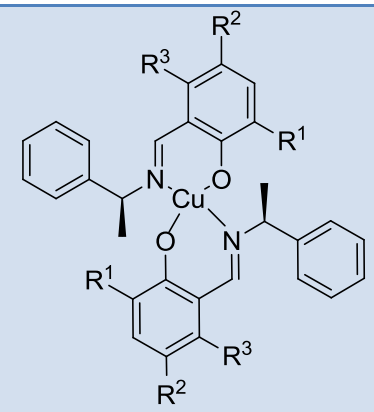
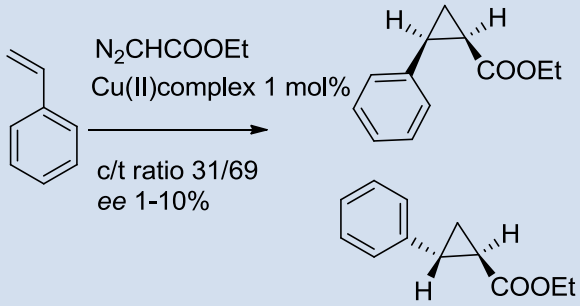
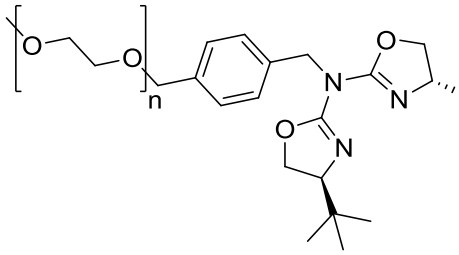
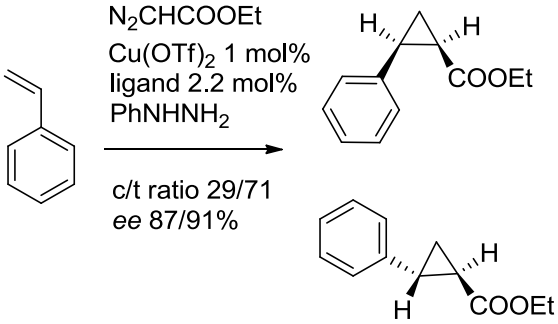
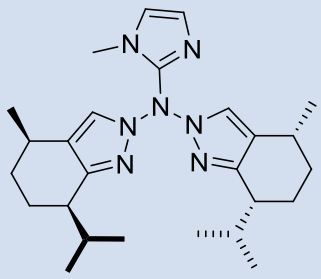
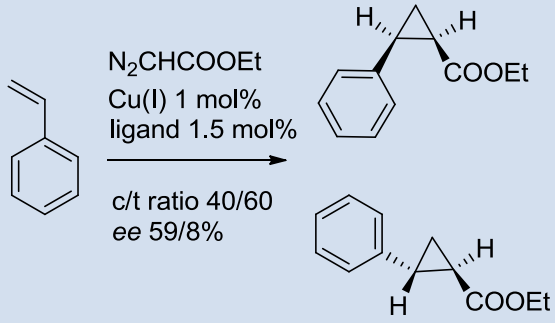
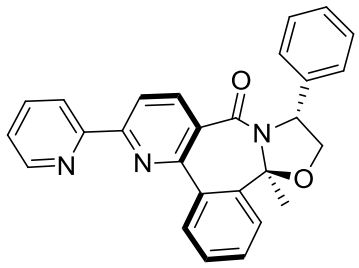
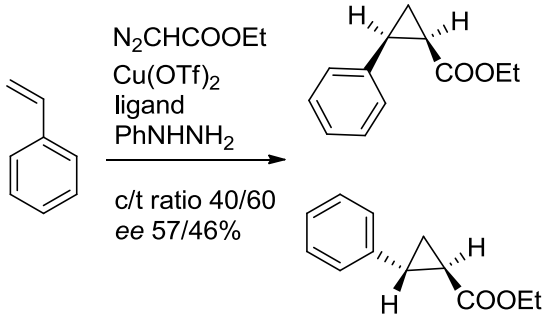
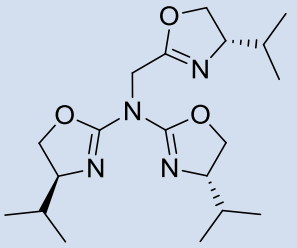
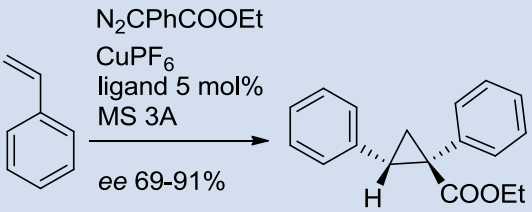
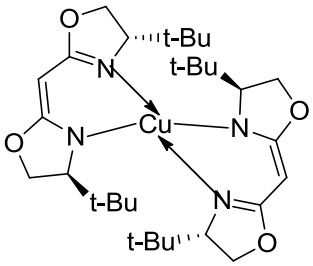
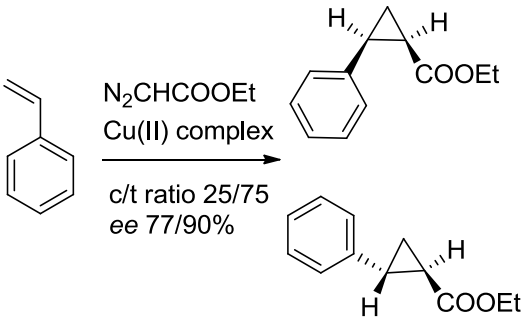
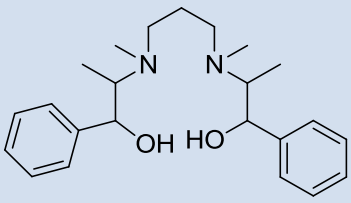
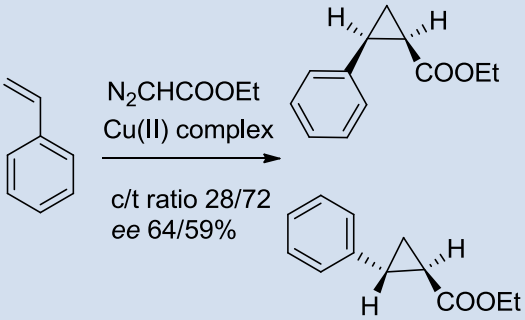
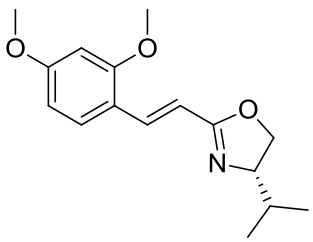
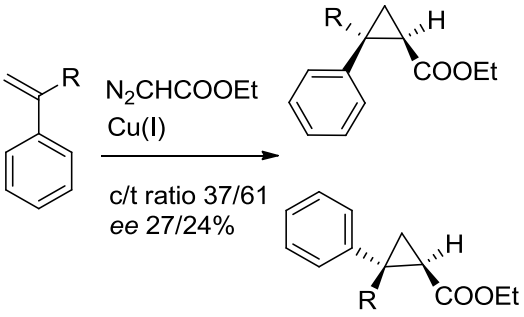
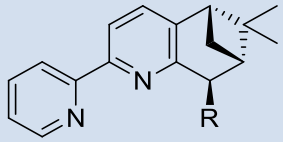
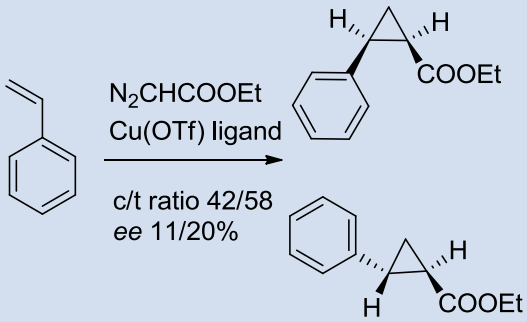
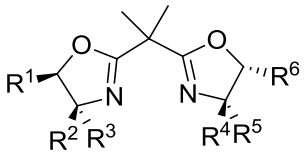
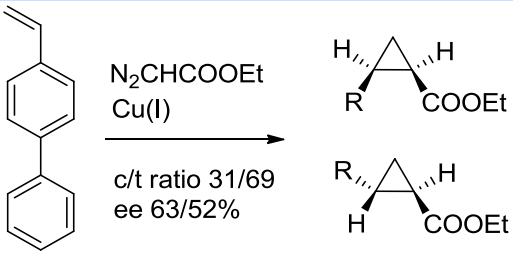
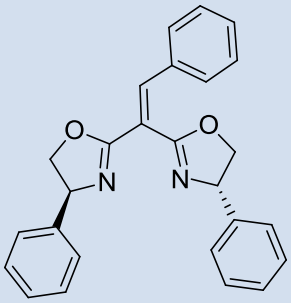
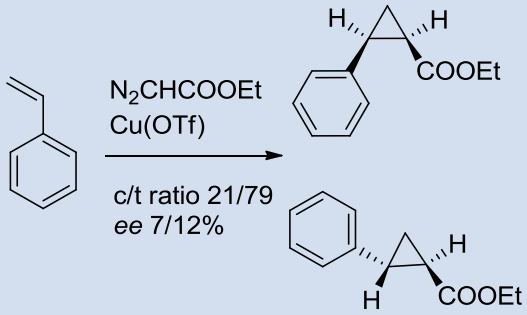
1			103
2			98
3			106

[105] Corma, A.; Dominguez, I.; Rodenas, T.; Sabater, M.J. *Journal of Catalysis*, **2008**, *259*, 26.
[106] Godau, T.; Bleifuß, S.M.; Müller, A.L.; Roth, T.; Hoffmann, S.; Heinemann, F.W.; Burzlaff, N. *Dalton Trans*. **2011**, *40*, 6547.

entry	chiral catalyst	Reaction	lit
4			107
5			99
6			108
7			101
8			109

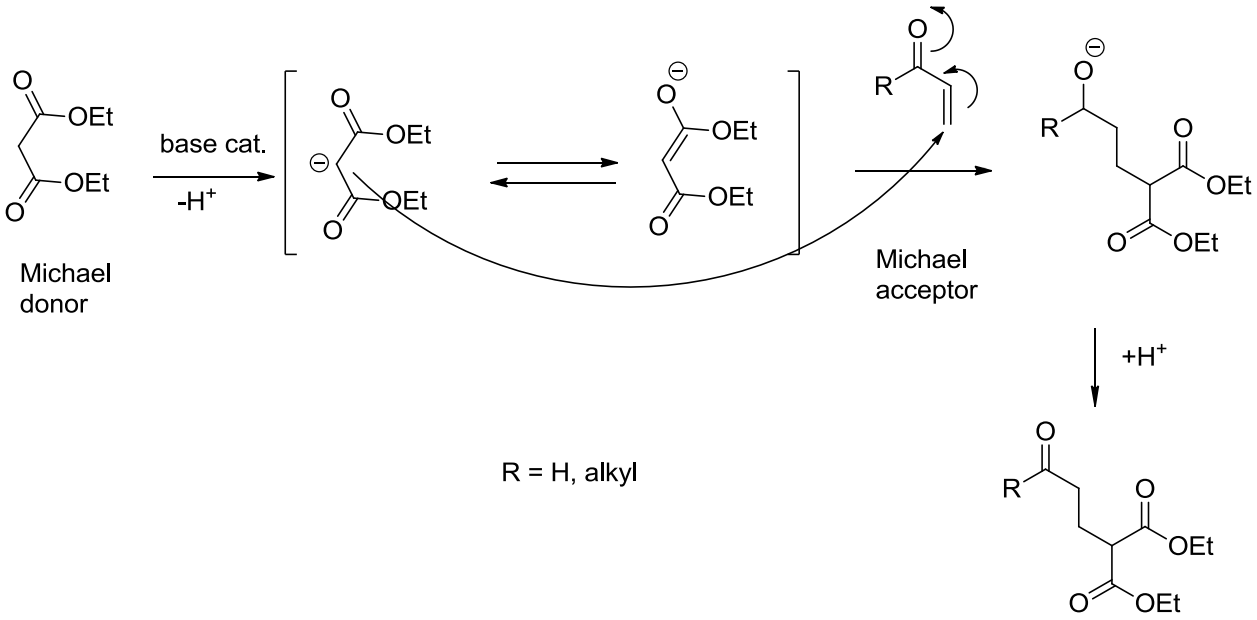
[107] Bouet, A.; Heller, B.; Papamicael, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, *5*, 1397.
[108] Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *42*, 6005.
[109] Carreiro, E.P.; Prates Ramalho, J.P.; Burke, A.J. *Tetrahedron*, **2011**, *67*, 4640.

entry	chiral catalyst	Reaction	lit
9			110
10			97
11			93

1.4.1.4 Asymmetric Michael addition

Michael addition is a classical and one of the most useful C-C bond-forming reactions and has wide applications in organic synthesis.[111] This reaction is usually catalysed by strong bases such as alkali hydroxides; however, undesirable side reactions require using transition metal catalysis in the constant search for neutral and mild conditions.[112]

[110] Chelucci G.; Gladiali, S.; Sanna, M.G.; Brunner, H. *Tetrahedron Asymmetry*, **2000**, *11*, 3419.
[111] Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series: Pergamon, Oxford, 1992; Vol. 9; Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419; Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 10486.
[112] Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246.



Scheme 15: Michael addition of malonate to a α,β-unsaturated carbonyl compound

Michael addition is a versatile tool in synthesis of chiral drug intermediates. [113] As example, chiral γ-amino butyric acid derivatives (GABA) used for treatment of central nervous system disorder can be synthesised *via* a pathway including Michael addition.[120]

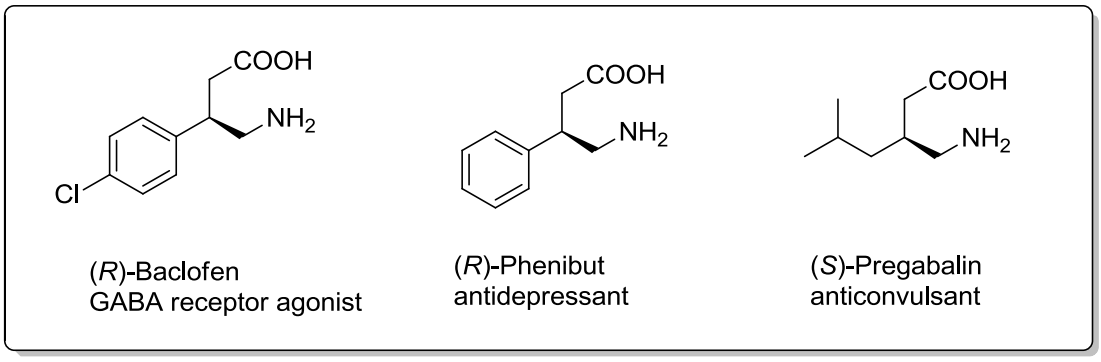
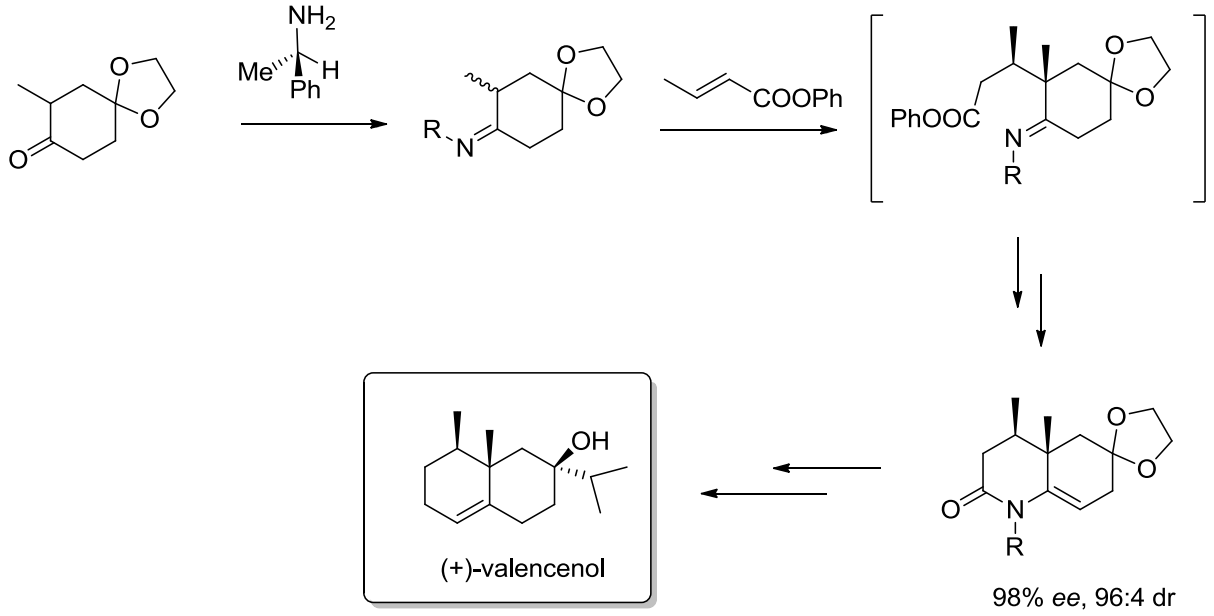


Figure 7: Biologically active chiral GABA analogues[120]

Although metal complex mediated processes afford Michael adducts in high yields and enantioselectivities (Table 6, entry 9),[114] especially the organocatalytic asymmetric Michael addition was widely used and reported in recent years.

[113] Luo, S.; M,i X.; Zhang, L.; Liu, S.; Xu, H.; Cheng J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093.
[114] Xu, D-Q.; Wang, T.; Luo, S.; Yue, H.; Wang, L.; Xu, Z. *Tetrahedron Asymmetry*, **2007**, *18*, 1788.

For example, imine-enamine activation with (*R*)-phenethylamine was reported by the group of Pfau in the synthesis of (+)-valencenol *via* Robinson annulation, shown in Scheme 16.[115]



Scheme 16: Synthesis of (+)-valencenol

Since the discovery of the organocatalytic potential of chiral pyrrolidines and imidazolines especially these functionalities are regarded as a unique backbone for asymmetric catalysis to facilitate enamine and imine based transformations.[116] Careful catalyst design is recommended, as even a subtle change in catalyst structure can sometimes improve catalytic activity. Hayashi published the observation that the introduction of a siloxy group into the proline structure led to an increase in catalytic activity of Michael reaction of propanal and nitro styrene, allowing a decrease in catalyst loading and shorter reaction times without compromising the enantioselectivity (Table 6, entry 4).[117] The reaction had broad applicability with respect to the Michael donor and nitro alkenes as well as α,β-unsaturated ketones could be employed as the Michael acceptor. Similar occurrence was observed by Mager (Table 6, entry 11).[118]

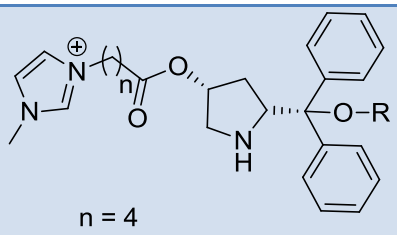
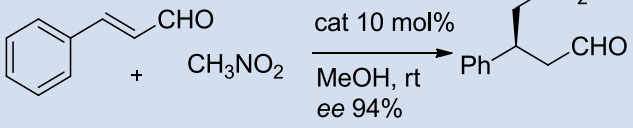
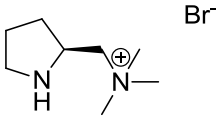
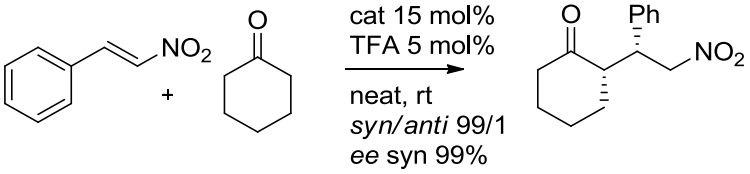
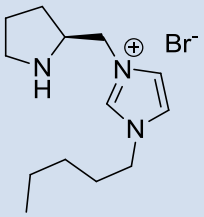
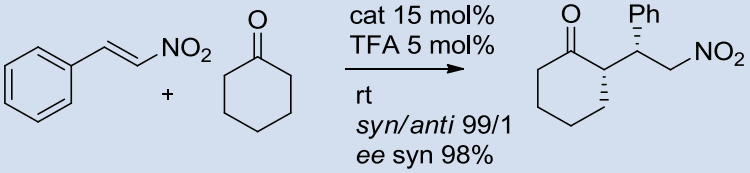
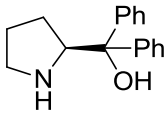
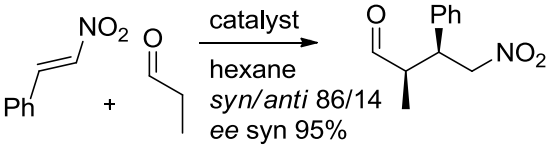
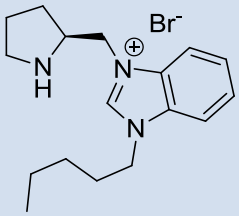
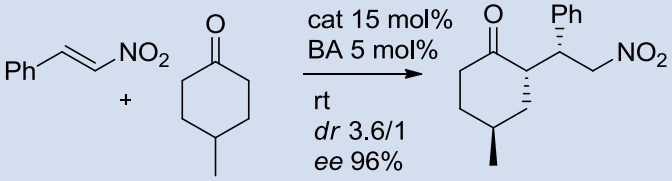
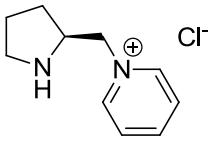
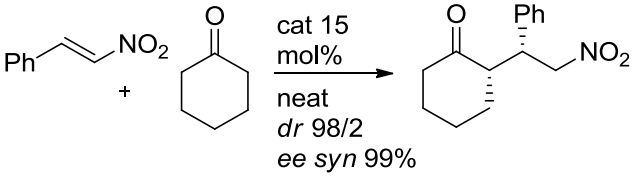
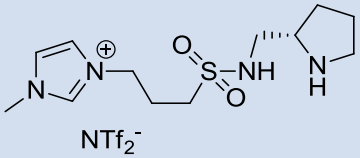
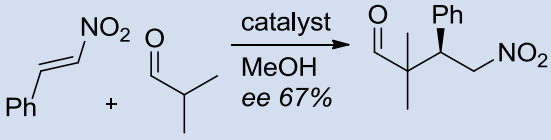
[115] Revial, G.; Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymmetry*, **2001**, *12*, 1683.
[116] Wu, L-Y.; Yan, Z.; Xie, Y.; Niu, Y.; Liang, Y. *Tetrahedron Asymmetry*, **2007**, *18*, 2086.
[117] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4212.
[118] Mager, I.; Zeitler, K. *Org. Lett*. **2010**, *12*, 1480.

Although excellent results were obtained in organocatalysis, a high catalyst loading up to 30% is required in most cases to achieve an acceptable yield, so efficient catalyst recovery has become a major concern.[119] Ionic liquids should be ideal components to overcome this issue and with the development of task specific ionic liquids the number of publications concerning ionic liquid functionalised amines as efficient organocatalysts in Michael addition was increasing exponentially. Luo´s imidazolium IL for example was considered to have two effects: the planar and bulky organic cation should impart space shielding to the reaction intermediate and the proximity of the ionic liquid unit creates a favourable microenvironment for chiral induction (Table 6, entry 10).[113] Recently Maltsev reported the development of a recoverable version of a diarylprolinol ether with an ionic liquid moiety (Table 6, entry 1).[120] The designed ionic liquid catalysed the addition of dialkyl malonates to α,β-enals and could be used several times without any decrease in activity or enantioselectivity. Moreover, ionic liquid catalyst worked well even without an acidic or basic additive. The ionic groups were held to be responsible for that observation.

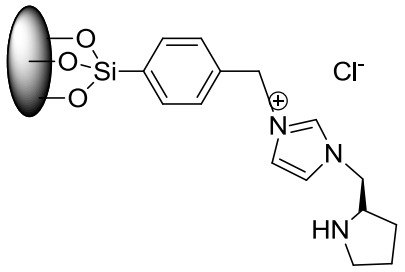
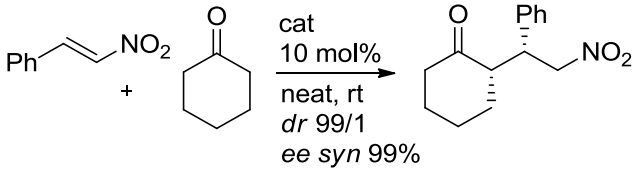
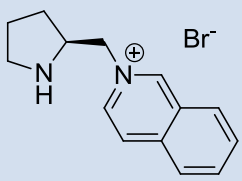
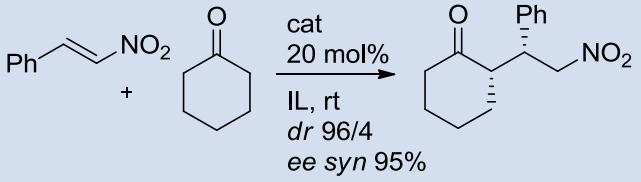
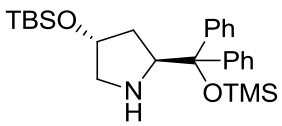
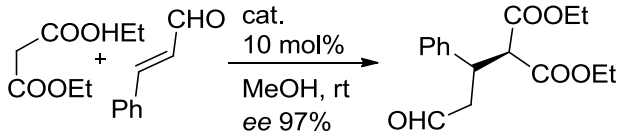
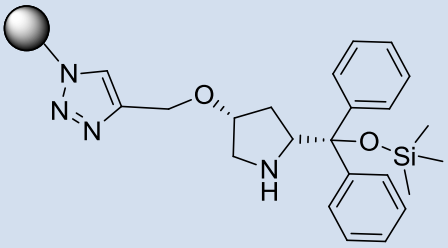
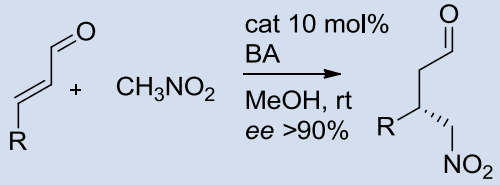
The following table gives an overview of the enormous scope of Michael reaction and presents a selection of efficient catalysts published so far.

[119] Zhang, Q.; Ni, B.; Headley, A. D. *Tetrahedron*. **2008**, *64*, 5091.
[120] Maltsev, O.V.; Kucherenko, A.S.; Bletskaya, I.P.; Tartakovsky, V.A.; Zlotin, S.G. *Eur. J. Org. Chem*. **2010**, 2927.

Table 6: Asymmetric Michael addition – a literature survey

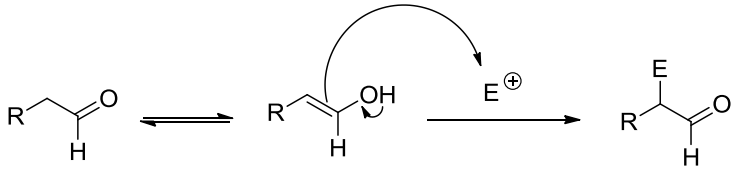
entry	catalyst	reaction	lit
1	 n = 4	 cat 10 mol% MeOH, rt *ee* 94%	120
2		 cat 15 mol% TFA 5 mol% neat, rt *syn/anti* 99/1 *ee* syn 99%	121
3		 cat 15 mol% TFA 5 mol% rt *syn/anti* 99/1 *ee* syn 98%	113
4		 catalyst hexane *syn/anti* 86/14 *ee* syn 95%	117
5		 cat 15 mol% BA 5 mol% rt *dr* 3.6/1 *ee* 96%	122
6		 cat 15 mol% neat *dr* 98/2 *ee syn* 99%	123
7		 catalyst MeOH *ee* 67%	124

[121] Wang, G.; Sun, H; Cao, X.
[122] Luo, S.; Zhang, L.; Mi, X.; Quia, Y.; Cheng, J.P. *J. Org. Chem*. **2007**, *72*, 9350.
[123] Ni, B.; Zhang, Q.; Headley, A. *Tetrahedron Lett*. **2008**, *49*, 1249.
[124] Zhang, Q.; Ni, B.; Headley, A. *Tetrahedron*, **2008**, *64*, 5091.

entry	catalyst	reaction	lit
8			125
9			114
10			126
11			118

1.4.1.5 Asymmetric alkylation

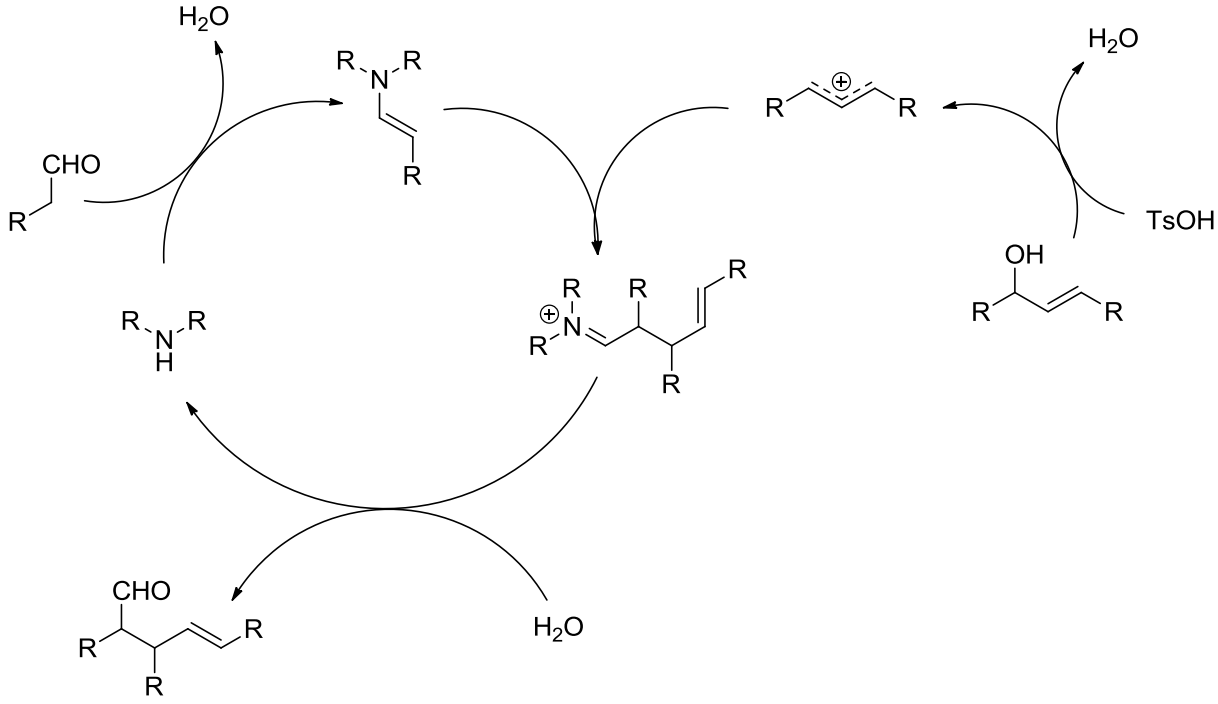
Beside the nucleophilic addition to carbonyls, α-alkylation of carbonyl compounds is another fundamental way to form C-C bonds. In α-position alkylated aldehydes and alcohols derived by simple reduction are again useful chiral synthetic intermediates.



Scheme 17: α-alkylation via silyl enolates

[125] Li, P.; Wang, L.; Zhang, Y.; Wang, G. *Tetrahedron*, **2008**, *64*, 7633.
[126] Hisayuki, S.; Fumiaki, N.; Takeshi, O. *Chem. Lett*. **2010**, *39*, 379.

There are only few examples in literature dealing with this kind of reactions. Even less papers reported a successful asymmetric implementation of α–allylic alkylation up to date. An example for a direct organocatalytic intermolecular effort was published in 2010. The group combined Brønsted acid and enamine catalysis (Scheme 18, Table 7, entry 5).[127]



Scheme 18: Combined Brønsted acid and enamine catalysis according to Xu et al.

N-Oxide based organocatalysts in combination with allyl trichlorosilane were reported to alkylate aromatic and α-β-unsaturated aldehydes.[128] Jacobsen published an effective asymmetric alkylation of α-branched aldehydes *via* a S_{N1} pathway.[129]

The first example of the combination of organocatalysis and transition metal catalysis for the direct intermolecular α-allylation of aldehydes and cyclic ketones was reported by Cordova and Ibrahem in 2006 (Table 7, entry 2).[130] In contrast to the conventional α-alkylation *via* the stoichiometric use of preactivated carbonyls as metal enolates or silyl enol ethers (Scheme 17), they successfully combined catalytic

[127] Xu, L.W.; Gao, G.; Gu, F.L.; Sheng, H.; Li, L.; Lai, G.Q.; Jiang, J.X. *Adv. Synth. Catal*. **2010**, *352*, 1441.
[128] Naicker, T.; Arvidsson, P.I.; Kruger, H.G.; Maguire, G.E.M.; Govender, T. *Eur. J. Org. Chem*. **2011**, 6923.
[129] Brown, A.R.; Kuo, W.H.; Jacobsen, E.W. *J. Am. Chem. Soc*. **2010**, *132*, 9286.
[130] Ibrahem, I.; Cordova, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 1952.

enamine activation and Pd catalysis. The α-allylic alkylated aldehydes and ketones were obtained in high yield and chemoselectivity.

The problem of intramolecular allylation (Figure 8) of aldehydes was solved *via* an organocatalysed Tsuji-Trost reaction in the course of the total synthesis of the antibiotic abyssomicin C (Table 7, entry 1).[131]

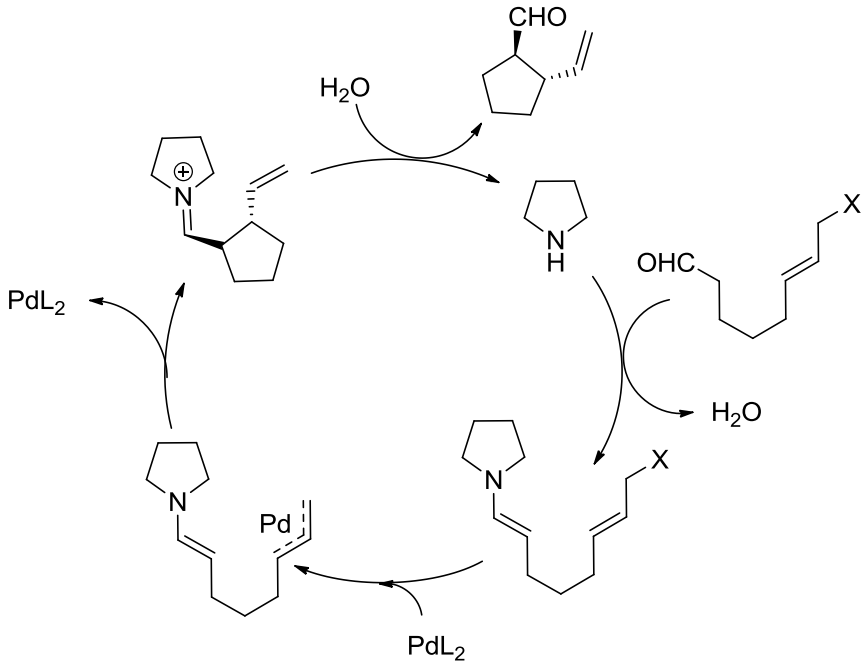
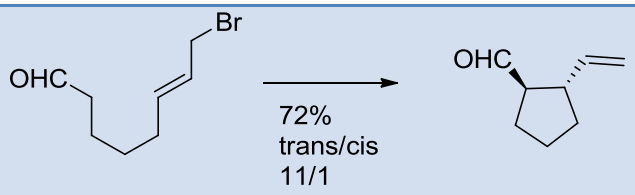
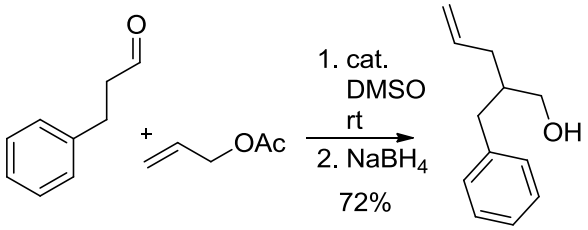
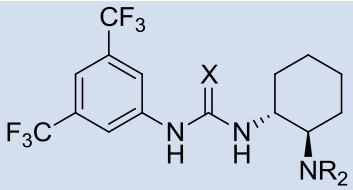
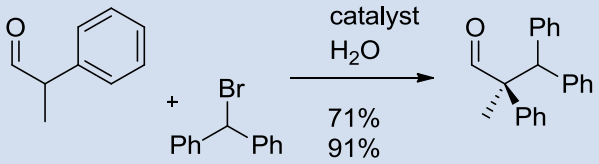
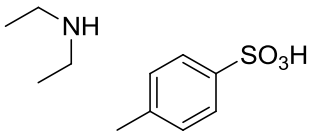
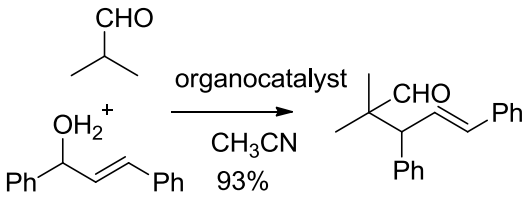
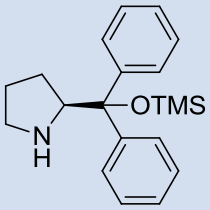
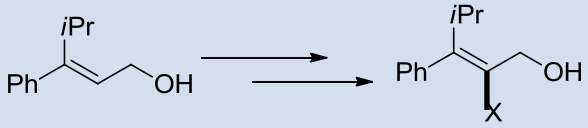
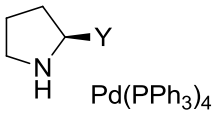
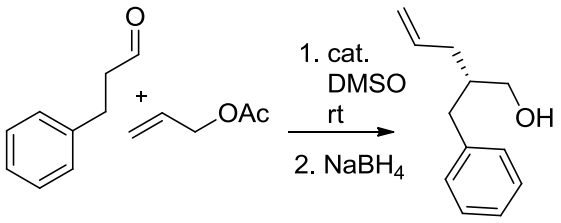


Figure 8: Mechanism of the Pd/amine co catalysed cyclisation according to Vulovic

In both examples pyrrolidine was used for enamine activation and $Pd(PPh_3)_4$ was the transition metal catalyst.

[131] Vulovic, B.; Bihelovic, F.; Matovic, R.; Saicic, R.N. *Tetrahedron*, **2009**, *65*, 10485.

Table 7: Asymmetric α-alkylation – a literature survey

entry	catalyst	reaction	lit
1	$Pd(PPh_3)_4$/pyrrolidine		131
2	$Pd(PPh_3)_4$/pyrrolidine		130
3	 X = S, O		132
4			133
5		 X = F, Cl, NR_2	134
6	 $Pd(PPh_3)_4$		135

[132] Brown, A.R.; Kuo, W.H.; Jacobsen, E.W. *J. Am. Chem. Soc*. **2010**, *132*, 9286.
[133] Xu, L.W.; Gao, G.; Gu, F.L.; Sheng, H.; Li, L.; Lai, G.Q.; Jiang, J.X. *Adv. Synth. Catal*. **2010**, *352*, 1441.
[134] Quintard, A.; Alexakis, A.; Mazet, C. *Angew. Chem. Int. Ed*. **2011**, *50*, 2354.
[135] Afewerki, S.; Ibrahem, I.; Rydford, J.; Breistein, P.; Cordova, A. *Chem. Eur. J.* **2012**, *18*, 2972

1.5 Ionic liquids in asymmetric synthesis

The variety of possible cations and anions of ionic liquids and their resulting tunable properties in combination with recyclability made them attractive in the field of asymmetric synthesis.[136] Surprisingly, it is not long since attention has been focused on the application of ILs for enantioselective processes. The first example in asymmetric synthesis was proposed by Chauvin in 1995,[137] however most of the related studies were published after the year 2000. Three different strategies how ILs can be applied in asymmetric synthesis are shown in Figure 9.

Though still at a preliminary stage, all these possibilities have been the subject of recent research.

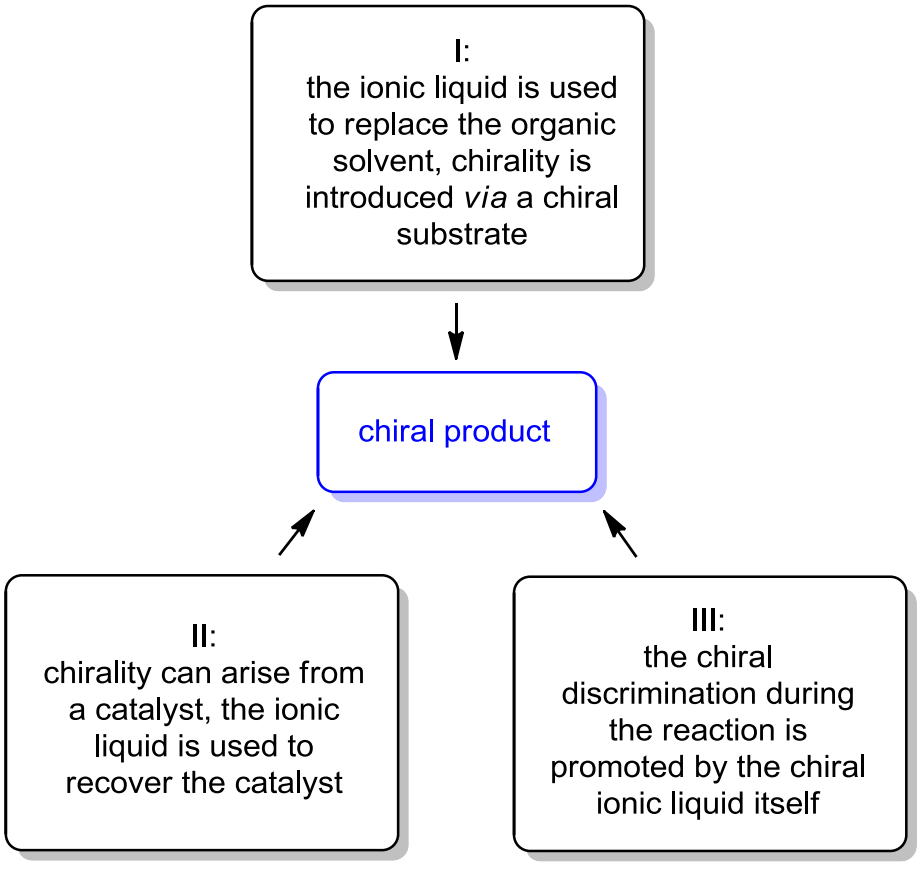


Figure 9: Strategies for ILs to introduce chirality

[136] Welton, T. *Chem.Rev*. **1999**, *99*, 2071; Dupont, J.; de Souza, R.F.; Suarez, P.A.Z. *Chem. Rev*. **2002**, *102*, 3667. Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 3772.
[137] Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2698.

1.5.1 Asymmetric reactions in ionic liquids as reaction media

Facile catalyst recyclation and product separation are besides an increase of activity and selectivity main advantages of ionic liquids used as reaction media, following prevention of toxic and environmentally hazardous organic solvents as a principle of green chemistry.[138] The comparable easy recovering of product and catalyst can be explained by an enhanced stability of many catalytic systems in ionic liquids.[139] The following chapter discusses various reactions in different fields of asymmetric synthesis and demonstrates the wide scope of applications of ionic liquids as reaction media.

Asymmetric metal catalysed hydrogenation in ionic liquids reported by Chauvin showed enantioselectivities of 64% and both the product and the ionic liquid could be easily isolated from the reaction mixture.[137] Wolfson however studied the influence of ILs in combination with other solvents. Whereas high solubility of the solvent promoted activity of hydrogenation, it caused leaching of IL and catalyst.[140] Dupont et al. showed an example for recyclation of the IL/catalyst system by using [C_4mim][BF_4]/alcohol mixtures.[141]

Asymmetric dihydroxylations in a mixed solvent system including [C_4mim][PF_6] reported by Song[142] and Sheldon[143] gave high reaction rates and high *ee* values. Another advantage of the IL in these reactions was that no over oxidation, commonly seen for dihydroxylations in organic solvents, was observed. The ionic liquids [C_4mim][BF_4] and [C_4mim][OTf] were found to be highly effective solvents giving *ee* values and yields up to 90% in asymmetric fluorination reactions while permitting recyclation up to seven times without loss of yield and selectivity.[139]

The organocatalysed Michael addition of nitro alkenes proceeded more smoothly in [C_4mim][PF_6] to give the desired product in higher yield and much better enantioselectivity than obtained in conventional solvents.[138] The ionic liquid/catalyst

[138] Xu, D.; Luo, S.; Yue, H.; Wang, L.; Liu, Y.; Xu, Z. *Synlett*, **2006**, *16*, 2569.
[139] Malhotra, S.V.; Kumar, V.; Parmar, V.S. *Current Organic Synthesis*, **2007**, *4*, 370.
[140] Wolfson, A.; Vankelecom, I.F.J.; Jacobs, P.A. *Organometalic Chem*. **2005**, *690*, 3558.
[141] Monteiro, A.L.; Zinn, F.K.; de Souza, R.F., Dupont, J. *Tetrahedron Asymmetry*, **1997**, *8*, 177.
[142] Song, C.E.; Jung, D.; Roh, E.J.; Lee, S.G.; Chi, D.Y. *Chem. Commun.* **2002**, 3038.
[143] Liu, Q.; Zhang, Z.; Rantwijk, F.V.; Sheldon, R.A. *J. Mol. Cat. A Chem*. **2004**, *224*, 213.

system was used for three consecutive runs to yield the product with comparable good results but prolonged reaction time. In contrast the group of Trombini studied the catalytic activity of proline derived organocatalysts for asymmetric aldol condensation in ionic liquids.[144] Loh also worked on aldol reactions and identified [C_4mim][PF_6] as most suitable IL, especially to avoid the formation of the elimination product. The enantiomeric excesses were comparable or higher than those obtained in DMSO.[145] Similar results were obtained in the reaction of propanon with benzaldehyde, where the catalyst/IL system could be reused three times.[146] Eight time recyclations of catalyst without any decrease of enantioselectivity or chemical yield in Diels-Alder[147] or Friedel-Crafts[148] reactions were reported. While Takahashi[149] used a cationic palladium oxazolidine catalyst, Shin showed excellent performance of a chiral copper complex immobilised in several butyl methyl imidazolium ILs.[150]

All these examples clearly demonstrate that ionic liquids are superior to classical organic solvents in many cases and ionic liquids can function as effective media for asymmetric catalysis. Benefits include easier recovery of products and catalysts as well as short reaction times and broad substrate scope.

1.5.2 Chiral ionic liquids as reaction media

It was early recognised that CILs even bear the potential to act as chiral environment and could be more efficient than conventional chiral solvents. Because of the high degree of organisation and the consequently polymer like behavior of ILs,[151] a significant transfer of chirality can be expected.[152, 153] Especially hydrophobic ionic liquids have attracted interest of organic chemists, because they are able to form

[144] Lombardo M.; Pasi F. ; Easwar S.; Trombini C. *Adv. Synth. Catal.* **2007**, *349*, 2061.
[145] Loh, T.P.; Feng, L.C.; Yang, H.Y.; Yang, J.Y. *Tetrahedron Lett*. **2002**, *43*, 8741.
[146] Kotrusz, P.; Kmentova, I.; Gotov, B.; Toma, S.; Solcaniova, E. *Chem. Commun*. **2002**, 2510.
[147] Doherty, S.; Goodrich, P.; Hardacre, C.; Knigt, J. G.; Nguyen, M. T.; Parvulescu, V. I.; Paun, C. *Adv. Synth.Catal.* **2007**, *349*, 951.
[148] Malhotra, S. V. ; Xiao, Y. *Aust. J. Chem*. **2006**, *59*, 468.
[149] Takahashi, K.; Nakano, H.; Fujita, R. *Chem. Commun*. **2007**, 263.
[150] Shin Y. J.; Yeom C.; Kim M. J.; Kim B. M. *Synlett.* **2008**, *1*, 89.
[151] Xiao, D.; Rajian, D.R.; Li, S.; Bartsch, R.A.; Quitevis, E.L. *J. Phys.Chem.* **2006**, *110*, 16174.
[152] Antonietty, M.; Kuang, D.; Smarsly, B.; Zhou, Y. *Angew. Chem. Int. Ed*. **2004**, *43*, 4988; Chiappe, C. *Chemical Monthly*, **2007**, *138*, 1035.
[153] Pastre, J.C.; Genisson, Y.; Saffon, n.; Dandurand, J.; Correia, C.R.D. *J. Braz. Chem. Soc*. **2010**, *21*, 821.

biphasic systems with water.[154] These might be useful for extraction and isolation of products from the reaction carried out in them.[155]

A set of amino acid derived CILs was synthesised and completely characterised by Luo in 2006.[113] An NMR discrimination study indicated that these CILs could provide a highly efficient chiral environment and applications in asymmetric synthesis are currently under investigation. The effect of the molar concentration of the chiral solvent was impressively demonstrated by Malhotra.[156] Pinane derived CILs were applied in diethyl zinc alkylation in an amount of 3 mol% to 35 mol%. Increasing the molar ratio of CIL improved the enantioselectivity gradually from 17% to 76% *ee*. Although the pinane CILs are used as additives or cosolvents in this application, they showed a comparable good chiral induction whereas imidazolium based CILs applied as green media for asymmetric Baylis-Hillman reaction afforded only fair enantioselectivities up to 25% but with improved yields.[157]

Other sets of imidazolium and pyridinium based CILs were applied as solvents and chiral additives in Heck reaction showing a satisfying overall performance of all ILs. Although in the context of homogenous catalysis, in particular with Pd(0), ILs have proven to be highly beneficial to stabilise and immobilise the metal catalyst,[158] no asymmetric induction was detected in the Heck study.[153]

One of the highest level of induced enantioselectivity reported by a solvent as the only source of chirality in an asymmetric reaction was published by Leitner.[159] Using an ionic liquid with a chiral anion, *ee* values up to 84% were obtained in the Baylis-Hillman reaction.

[154] Payagala, T.; Armstrong, D.W. *Chirality*, **2012**, *24*, 17
[155] Fukumoto, K.; Ohno, H. *Chem. Comm*. **2006**, 3081.
[156] Malhotra, S.V.; Wang, Y. *Tetrahedron Asymmetry.* **2006**, *17*, 1032.
[157] Garre, S. ; Parker, E. ; Ni, B. ; Headley, A.D. *Org. Biomol. Chem.* **2008**, *6*, 3041.
[158] Kabalka, G.;W.; Dong, G.; Venkatalaha, B.; *Tetrahedron Lett*. **2004**, *45*, 2775.
[159] Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann., C.W.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed*. **2006**, *45*, 3689.

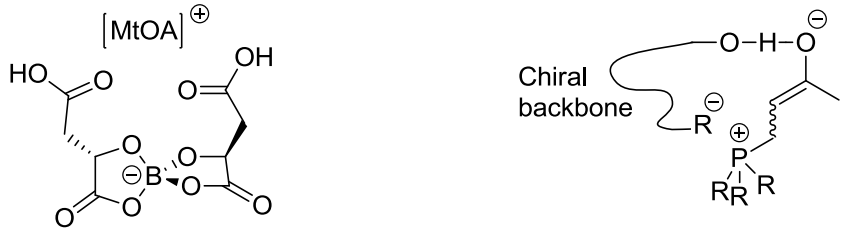


Figure 10: Anion chiral ionic liquid and possible bifunctional interaction of the zwitterionic intermediate of the aza-Baylis-Hillman reaction with the hydrogenbond donor containing anion of the IL

These results indicate that the key to effective chirality transfer lies in strong intermolecular interactions such as electrostatic attraction and hydrogen bonding between the solvent molecules and the transition state of the enantioselective reaction step.[153]

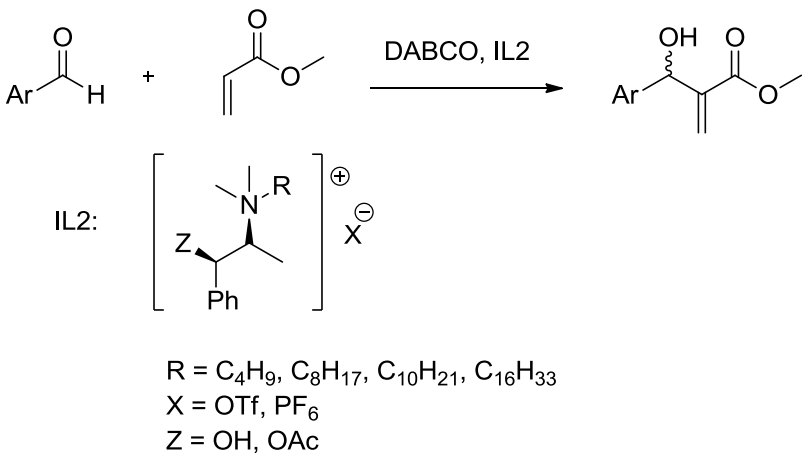
However, taking into account the enormous high costs and the lack of benefit, examples of asymmetric reactions based on the use of chiral ionic liquids as reaction media remain spare and seem to be an exceptional application in future.

1.5.1 Chiral ionic liquids as catalysts

The number of publications dealing with CILs is growing rapidly and a large pool of CILs bearing either a chiral cation or anion or seldom both is reported.[75, 160] Different CILs designed as chiral agents for asymmetric synthesis had been synthesised until now - often started from "chiral pool" derived preexisting chiral substances like amino acids.[161]But only a few have been proven to be successful catalysts. [162]

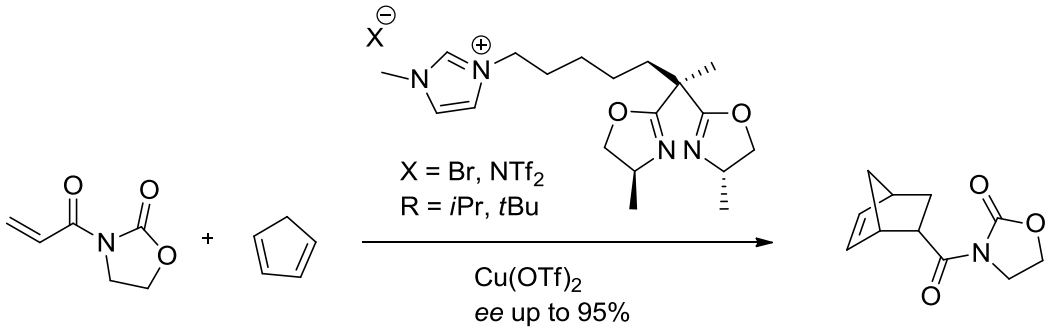
In 2004 Vo-Thanh reported one of the first effective chiral induction with an ephedrine derived CIL in a Baylis-Hillman reaction (Scheme 19).[163] The reported 44% *ee* was the largest *ee* value reported with the use of CILs in asymmetric synthesis before 2005.

[160] Zhang, Q. ; Ni, B. ; Headley, A.D. *Tetrahedron*. **2008**, *64*, 5091.
[161] Payagala, T.; Armstrong, D.W. *Chirality*, **2012**, *24*, 17.
[162] Guillen, F.; Bregeon, D.; Plaquevent, J.C. *Tetrahedron Lett*. **2006**, *47*, 1245.
[163] Pegot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett*. **2004**, *45*, 6425.



Scheme 19: Asymmetric Baylis-Hillman reaction in the presence of chiral ILs as reaction media

A current published example for an asymmetric Diels-Alder reaction catalysed by a copper (II) species incorporated into an ionic liquid is presented in Scheme 20. High conversions in combination with excellent *ee* values and up to 10 recyclations are reported.[164]



Scheme 20: Cu(II) catalysed asymmetric Diels-Alder reaction with IL ligands

1.5.2 Chiral ionic liquids as organocatalysts

Organocatalysis is a relatively new and popular field within the domain of chiral molecule synthesis. It was not until 2000 that the field of organocatalysis was launched by two almost simultaneous publications from List[165] and MacMillan,[166] showing that the concept of enamine or iminium catalysis could be applied to a

[164] Doherty, S.; Goodrich, P.; Hardacre, C.; Knight, J.G.; Nguyen, M.T.; Parvulescu, V.; Paun, C. *Adv. Synth. Catal.*, **2007**, *349*, 951.
[165] List, B.; Lerner, R.A.; Barbas, C.F. *J. Am. Chem.. Soc*. **2000**, *122*, 2395; Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
[166] Ahrendt, K.A.; Borth, C.J.; MacMillan, D.W.C. *J. Am. Chem Soc*. **2000**, *122*, 4243; MacMillan, D.W.C. *Nature*, **2008**, *455*, 304.

broad variety of transformations. These pioneer works inspired the scientific community and catalysis of asymmetric reactions by metal free organic molecules has received much attention by synthetic chemists in the last years. It's a rewarding alternative to transition metal catalysis or biocatalysis, mimicing the action of enzymes with small organic molecules.[167] Fundamental advantages compared to transition metals are first the insensitivity of organic molecules to oxygen and moisture and second that a wide variety of organic molecules are naturally available from biological sources as single enantiomers. The environmentally friendly, green aspect of this chemistry coupled with the sustainability of the catalyst is more and more considered when replacing standard metal based reactions.[39]

Asymmetric transformations mediated by amino acids have been especially successful.[76] In particular, the use of proline derivatives as organocatalysts involving enamine chemistry has been highly effective in asymmetric synthesis and an extensive number of reports on reactions catalysed by proline showed high reactivity and stereoselectivity (Figure 12).[168] The secondary amine allows forming an iminium ion with aldehydes or ketones, reacting by imine-enamine tautomerism to a reversible enamine species which can be trapped by an activated π-electrophile.[169] A new C-C bond between enamine and acceptor is formed. Hydrolysis of the iminium gives the product and liberates the secondary amine organocatalyst again.

[167] Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, 3235; Lombardo, M. ; Pasi, F. ; Easwar, S. ; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 276;
[168] Dahlin, N. ; Bogevig, A. ; Adolfson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101.
[169] Dalko, P.I.; Moisan, L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138.

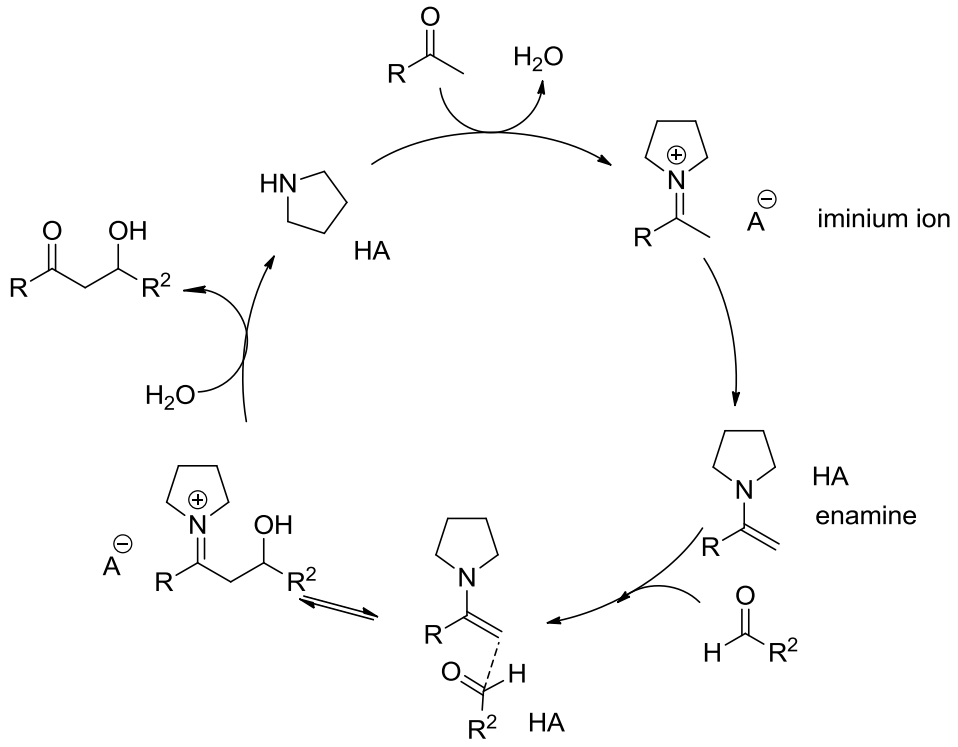


Figure 11: Enamine catalytic cycle

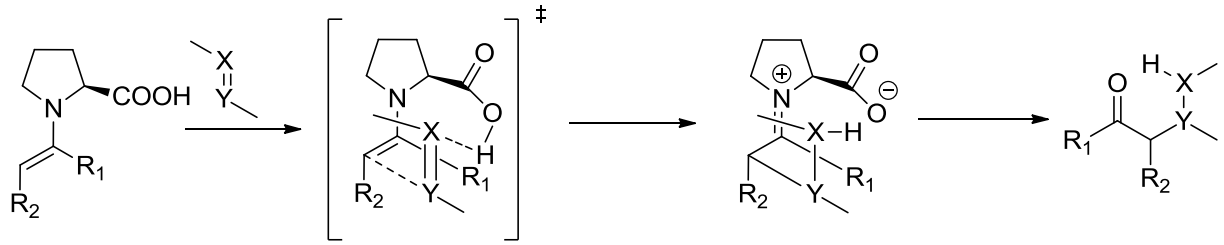


Figure 12: *L*-Proline mediated enamine catalysis

The two major goals of organocatalysis are both optimising catalyst activity as well as designing new recoverable catalysts to make the reactions economically and environmentally friendly. Drawback of organocatalysis is the use of high loadings of organocatalyst, usually up to 30% to achieve an acceptable yield,[170] wherefore recovery of the catalyst is stongly desired.

Although proline for sure will continue to play a central role in organocatalysis, it is challenging to find new synthetic derivatives.

[170] Wu, L-Y.; Yan, Z. ; Xie, Y. ; Niu, Y. ; Liang, Y. *Tetrahedron Asymmetry*. **2007**, *18*, 2086.

Room temperature ionic liquids with their unique properties have been tested by several research groups as an approach for recycling and reuse of organocatalyst (Figure 13).[171]

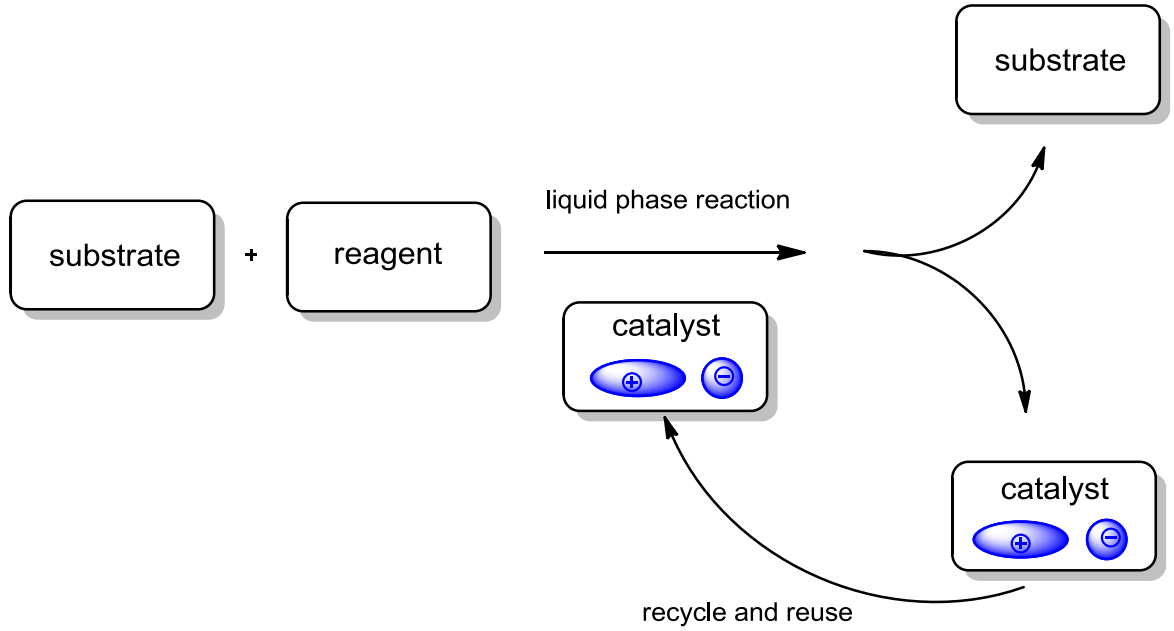


Figure 13: Concept of ionic liquid catalyst recyclation

Ionic liquid type organocatalysts maintain the unique properties of an ionic liquid on the one hand and induce chirality to the desired product on the other hand.[168] The proximity of the ionic liquid unit to the organocatalytic active site may create a favourable environment exerting synergistic effects on some organic reactions.[113] Organocatalysis with ionic liquid catalysts is a fast growing field, so it is not possible to cover all of the developments. Instead a selection of useful applications in the synthesis of chiral molecules should be presented to provide an overview of this exciting topic.

Especially Michael addition[165] served as model reaction in several publications with ionic liquids as organocatalysts.[172] Luo reported quantitative yield and high enantioselectivities up to 98% *ee* for his Michael addition catalysed with chiral pyrrolidine-imidazolium bromide and tetrafluoroborate systems.[113] In another

[171] Miao, W.; Chan, T.H. *Adv. Synth. Catal.* **2006**, *348*, 1711
[172] Wu L-Y.; Yan Z. ; Xie Y. ; Niu Y. ; Liang Y. *Tetrahedron Asymmetry.* **2007**, *18*, 2086. Zhang Q. ; Ni B. ; Headley A. D. *Tetrahedron*. **2008**, *64*, 5091. Wang, G.; Sun, H.;Cao, X.; Chen, L. *Catal. Lett*. **2011**, *141*, 1324.

publication the group used an effective and reusable ionic liquid organocatalyst based on proline and showed a positive effect of acidic additives enhancing the catalytic activity *via* assisting the enamine catalytic cycle.[173, 174]

Examples of a low catalyst loading were shown with silica gel supported pyrrolidine based ionic liquid organocatalysts or by excellent results of Xu and Headley. [175, 176, 177] Truong studied the application of ephedrine based chiral ammonium, imidazolium and pyridinium ILs as catalysts for the asymmetric Michael addition reaction of diethyl acetamido malonate to chalcone.[178] Enantioselectivities up to 70% were obtained in this challenging Michael addition with less activated Michael acceptors. More examples of ionic liquid catalysed Michael addition are presented in chapter 1.4.1.4.

Starting from *trans*-4-hydroxyproline some efficient IL organocatalysts for aldol reactions in the presence of water were reported. [179] An increasing amount of water in the aldol reaction improved both yield and stereochemical outcome accompanied by an excellent diastereoselectivity.[180] Additionally successful recycling was reported due to the insolubility of the ionic liquid catalysts in ether but a good solubility in water, forming the basis of an efficient separation of the catalyst from the product. An ionic liquid catalyst in combination with other ionic liquids as solvents for aldol reaction was examined by Wang, giving excellent yields and good enantioselectivities in the reaction of aldehydes with acetone.[181] One of the first reported organocatalysts for asymmetric *syn*-aldol reactions in high diastereo- and enantioselectivities was synthesised by the group of Zlotin containing (*S*)-threonine and (*S*)-diphenylvalinol units combined with an ionic liquid part.[182]

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[173] Pansare, S.V.; Panday, K.J. *J. Am. Chem. Soc*. **2006**, *128*, 9628.
[174] Luo, S.; Zhang, L.; Mi, X.; Qiao, Y.; Cheng, J. *J. Org. Chem.* **2007**, *72*, 9350.
[175] Xu, D-Q. ; Wang, T. ; Luo, S. ; Yue, H.; Wang, L.; Xu Z. *Tetrahedron Asymmetry.* **2007**, *18*, 1788.
[176] Ni, B. ; Zhang, Q. ; Headley, A. D. *Tetrahedron Letters.* **2008**, *49*, 1249.
[177] Li, P.; Wang L.; Zhang, Y.; Wang, G.; et al. *Tetrahedron.* **2008**, *64*, 7633.
[178] Truong, T.K.T.; Vo-Thanh, G. *Tetrahedron*, **2010**, *66*, 5277.
[179] Siyutkin, D. E.; Kuchero, A. S.; Struchkova, M. I.; Zlotin, S. G. *Tetrahedron Letters.* **2008**, *49*, 1212.
[180] Lombardo, M. ; Easwar, S. ; De Marco, A.; Pasi, F.; Trombini, C. *Org. Biomol. Chem*. **2008**, *6*, 4224.
[181] Zhou, L.; Wang, L. *Chemistry Lett.* **2007**, *36*, 628.
[182] Larionova, N.A.; Kucherenko, A.S:; Siyutkin, D.E.; Zlotin, S.G. *Tetrahedron*, **2011**, *67*, 1948.

It is fascinating how simple organic molecules like amino acids have stimulated the synthetic creativity of researchers and how many different ionic liquid catalysts have been presented up to date. The given short overview of ionic liquid applications in organocatalysis clearly shows, that numerous classical asymmetric reactions can be realised in and with ionic liquids. Obviously the ionic liquid catalyst has to be fine tuned to the substrate, but due to the large choice of ionic liquids it should be likely to find one with satisfying properties.3

2 Task

This work was inspired by the work of Katharina Bica[37] who applied chiral ionic liquid catalysts with amino alcohol functionality in diethyl zinc alkylation of aldehydes. Encouraged by the obtained results the concept of amino alcohol functionalised ionic liquids should be extended to other C-C bond forming reactions.

So the task of this thesis was the synthesis of novel chiral ionic liquids starting from chiral-pool derived amino acids. The desired chiral ionic liquids should contain amino alcohol functionalities as nucleophilic centres capable of coordinating to transition metals. In suitable asymmetric reactions like the copper catalysed Henry reaction and cyclopropanation, the application of the synthesised CILs as sole inducer for chirality to the product was to be investigated.

Another aim was the design and synthesis of organocatalytic active ionic liquids combining an ionic liquid part for easy recovery and recycling with a chiral secondary amine for imine or enamine activation. Application of these ionic liquids as catalysts in asymmetric alkylation reactions should be explored.

These requirements in mind, the following schematic target molecules were designed.

Figure 14: A: chiral organocatalytic ionic liquid. B: coordinating ionic liquid as charged ligand to form complexes with transition metals

3 Results and Discussion

3.1 Synthesis of ionic liquids

3.1.1 Chiral ionic liquids with an amino alcohol functionality

3.1.1.1 Amino alcohols in asymmetric synthesis

Amino alcohol functionality is present in a relative large number of natural products.[37] Especially 1,2-amino alcohols of both acyclic and cyclic derivatives are useful compounds to affect a wide range of transformation and are successfully applied as auxiliaries or ligands in asymmetric synthesis.[183]

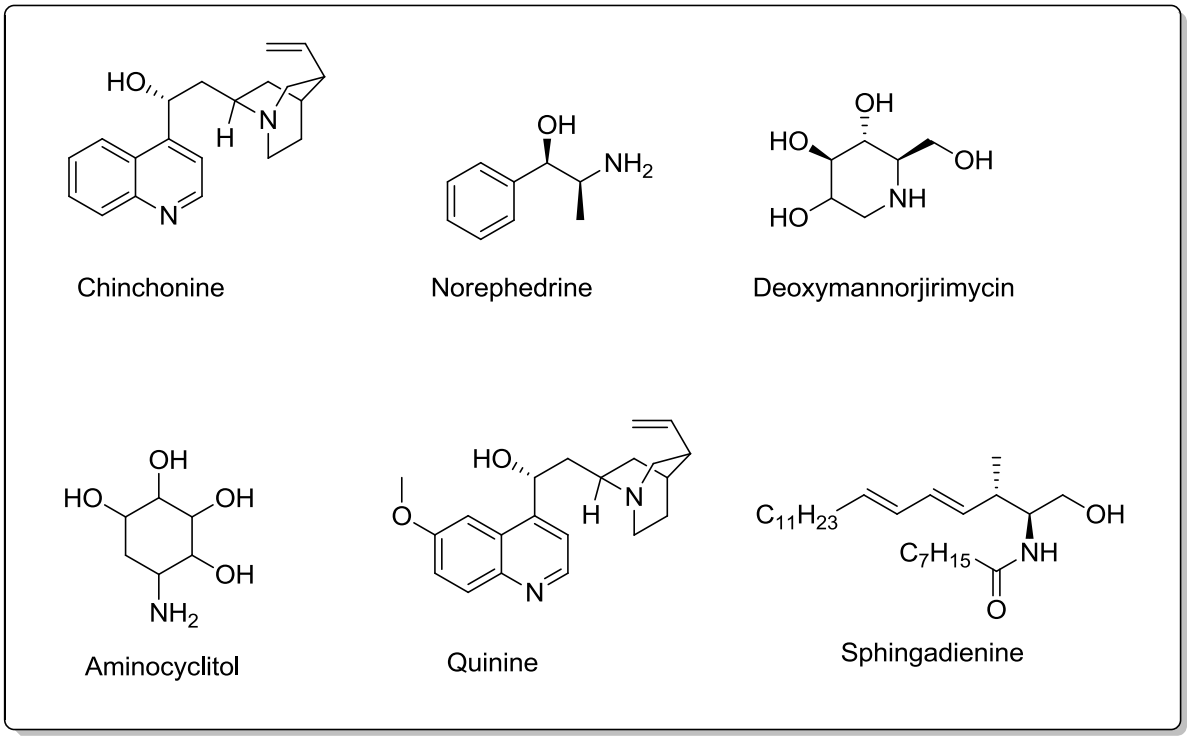


Figure 15: Examples for natural amino alcohols

A simple set of chiral 1,2-amino alcohols is easily accessible via reduction of native α-amino acids with $LiAlH_4$ in THF[184] or borane reagents.[185] However, in many applications more complex and sterically demanding amino alcohols are required

[183] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
[184] Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974; Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth.* **1990**, *Coll Vol. 7*, 530.
[185] McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

and functionalisation of *N*-protected amino acid derivatives with Grignard reagents is hence done before the reducing step.[186] Methods for the preparation of chiral 1,2-amino alcohols include reduction of α-amino carbonyls, alkoxy carbonyls or cyanohydrins, the ring opening of epoxides or cyclic sulphates or the oxyamination of alkenes.[187] Further cyclic derivatives like oxazolidines, oxazines, oxazolidinons and oxazolines are used as auxiliaries.[188]

3.1.1.2 Synthesis of coordinating ionic liquids

Starting from cheap and renewable 1,2-amino alcohols of different origin, a straight forward synthetic protocol for a new type of chiral tridentate ligands and chiral ionic liquids according to previous work of K. Bica was developed, that can be generally applied to any primary or secondary amino alcohol.[37] The introduction of a third nitrogen functionality in close proximity to the 1,2-amino alcohol functionality provides an additional possible coordination site. Thus three different nucleophilic centres in the reasonable distance of 3 or 4 bond lengths are available for direct interaction with coordinating metals or substrates.[189]

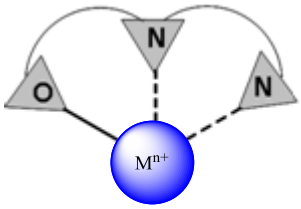
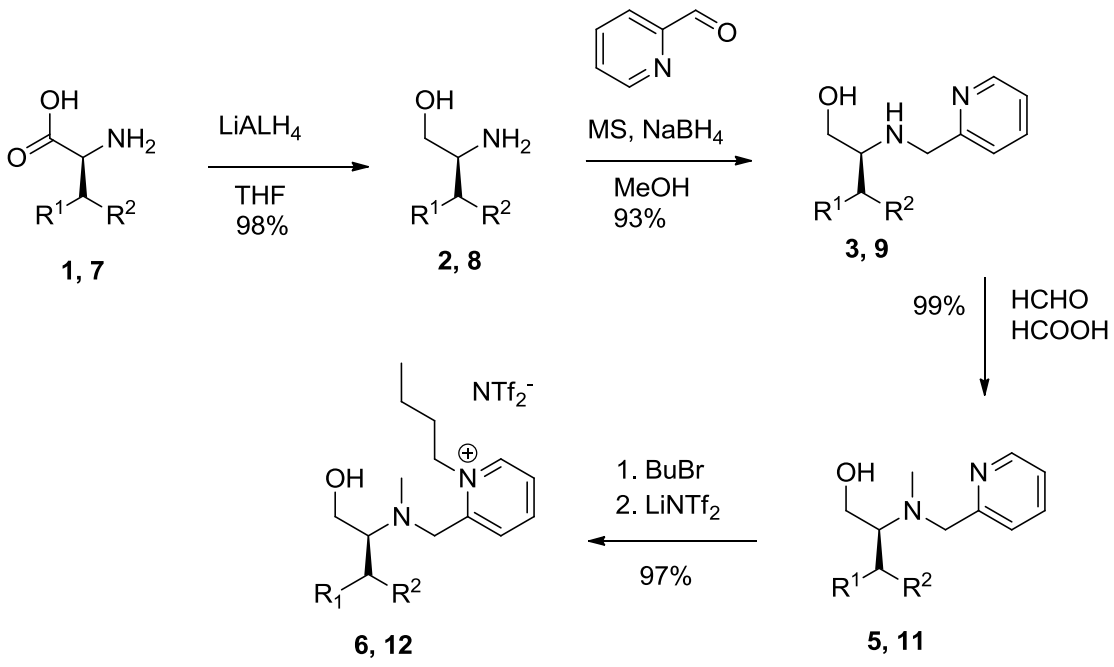


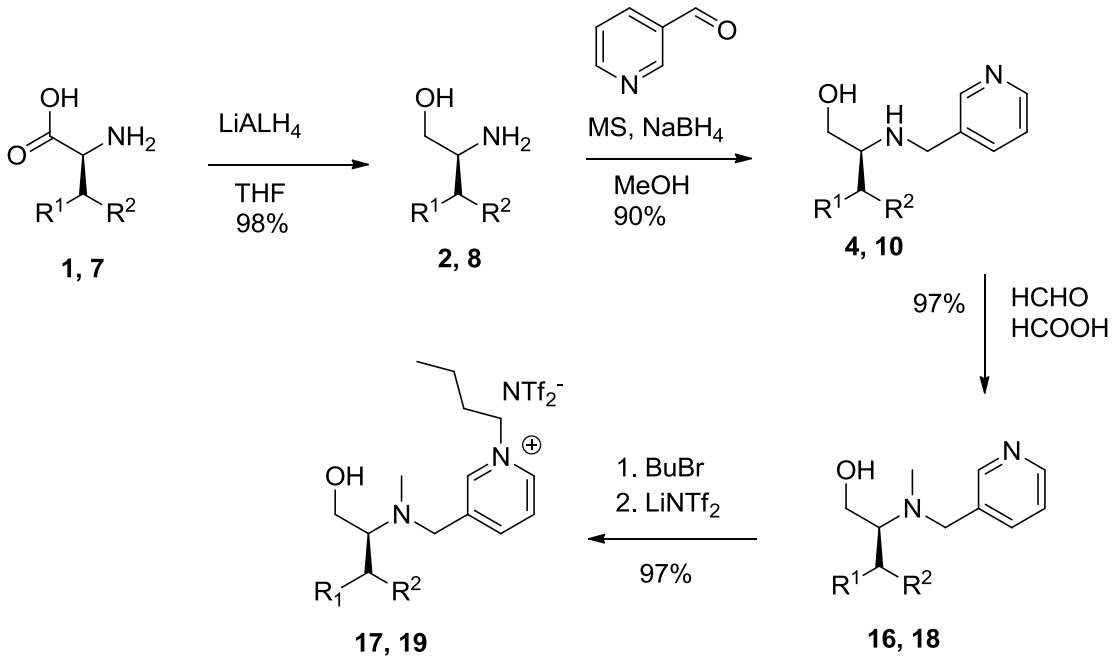
Figure 16: Scheme of a chelating chiral tridentate ligand coordinating to a metal ion

Synthesis of ligands and CILs were performed according to a straight forward synthetic pathway shown in Scheme 21 and Scheme 22.

[186] Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1994**, *59*, 4680.
[187] Schaus, S.E.; Larrow, J.F.; Jacobsen, E.N. *Cheminform*. **1997**, *28*, 45.
[188] Agami, C.; Couty, F. *Eur. J. Org. Chem*. **2004**, *4*, 677.
[189] Bica, K.; Leder, S.; Mereiter, K.; Gaertner, P.*Chemical monthly*, **2012**, accepted for publication.

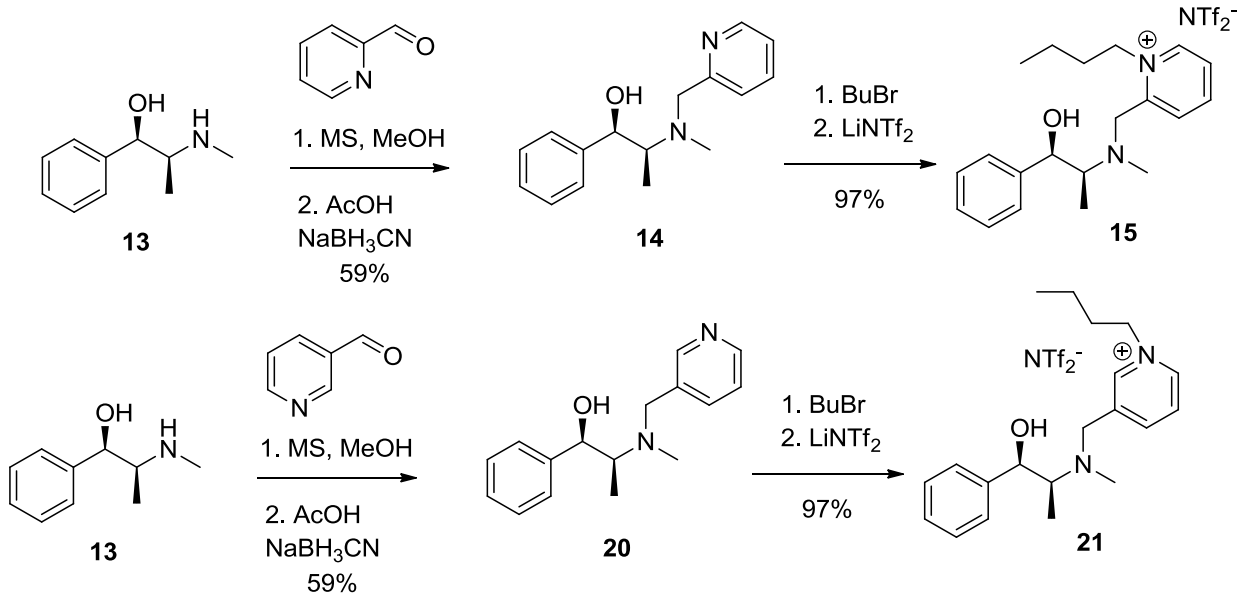


1, 2, 3, 5, 6: R^1 = H, R^2 = Ph
7, 8, 9, 11, 12: R^1 = CH_3, R^2 = CH_3



1, 2, 4, 16, 17: R^1 = H, R^2 = Ph
7, 8, 10, 18, 19: R^1 = CH_3, R^2 = CH_3

Scheme 21: Synthetic pathway to chiral ligands and ionic liquids starting from valine or phenylalanine

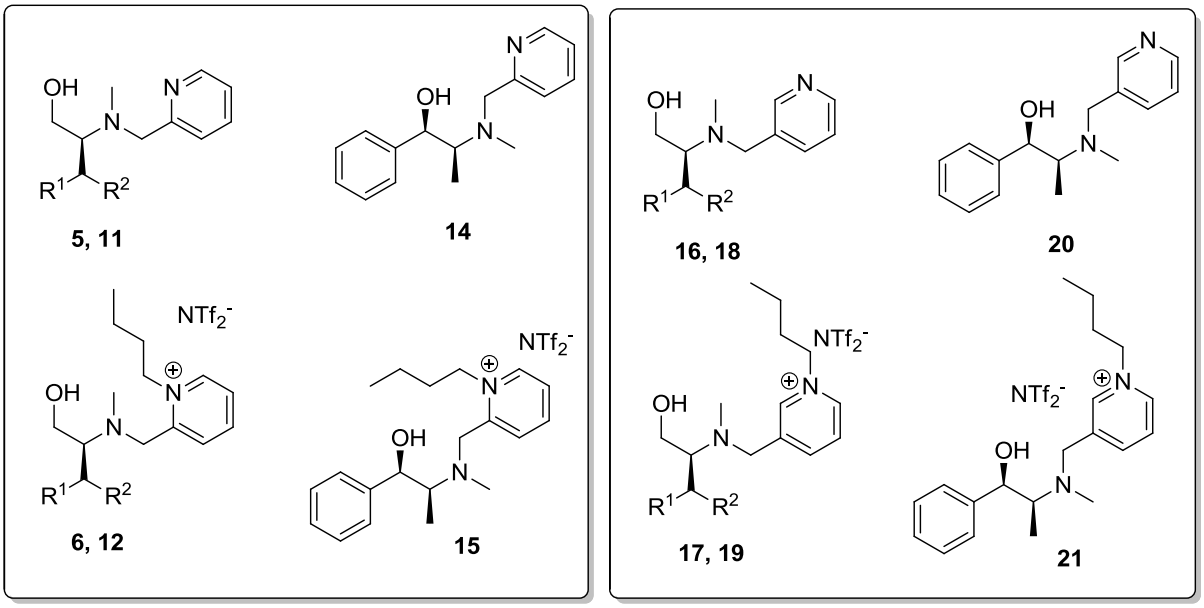


Scheme 22: Synthetic pathway to chiral ligands and ionic liquids starting from ephedrine

Synthesis started from chiral pool derived *L*-valine **7** and *L*-phenylalanine **1**. Both amino acids were reduced with $LiAlH_4$ in dry THF yielding the corresponding amino alcohols in quantitative yield which were directly used in the following reaction. In a reductive amination step the enantiopure amino alcohol was connected to a substituted pyridinium moiety, planned to form the ionic liquid part. In presence of freshly activated 4 Å molecular sieves in anhydrous methanol the amino alcohols were stirred with equimolar amounts of pyridine-3-carbaldehyde or pyridine-2-carbaldehyde. After *in situ* reduction of the iminium intermediate, the secondary animo alcohols were isolated. While the obtained products do already qualify as chiral ligands, the presence of a secondary nitrogen functionality might limit the application of these ligands particularly in reactions with strong nucleophiles.[37, 75] Therefore further N-methylation using the classical Leukart-Wallach conditions was implemented. Secondary amines were dissolved in concentrated HCOOH and aqueous HCHO solution was added. Refluxing over night followed by alkalization with NaOH, extractive workup and chromatographic purification gave the methylated ligands **5**, **11**, **16** and **18** in good overall yields. In contrast to the primary amino alcohols this general procedure was slightly adapted for the secondary amino alcohol (1*R*,2*S*)-ephedrine **13** (Scheme 22). In the first step, reaction with pyridine

carbaldehyde at room temperature took place. After complete conversion the molecular sieve was filtered off and $NaCNBH_3$ and acetic acid were added to the crude solution of oxazolidine intermediate to give the reduced products **14** and **20**. All obtained tertiary amino alcohols could be selectively alkylated on the pyridinium N with a 1.8 fold excess of butyl bromide at 70 °C. Anion exchange in water using $LiNTf_2$ followed by extraction with DCM finally yielded the corresponding CILs **6**, **12**, **15**, **17**, **19** and **21** of all amino alcohols.

The two sets of amino alcohol ligands and CILs were applied to introduce chirality in asymmetric Henry reaction as well as in asymmetric cyclopropanations.



5, 6, 16, 17: R^1 = H, R^2 = Ph
11, 12, 18, 19: R^1 = CH_3, R^2 = CH_3

Figure 17: Set of coordinating ligands and ILs

3.1.2 Chiral ionic liquids with a secondary amine functionality

3.1.2.1 Proline derivatives in asymmetric synthesis

Proline **22** is the only natural amino acid with a secondary amine functionality and thus has a higher p*K*a value and enhanced nucleophility.[169] It can react as nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines. Although proline itself continues to play a central role in amino catalysis, a great

number of new synthetic analogues or more complex oligopeptides are available as organocatalysts nowadays. A selection of them is shown in Figure 18.

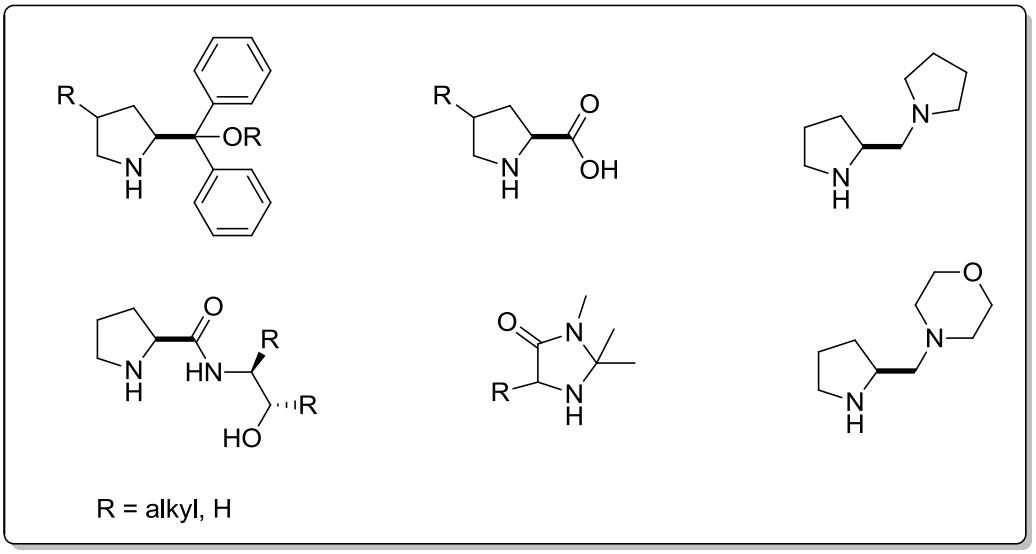


Figure 18: Proline analogues used as organocatalysts

Even subtle changes in molecular structure can sometimes improve catalytic activity, as observed by Hayashi.[190] The introduction of a silyl group into the proline structure allowed decrease of catalyst loading and shorter reaction times accompanied by broadening the substrate scope. Diaryl prolinol ethers are among the most successful organocatalysts and are reported for Michael addition[191] as well as aldol reactions.[144] An ionic liquid analogue of a diaryl prolinol derivative was successfully applied by Maltsev and recycled up to four times (Figure 19).[192]

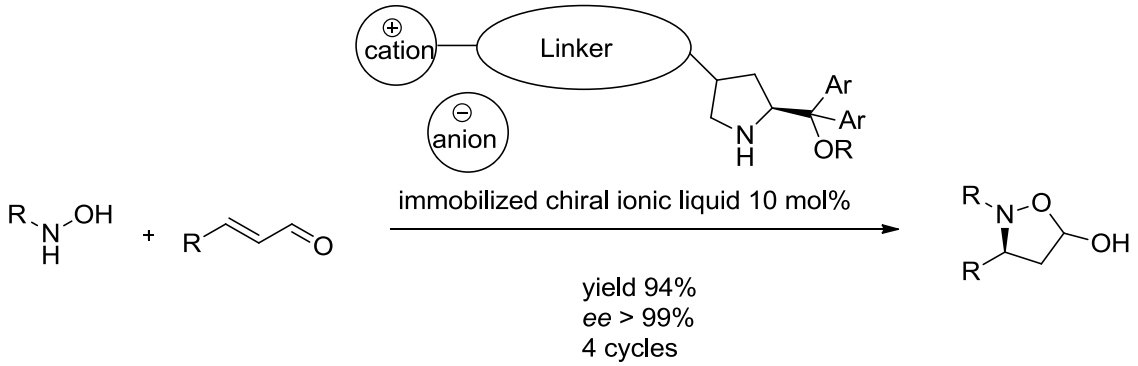


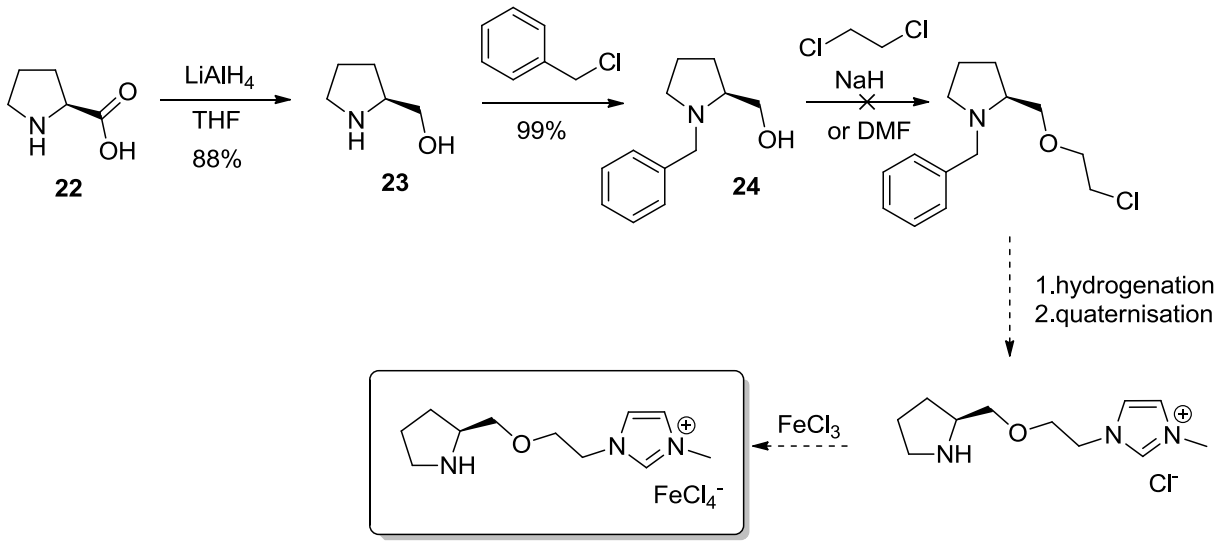
Figure 19: Organocatalysed Michael addition according to Maltsev

[190] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4212.
[191] Sato, H.; Nagashima, F.; Oriyama, T. *Chem. Lett*. **2010**, *39*, 379.
[192] Maltsev. O.V.; Kucherenko, A.S.; Chimishikyan, A.L.; Zlotin, S.G. *Tetrahedron Asym*. **2010**, *21*, 2659.

3.1.2.2 Synthesis of ionic liquids as organocatalysts

3.1.2.2.1 Bifunctional CILs derived from *trans*-4-hydroxyproline

Starting from cheap chiral pool derived proline derivatives, a straight forward synthetic strategy was designed to synthesise bifunctional ionic liquids containing a chiral organocatalytic part for asymmetric induction on the one hand and an iron molecule in the anion on the other hand. Two different synthetic strategies are shown in Scheme 23 and Scheme 25.

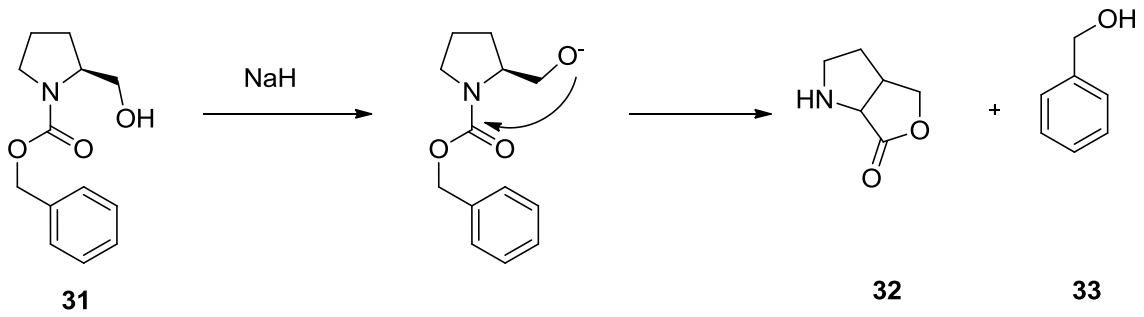


Scheme 23: Synthetic strategy 1 for iron containing catalyst

The first pathway depicted in Scheme 23 started from *L*-proline **22** which was reduced with an excess of $LiAlH_4$ to *L*-prolinol **23**. The amino group of the freshly distilled prolinol was protected with a benzyl- or carboxybenzyl (Cbz)-group and the purified molecule was subsequently taken to a Williamson etherification with NaH. Improvement of the etherification step turned out to be challenging. Neither 1,2-dichloro ethane nor 1,2-dibromo ethane in THF or DMF as solvent succeeded, although up to 10 eq. NaH were used.

When the benzyl protected prolinol **24** was applied, only starting material was isolated, whereas the Cbz-prolinol **31** underwent an unwanted side reaction. The deprotonated hydroxyl functionality was reacting intramolecular with the carbonyl

carbon of the protecting group forming the lactone **32** and benzyl alcohol **33** shown in Scheme 24.

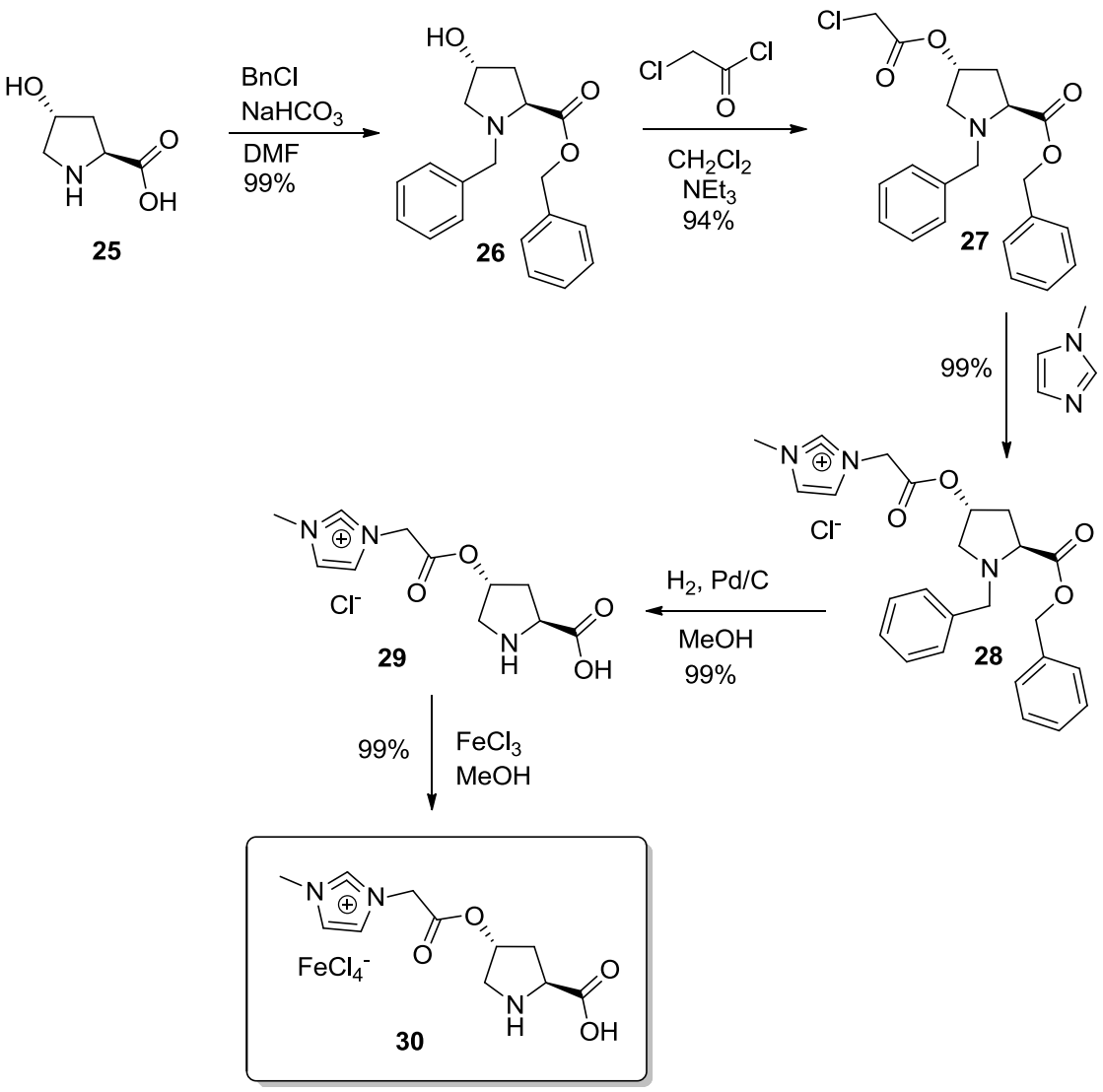


31 **32** **33**

Scheme 24: Formation of lactone as side product in etherification

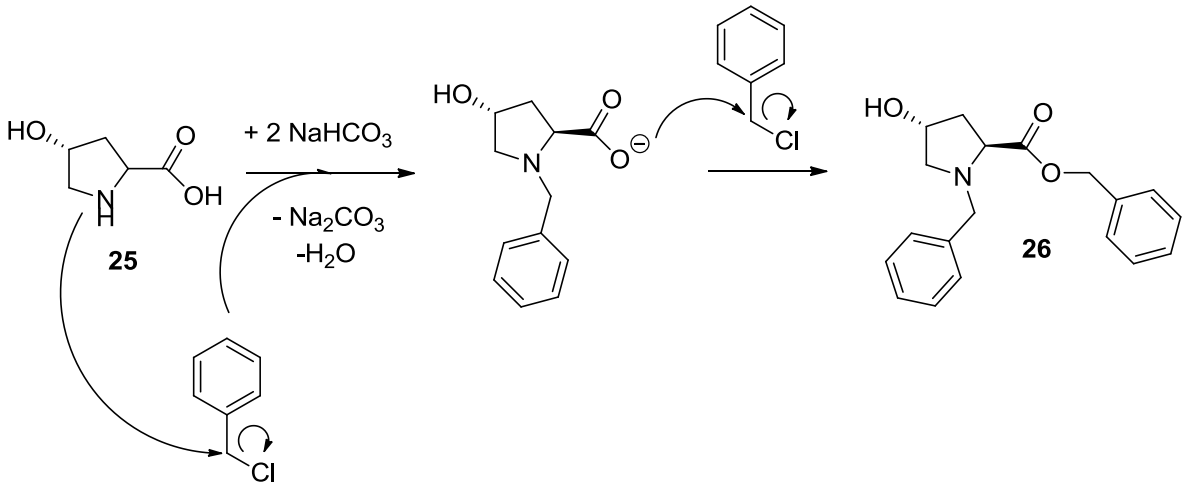
Although the step was reported in literature[193] and great efforts were done to manage it, the etherification of prolinol did not work satisfactoring. No halide product could be separated after reaction times of up to 7 days. As a consequence, synthetic strategy 1 was cancelled and attention was turned to the alternative strategy 2, starting from *trans*-4-hydroxyproline **25,** depicted in Scheme 25.

[193] Zhou, L.; Wang, L. *Chemistry Lett*. **2007**, *36*, 628. Chen, Z.; Xie, H.; Hu, C-G.; Dong, X.; Li, Y. *Russian Journal of Organic Chemistry*, **2008**, *44*, 1807. Miao, W.; Tak Hang, C. *Adv. Synth. Catal*. **2006**, *348*, 1711.



Scheme 25: Synthetic strategy 2 for iron containing CIL catalysts

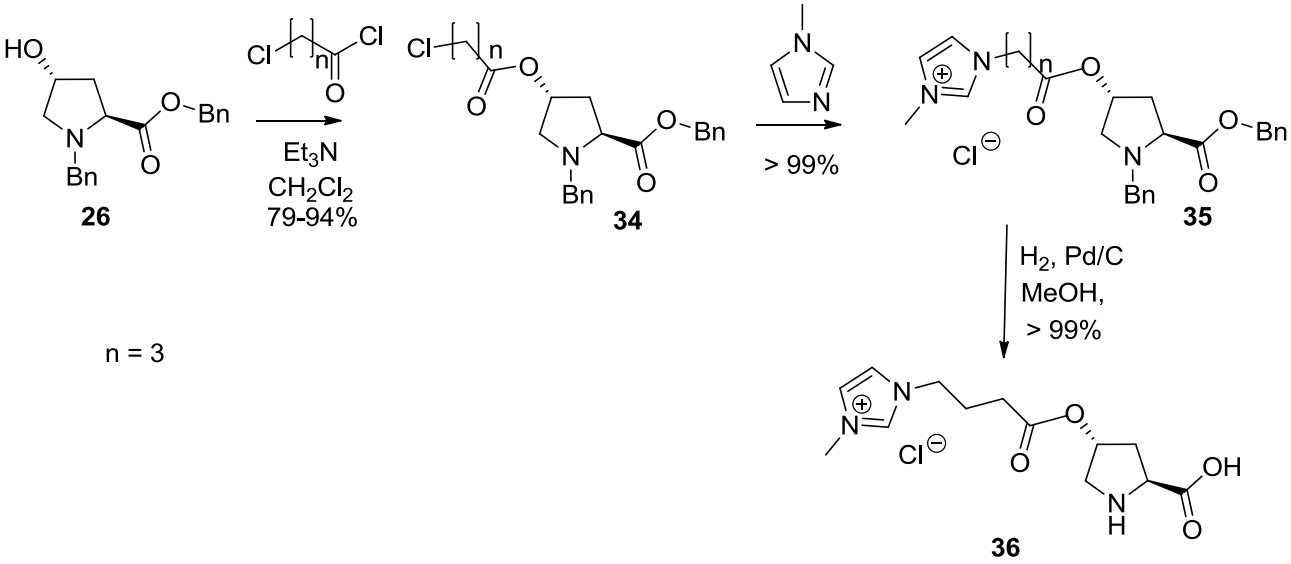
Due to simplicity, benzyl protecting groups were introduced for both the amino and the carboxylic group (Scheme 26). This gave another advantage for the deprotection step at the end of the synthetic pathway. Deprotection takes place after the quaternisation with methyl imidazole to give an N-protected ionic liquid. Purification of the target IL is challenging and often only possible by extraction or evaporation of the impurities under vacuum. So the substances resulting in deprotection must either be volatile or possess other solubility properties than the IL. Hydrogenolysis of a benzyl protecting group in general is running neatly and only resulting in toluene, which is easily removed under high vacuum. The reaction was performed in *N,N*-dimethylformamide at 100 °C with $NaHCO_3$ as base and gave the protected hydroxyproline **26** in excellent yield.



Scheme 26: Introduction of a benzyl protecting group

Ester **27** was formed by converting the secondary alcohol with 2-chloro acetyl chloride in the presence of NEt_3 as base in dry DCM at rt. The desired ester was obtained in good overall yield and high purity after a reaction time of 18 h. After subsequent chromatographic purification, quaternisation of the resulting chloride with N-methyl imidazole took place at 80 °C, yielding the desired ionic liquid **28** in only 5 h reaction time, which was quite fast in comparison to other quaternisation reactions. The fast quaternisation led to the presumption that the close proximity of the ester functionality accelerated the formation of the imidazolium salt. Subsequent catalytic hydrogenation of the ionic liquid **28** at 5 bar pressure in methanol took place to cleave the protecting groups and to give ionic liquid **29**. Hydrogenation proved to be challenging again, as the unprotected ionic liquid turned out to be rather unstable in methanolic solution. Only high pressures in combination with reaction times of about 30 to 40 min were successful. Lower H_2 pressure and as a consequence reaction times over 2 h in methanol or even solvent removal at temperatures over 40 °C inevitably led to decomposition of the ester functionality. The NMR spectra shown in Figure 21 clearly demonstrate decomposition of the ionic liquid within a few days. The decreasing ^{1}H-NMR signals at 5.55 ppm and the increasing signal at 4.55 ppm indicate cleavage of ester bond. To overcome the unfavourable cleavage of the ester bond of the catalyst, supposably caused by the close proximity of the imidazolium and to obtain a more stable catalyst, approach 2 was slightly adapted and two more carbon atoms were introduced between the ester and the imidazolium functionality

(**Scheme 27**). This strategy was successful. While ester bond of IL **29** was sensitive to hydrolysis and decomposed easily, ester bond of CIL **36** proved to be stable, demonstrated in another NMR experiment shown in Figure 22.



Scheme 27: Synthetic strategy 3

Finally a five step synthesis and an anion exchange from chloride to tetrachloro metalatewith $FeCl_3$ and $CuCl_2$ gave the desired metal containing catalysts **30a, 30b**[194] and **37** - shown in Figure 20 - in good overall yield.

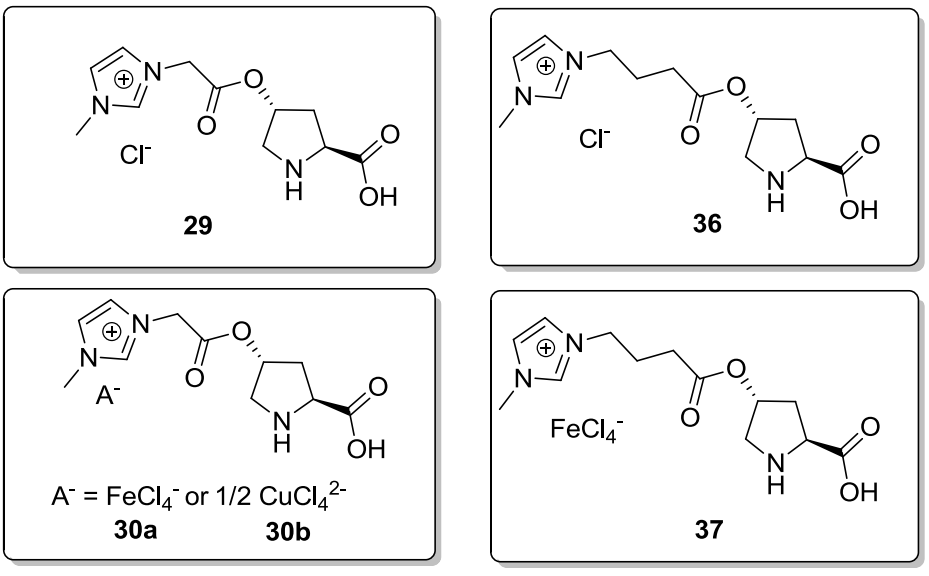


Figure 20: Chiral ionic liquids with a secondary amine functionality

[194] Winter, A.; Zabel, A.; Strauch, P. *Int. J. Mol. Sci.* **2012**, *13,* 1612; Thiel, K.; Klamroth, T.; Strauch, P.; Taubert, A. *Phys. Chem. Chem. Phys.*, 2011, **13**, 13537.

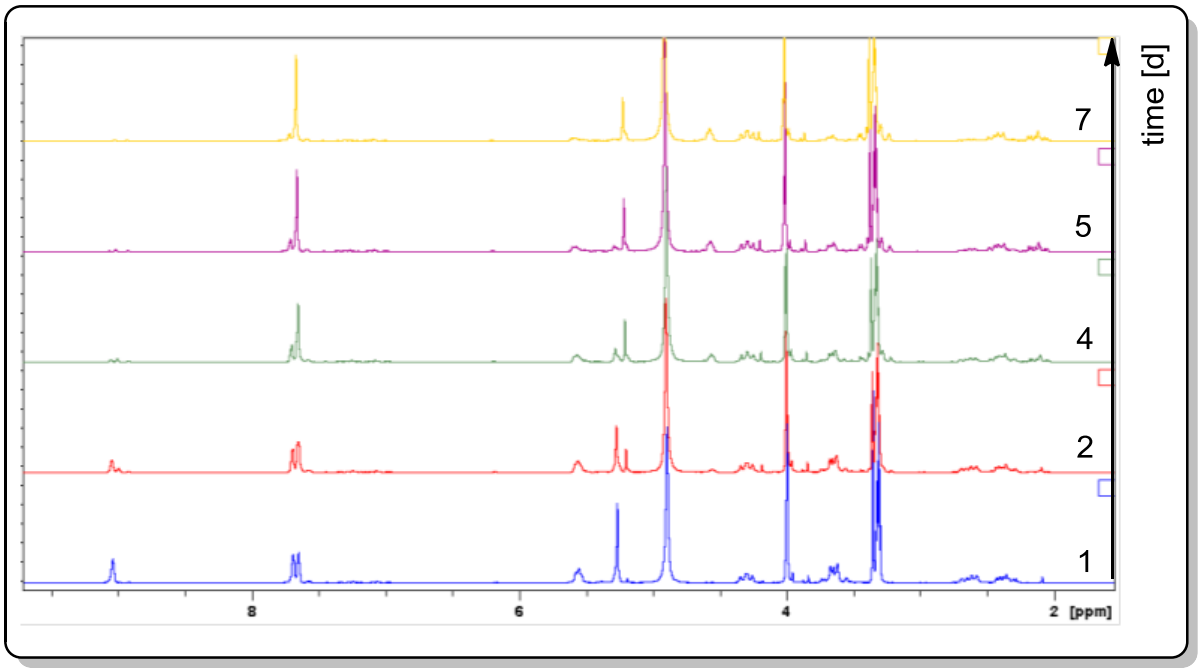


Figure 21: NMR spectrum of **29**. The decreasing ^{1}H-NMR signals at 5.55 ppm and the increasing signal at 4.55 ppm indicate decomposition of the ester bond. The spectrum at the bottom shows signals of intact ester bond, the spectrum on the top shows 80% decomposition of ester bond within one week.

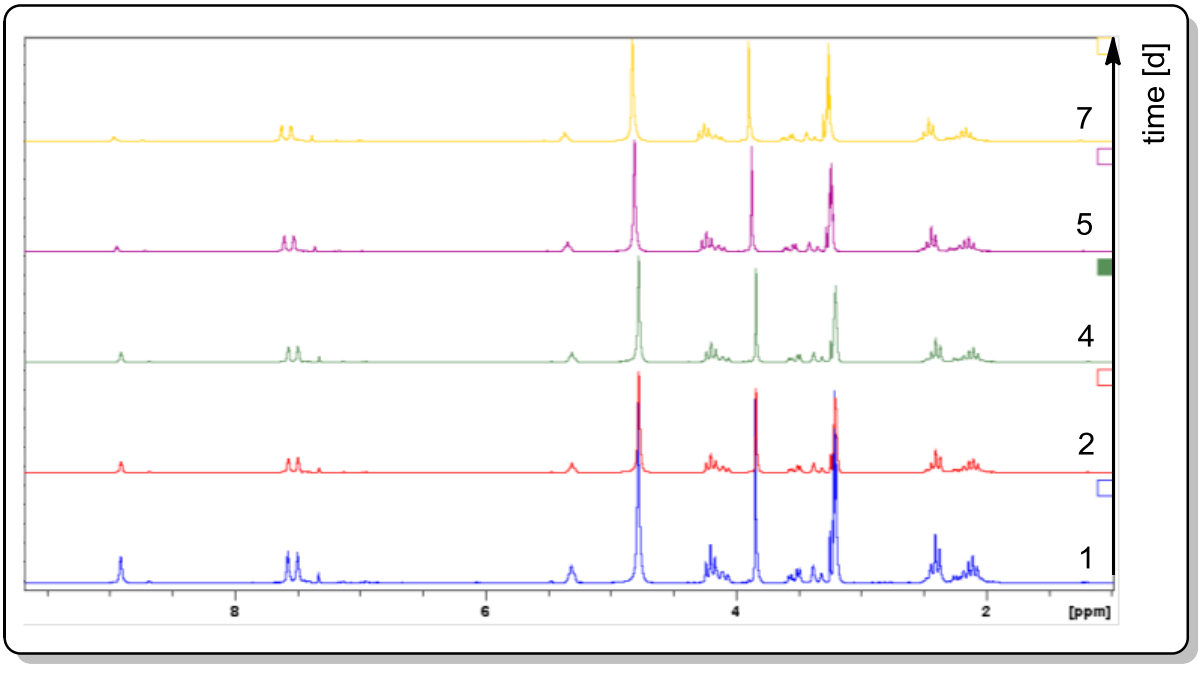
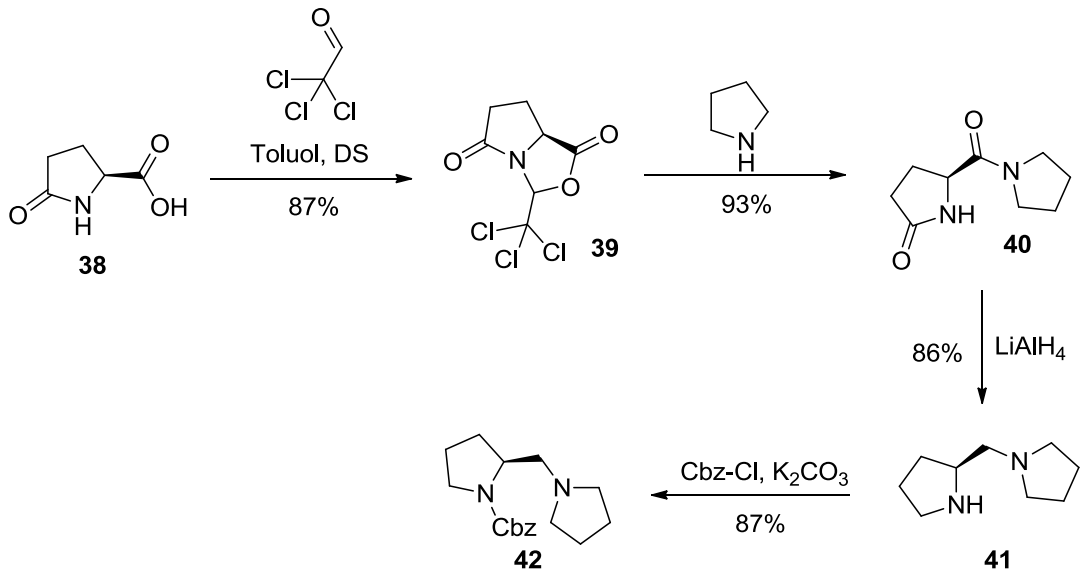


Figure 22: NMR spectrum of CIL **36.** No decomposition of ester bond within one week can be observed

While iron containing CILs **30a, 30b** and **37** were applied as catalysts in asymmetric transition metal catalysed hydroxymethylation, the corresponding halide CILs **29** and **36** were used in asymmetric α-alkylation.

3.1.2.2.2 Organocatalytic CILs derived from *L*-proline

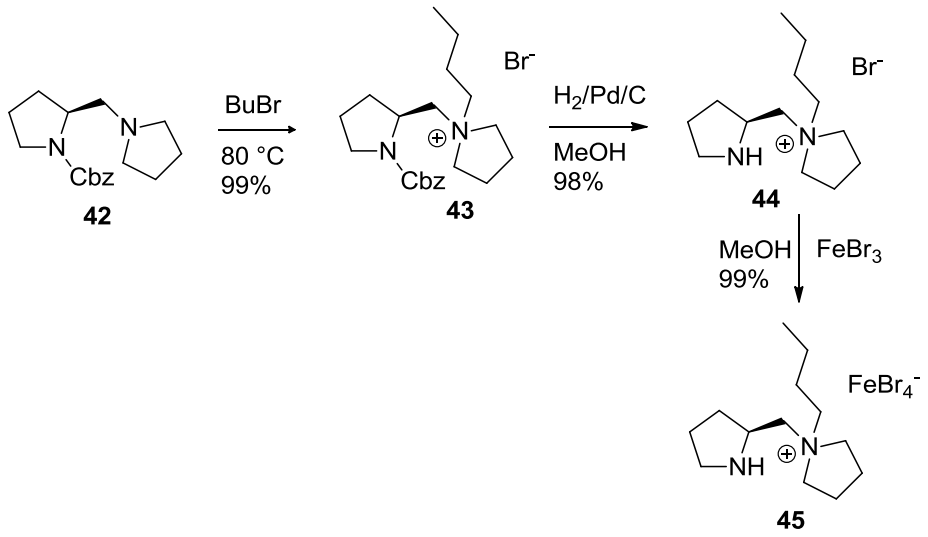
According to a procedure developed by Maria Vasiloiu in her diploma thesis, another iron containing CIL was synthesised starting from chiral pool derived *L*-proline **22**.[195] A straight forward synthetic strategy was followed (Scheme 28). The quaternisation step was slightly adapted to get a halide as anion necessary for anion metathesis to the desired iron containing CIL shown in Scheme 29. As quaternisation with *n*-butyl chloride did not work, n-butyl bromide was used. Reaction with a 1.5 fold excess of butyl bromide at 80 °C yielded the ionic liquid **43** in quantitative yield after 3 days. Subsequent catalytic hydrogenation in MeOH at a pressure of 5.5 bar to cleave the Cbz protecting group followed by anion metathesis wit $FeBr_3$ gave the desired iron containing CIL **45** in excellent overall yield.



Scheme 28: Synthesis of CIL according to M. Vasiloiu[196]

Beside an application of iron containing CIL in hydroxymethylation, several organocatalytic type CILs **29**, **36** and **44** were tested in combination with a Pd^0 catalyst in asymmetric α-alkylation to examine their ability for stereochemical induction in another C-C bond forming reaction.

[195] Vasiloiu, M. *Diploma Thesis*, Vienna Technical University of Technology, **2009.**
[196] Article in press: Vasiloiu, M.; Rainer, D.; Gaertner, P.; Reichel, Ch.; Schröder, Ch.; Bica, K. *Catal. Today*. **2012**

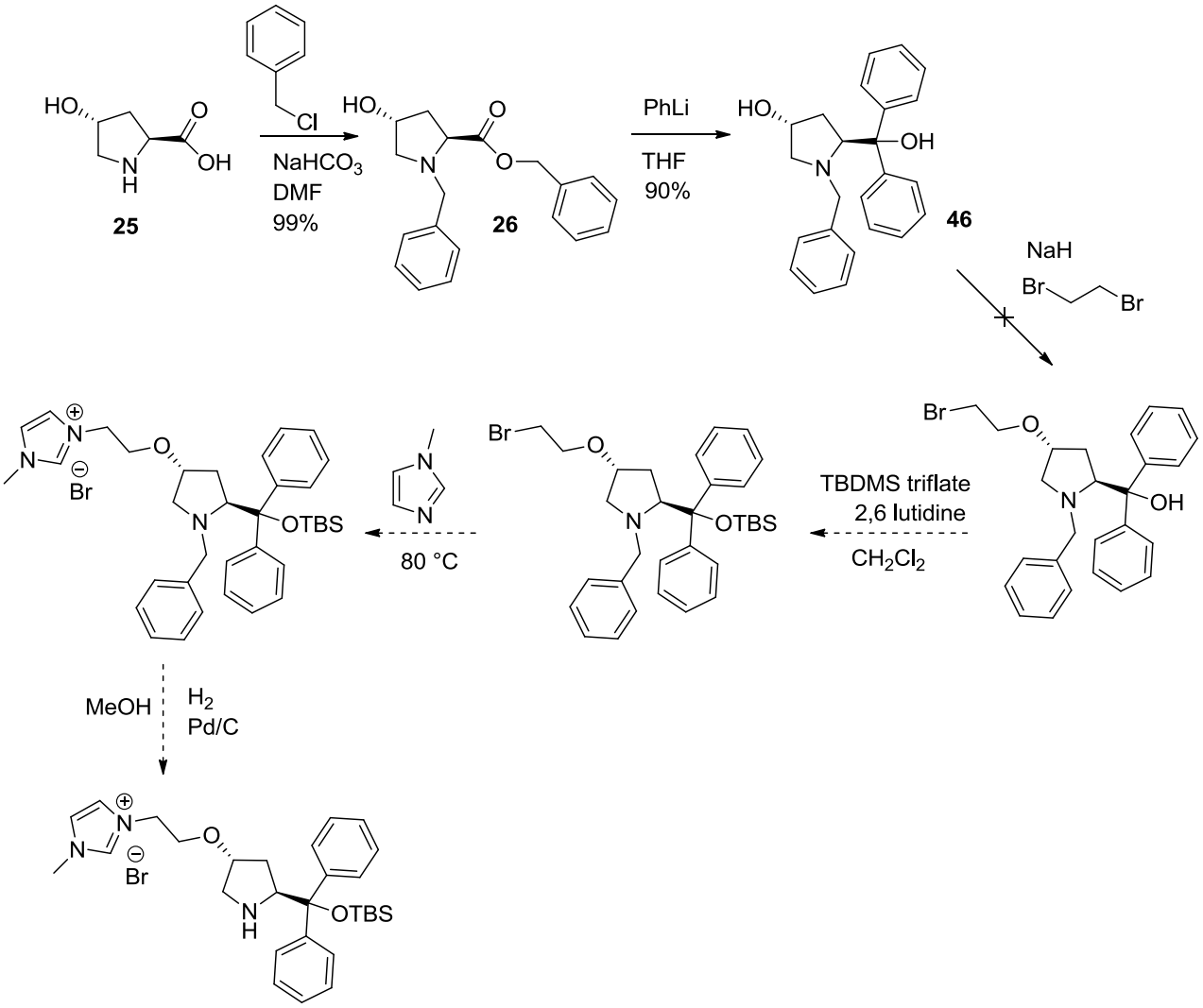


Scheme 29: Adapted quaternisation step and anion metathesis

3.1.2.2.3 Chiral ionic liquids with an aryl prolinol unit

Another approach for synthesis of chiral ionic liquids for organocatalysis starting from chiral pool derived hydroxyproline **25** was developed. In contrast to the synthesised systems **29** and **36** described in the previous chapter, an ether bond was introduced instead of the ester because it is known to be more stable.

Additionally to the ether bond sterically demanding groups should be introduced to the proline part of the molecule to improve stereochemical induction during organocatalysis. So eventually a new target molecule was designed. The synthetic strategy was modified as follows and is shown in Scheme 30.



Scheme 30: Synthetic approach for novel CIL organocatalysts

The first step was to introduce protecting groups and covers two purposes: protecting the amino group and activating the carboxylic acid. The protection group on the amine should remain in place until the last step so it also should not interfere with any of the following reactions, rendering a carboxybenzyl (Cbz) group useless. Another advantage of the benzyl protecting group is, as already mentioned in chapter 3.1.2.2.1, that hydrogenolysis of a benzyl protecting group in general is running neatly and only resulting in toluene which is easily removed under high vacuum.

The reaction was performed in *N,N*-dimethylformamide at 100 °C with $NaHCO_3$ as base. The use of stronger base such as sodium hydride would have led to protection

of the alcohol functionality as well, which should be avoided. The reaction proceeded smoothly within a few hours with satisfying yields of **26**. Purification was performed either by column chromatography or by simple evaporation of the excess benzyl chloride under high vacuum.

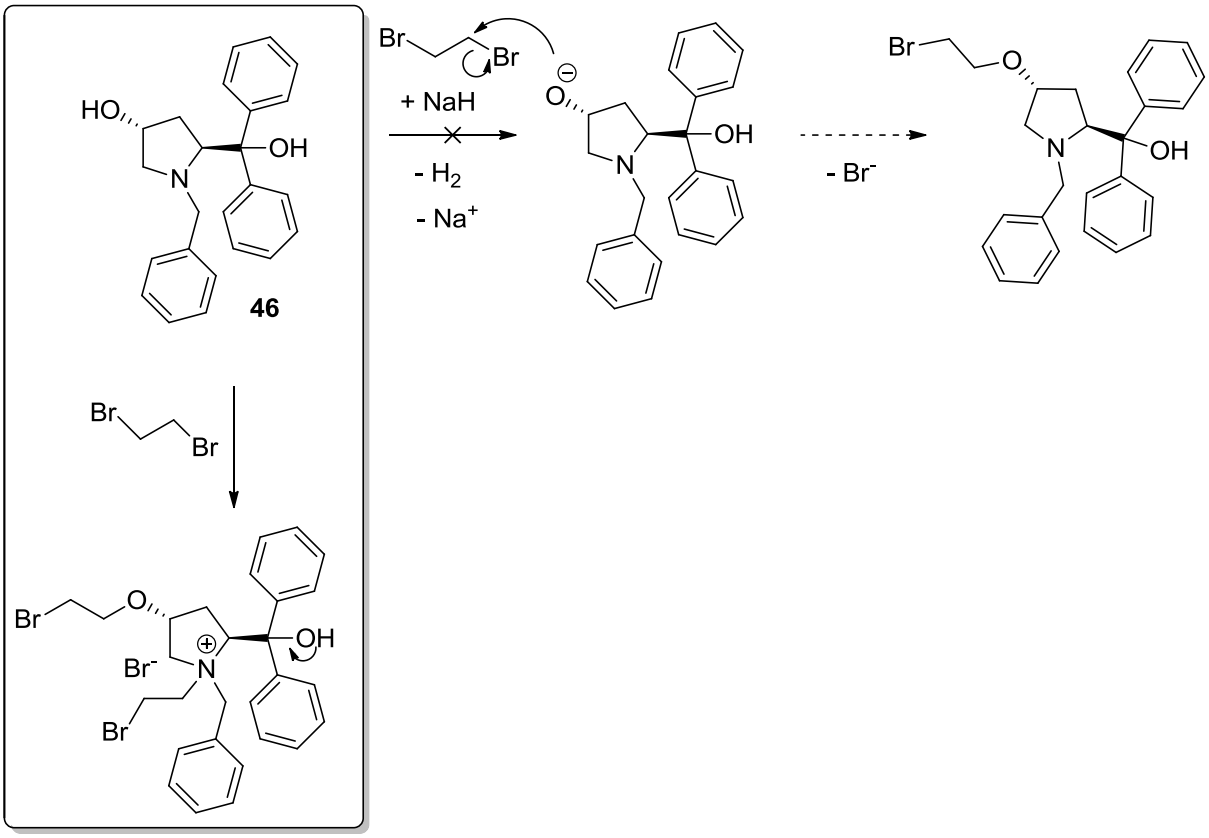
In the next step sterically demanding phenyl moieties were introduced to improve stereochemical induction. This easily can be achieved by treatment with organometallic compounds such as phenyl Grignard reagent or phenyllithium.[197] For this work a solution of phenyllithium in dibutyl ether was chosen.

The reaction was carried out in dry THF under argon. Addition of the phenyllithium solution was performed at -70 °C to -80 °C. Then the reaction was allowed to warm up to room temperature resulting in full conversion after one hour. Purification was carried out either by column chromatography or by recrystallization from ethyl acetate and *n*-hexane, yielding **46** as pale yellow solid.

The crucial step in this synthesis was the insertion of the ether bond to get the bromide. Again, the halide of choice was 1,2-dibromoethane because of its appropriate chain length and mediocre reactivity. While 1,2-dichloroethane was considered to be too unreactive, especially in the following quaternisation step, 1,2-diiodoethane should be too reactive, resulting not in etherification but in alkylation of the protected tertiary N. The reaction depicted in Scheme 31 was first carried out in a 10:1 mixture of THF and DMF at -15 °C with one equivalent of NaH and dibromo ethane, respectively. The concentration of the reactant was adjusted to be 0.02 mol/L. However, TLC showed no conversion. Another experiment with the same parameters in pure DMF led to no conversion either. Addition of one equivalent of tetrabutylammonium iodide did not change the outcome - the reaction failed under the chosen conditions and no product could be isolated. Upon further investigation, TLC-MS analysis revealed the presence of benzophenone in the crude mixture, leading to the presumption of another reaction mechanism. A quaternisation step of the amine and the alkyl bromide followed by either an

[197] See for example: Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.

intermolecular mechanism instead of etherification or an intramolecular, since the hydroxyproline and the bromoethane chain form a six-membered ring. The alcohol and the quaternary amine undergo Hofmann elimination, yielding benzophenone (Scheme 31).



Scheme 31: Possible side reaction of etherification with dibromo ethane

Considering this reaction a dead end, a new strategy was developed.

First, an introduction of a protecting group on the tertiary alcohol should prevent elimination of benzophenone. In addition to the stabilizing effect, the protecting group on the alcohol should greatly improve catalytic turnover.[190] It is reported that unprotected diarylprolinol derivatives used for enamine or imine type activations can form undesired and unreactive oxazolidine by-products (Figure 23). [198]

[198] Franck, X.; Figadere, B.; Cave, A. *Tetrahedron Lett.***1995,** *36*, 711.

Second, the introduction of the spacer was adapted according to Bolm´s procedure[199] and the next approach included following steps demonstrated in Scheme 32. Starting with diarylprolinol **46,** an allyl ether functionality should be introduced *via* Williamson ether synthesis. The classical Williamson protocol with NaH as base and a 10 fold excess of allyl bromide in DMF gave the desired allyl ether **47** in excellent yield.

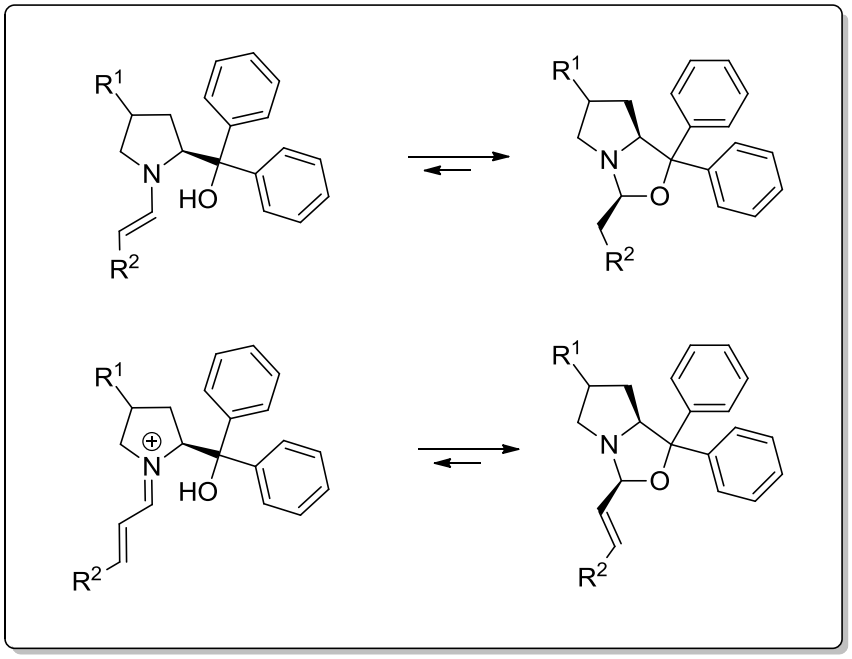
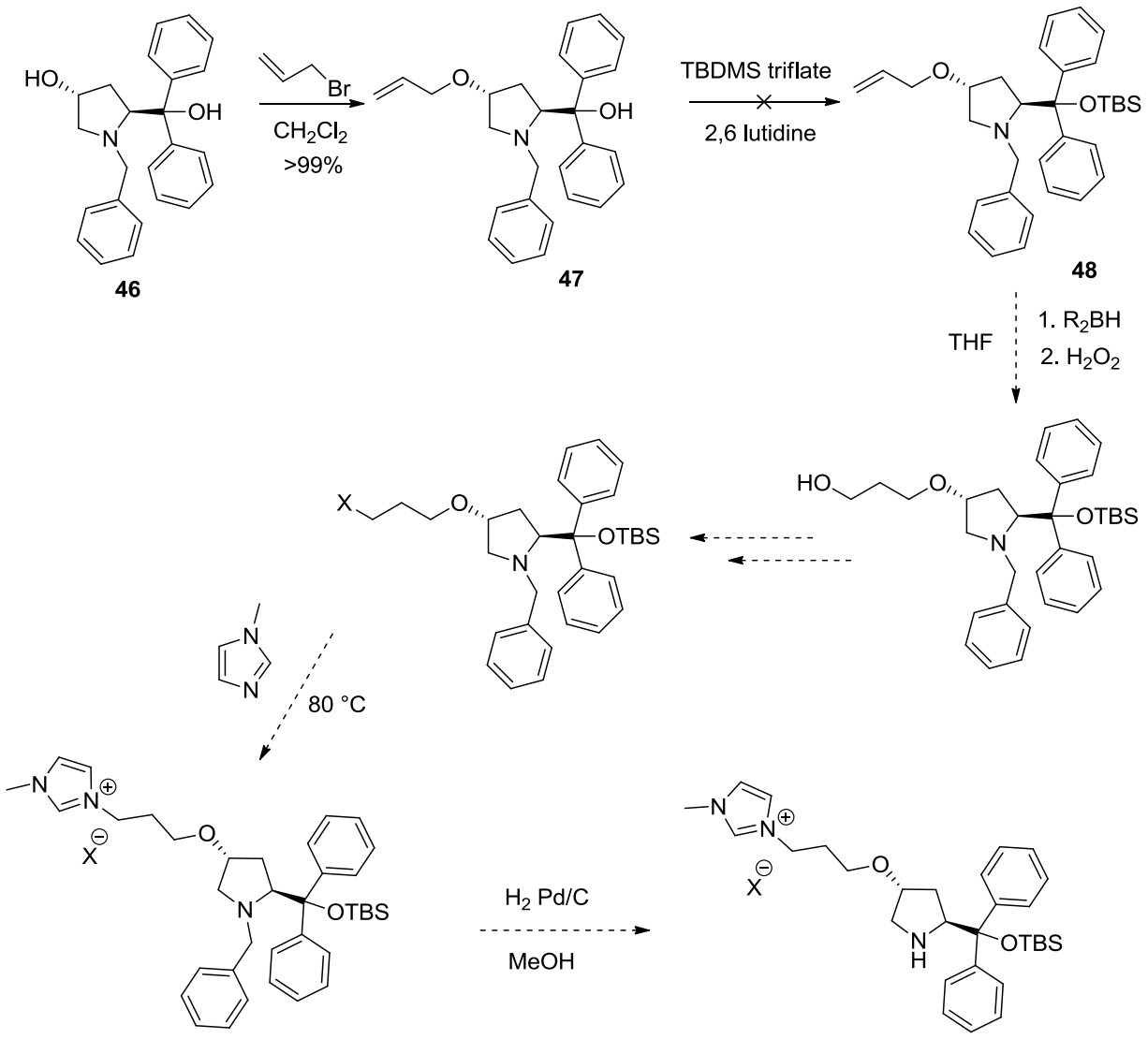


Figure 23: Hindering side reactions of unprotected diarylprolinols according to Franck

The double bond should then be converted into a primary alcohol in an anti-Markovnikov-addition *via* hydroboration-oxidation. Subsequently the terminal OH group is to be substituted with a leaving group, preferably bromine or trifluoromethanesulphonate (OTf), followed by quaternisation of methyl imidazole to give an ionic liquid. As an alternative route the hydroboration – bromination reaction was investigated as well.

[199] Bolm, C.; Tanyeli, C.; Grenz, A.; Dinter, C. L. *Adv. Synth. Catal.* **2002**, *344*, 649.



Scheme 32: New synthetic strategy *via* allyl ether; X = Br, pTOS, OTf

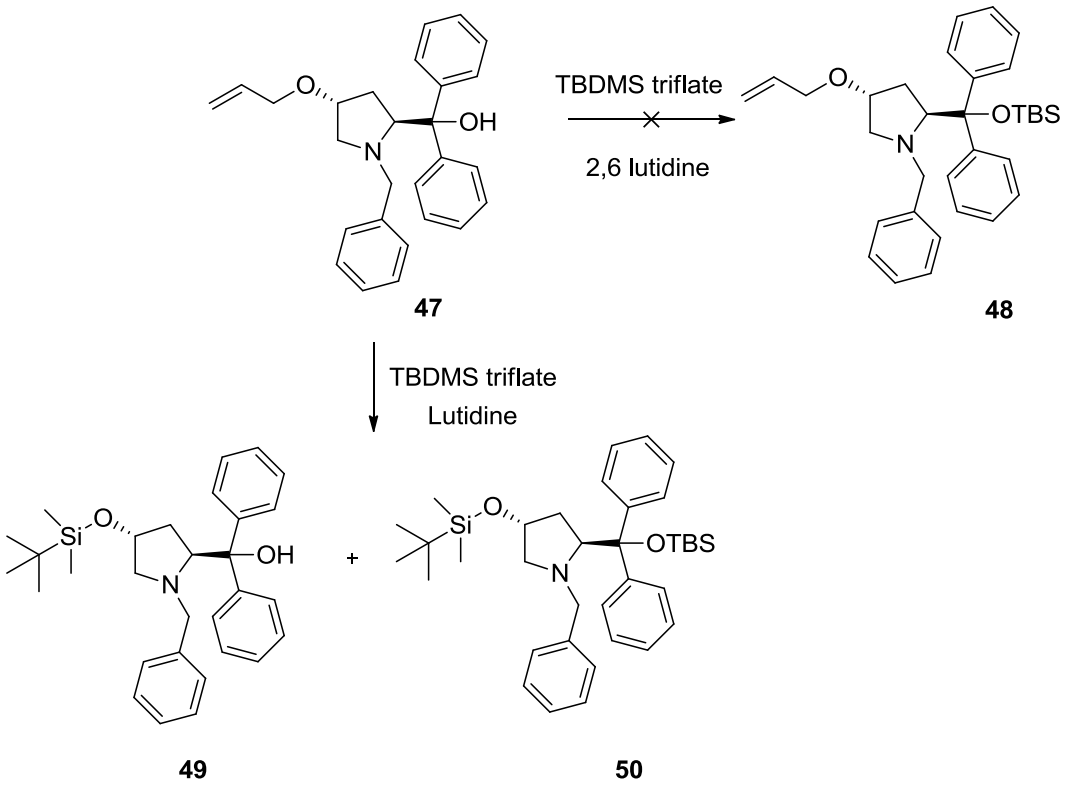
Subsequently after step one of the new strategy shown in Scheme 32, the introduction of the allyl ether functionality, a protecting group on the tertiary alcohol should be inserted to give **48**. A silyl ether system was planned as ideal match for our needs. Examples of silyl protected diarylprolinols as organocatalysts are literature known[200] and silyl ethers are quite stable in most environments and can be introduced under mild conditions.

Among the various possibilities to protect alcohols, for our purpose a stable and non-reactive moiety was required. The number and variety of the following steps as well

[200] Jensen, K.L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jorgensen, K.A. *Acc. Chem. Res.* **2012,** *45*, 248.

as the desired use of the target molecule as organocatalyst rule out esters or acetales. The protecting group should not only sustain all following synthetic steps but also remain in place and survive several catalytic cycles. As a compromise the *tert*-butyldimethylsilyl group (TBDMS or TBS) was chosen, being small enough to provide satisfying yields at appropriate reaction conditions on the strongly hindered tertiary alcohol. Even smaller groups like trimethylsilyl would be too unstable for our requirements, suffering hydrolysis in protic solvents. Larger moieties on the silicon render the introduction of the protecting group at the tertiary alcohol functionality problematic.

For the introduction of the silyl ether group on compound **47**, TBDMS triflate was used as reagent in presence of 2,6 lutidine in dry DCM. Unexpectedly the ether bond was cleaved under the reaction conditions and instead of protection of the desired tertiary alcohol to obtain **48**, formation of a silylether of the released secondary alcohol took place to give a mixture of **49** and **50** (Scheme 33).

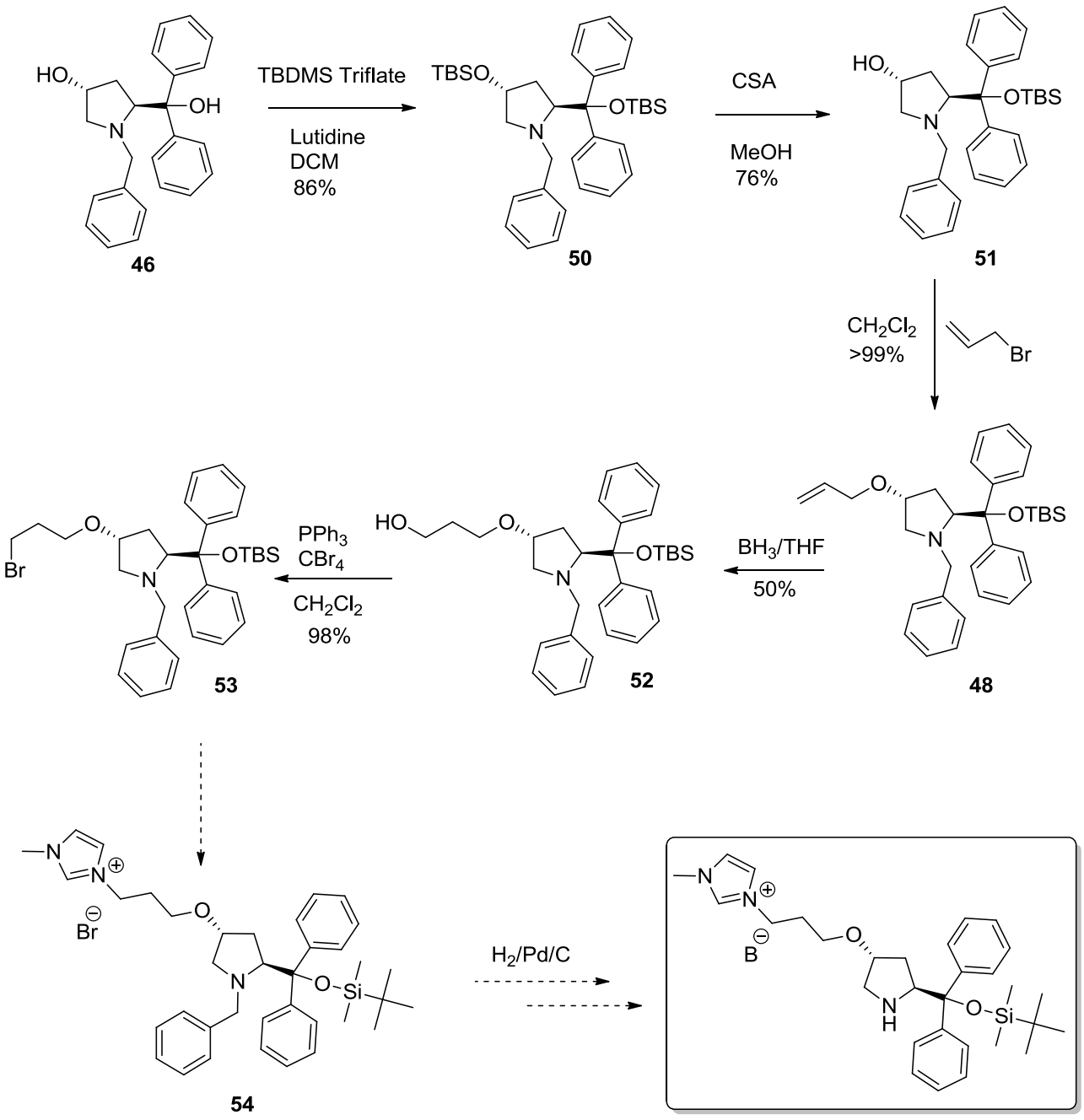


Scheme 33: Unwanted side reaction with ether cleavage

The answer was found in literature: Franck *et al.* reported the conversion of *tert*-alkyl ethers to silyl ethers with TBDMSOTf in the presence of base.[198] As the target OH group is a strongly hindered tertiary group, while the allyl ether is more accessible, we observed that ether cleavage is preferred to OH protection. A complex mixture of side products **49** and **50**, starting material and a small amount of product was isolated. Although a few mg of the desired product **48** could be separated *via* column chromatography, the synthetic protocol was adapted again.

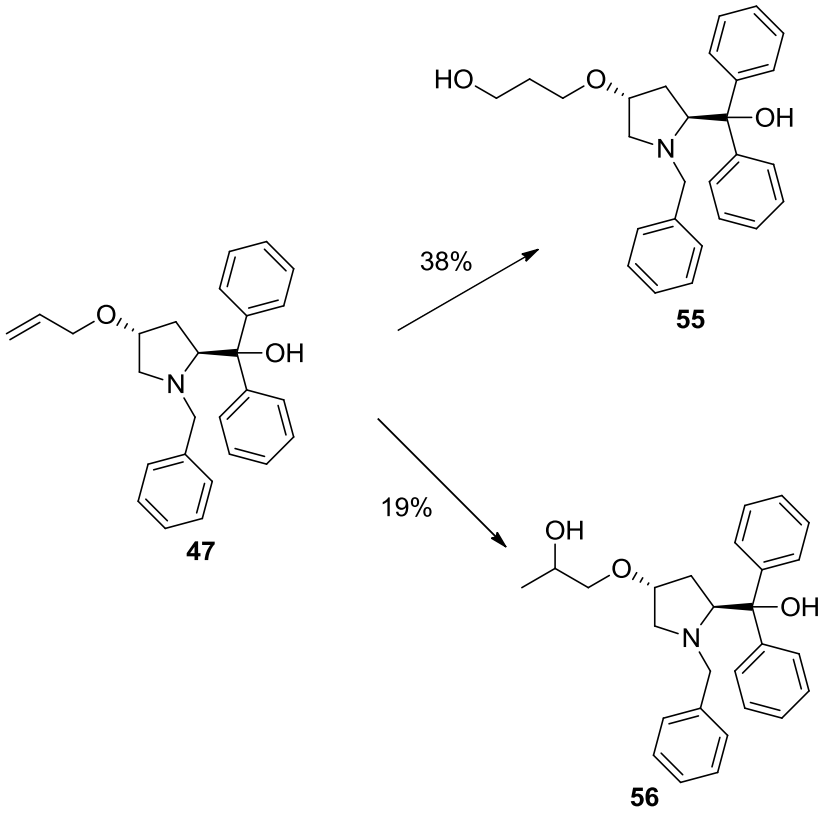
The silylation of the alcohol functionality was done now before etherification, directly after the introduction of the two aryl rings. Again TBDMS triflate was used as reagent in presence of 2,6 lutidine in dry DCM to protect both, the tertiary and the secondary alcohol functionality to yield **50**. Subsequently deprotection of the secondary alcohol with a 1.5 fold excess of camphor sulfonic acid CSA was performed giving **51**. Further etherification according to the Williamson protocol with NaH as base and a 10 fold excess of allyl bromide in DMF gave the silyl protected allyl ether **50**. Synthetic pathway is shown in Scheme 34.

In a first attempt again Bolm's procedure[199] for etherification was applied. The reactant was dissolved in dry DMF and treated with sodium hydride for 1.5 hours. Then allyl bromide was added followed by another 1.5 hours of stirring. Yet, it was found that the protecting group seemed to decrease reactivity. To ensure complete conversion more than 5 equivalents of NaH had to be used, although only one OH group had to be deprotonated and reaction time had to be increased in comparison to the etherification of unprotected alcohol **46** up to three days. The obtained allyl ether **48** was directly used in the next step without further purification.



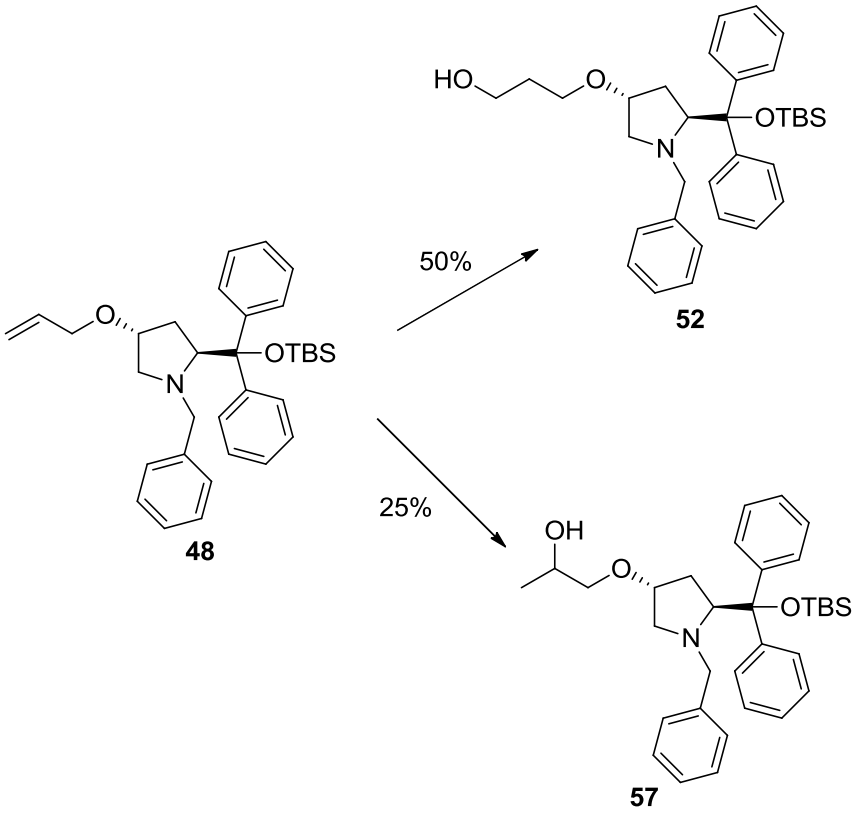
Scheme 34: Synthetic pathway *via* hydroboration

To introduce the OH functionality at the anti Markovnikov position of the allylic moiety, hydroboration was used as synthetic tool. Preliminary studies on hydroboration-oxidation were carried out using allylether **47** (Scheme 35). Treatment of obtained organoborane with alkaline hydrogen peroxide led to the corresponding alcohols in acceptable yields.



Scheme 35: Products of hydroboration oxidation of allyl ether **47**

Further investigations were carried out with protected allyl ether **48**. Although sterically demanding organoboranes are often less reactive than BH_3, according to literature[199] catecholborane was used as first approach. Unfortunately no conversion could be observed. Further investigations similar to the preliminary experiments with BH_3-THF complex or 9-BBN succeeded. While hydroboration with the latter gave 35% yield of the desired alcohol and none of the unwanted secondary alcohol after 5 days of reaction und subsequent oxidation with alkaline hydrogen peroxide, hydroboration with a 3 fold excess of BH_3-THF yielded the anti-Markovnikov alcohol **52** and the Markovnikov alcohol **57** in a 2:1 ratio in overall 75% yield in 24 h (Scheme 36).



Scheme 36: Hydroboration-oxidation products of allyl ether **48**

With the synthesis plan in mind, the direct way to convert the borane to the corresponding bromide was investigated.[201] Small-scale reactions of hydroboration–bromination were conducted. Workup with bromine and sodium methanolate as base should lead to the corresponding bromide. Sodium hydroxide must not be used, since bromine forms hypobromite in presence of NaOH, which oxidises the organoborane to the alcohol.[201] Eventually none of the experiments yielded any product according to NMR.

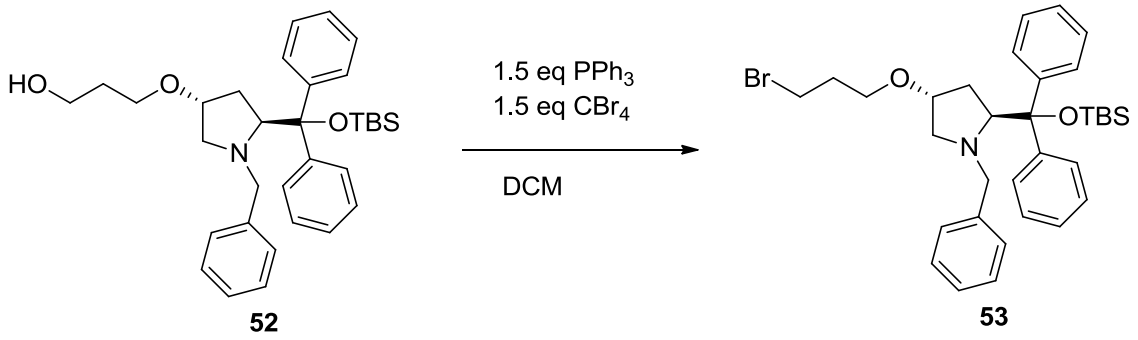
As a consequence, the already successful applied hydroboration-oxidation was repeated in a large scale, followed by the subsequent introduction of an appropriate leaving group. The leaving group to be introduced had to meet two requirements:

First, the reactivity should be rather high allowing a quick, quantitative conversion with methyl imidazole under mild conditions.

[201] Brown, H.C.; Lane, C.F. *Tetrahedron* **1988,** *44*, 2763.

Second, the resulting IL should either incorporate an appropriate anion or allow an anion exchange. Therefore the conversion of the alcohol to a triflate or a bromide was preferred, as triflates or halides can easily be exchanged by any other anion.

While first experiments to introduce a triflate gave not the anticipated products, the Appel reaction with a stoichiometric amount of CBr_4 and PPh_3 was successful. The driving force of the reaction is the formation of triphenyl phosphine oxide as an excellent leaving group. Reaction was carried out in dry DCM with a slight excess of CBr_4 and PPh_3 and proceded within two hours according to TLC. Standard workup and subsequent chromatographic purification gave the desired bromide **53** in up to 98% yield.



52 **53**

Scheme 37: Appel reaction of alcohol **52**

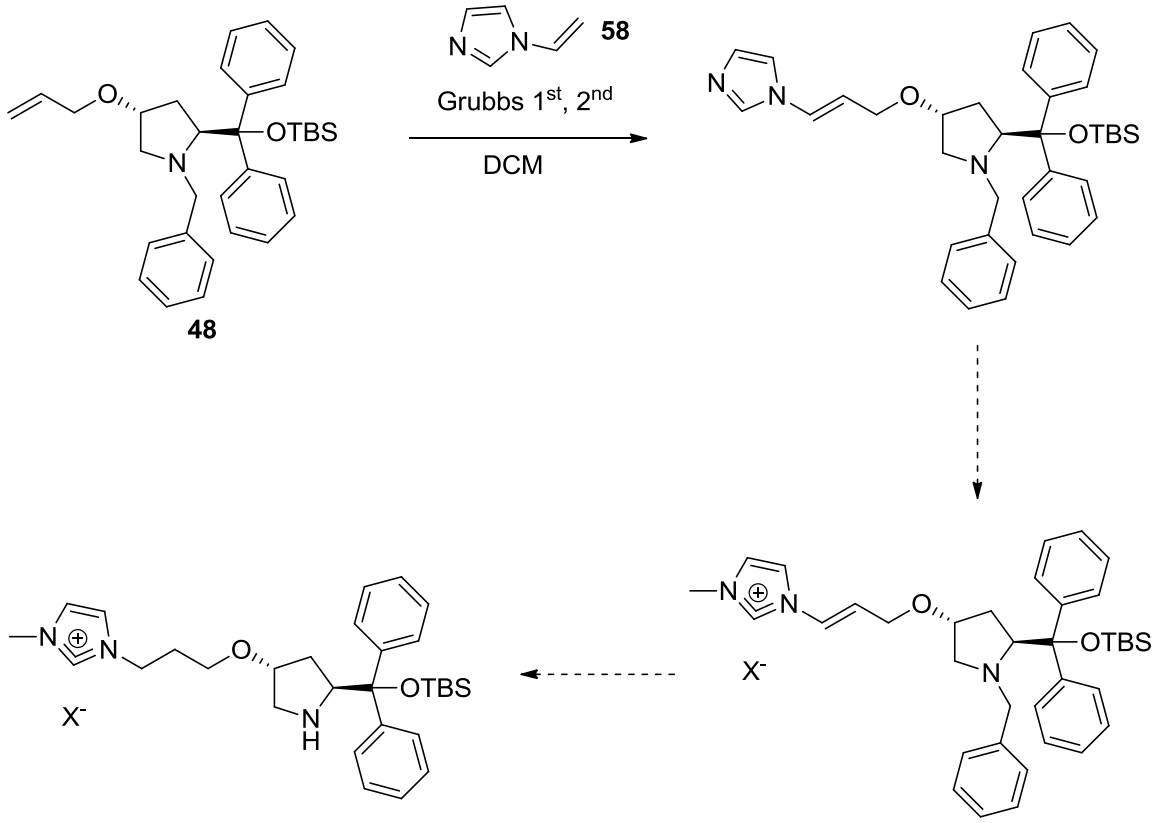
Alternative approach

An alternative synthetic approach to abbreviate the whole synthesis was developed. Starting from allyl ether **48** an olefin metathesis with vinyl imidazole was planned. Subsequent quaternisation of the imidazole should be done with dimethyl sulphate or methyl iodide, yielding an ionic liquid. Cleavage of the benzyl protecting group in a hydrogenation step should also reduce the olefinic double bond to finally end with the desired ionic liquid. Reaction strategy is depicted in Scheme 38.

Metathesis was done according to literature[202] in a flame dried Schlenk flask under argon. According to Grubbs´ general model for selectivity in olefin cross metathesis, a fourfold excess of vinyl imidazole **58** was used, to give a statistical distribution of

[202] Dash, J.; Mellilo, B.; Arseniyadis, St.; Cossy, J. *Tetrahedron Lett.* **2011**, *52*, 2246.

80% of cross metathesis product.[203] Reaction in presence of 5 mol% Grubbs 2nd generation catalyst under reflux was not successful and no product was obtained, but starting material could be recovered. As vinyl imidazole is reported to be able to coordinate to ruthenium, producing bisimidazole coordination complexes which do not catalyse ROMP,[204] it was presumed that in our reaction the N at the 3 position of the vinyl imidazole is coordinating to Ru interfering the catalytic activity of the catalyst. Therefore vinyl imidazole was converted with p-tolyl sulfonic acid into its salt prior the next experiment.

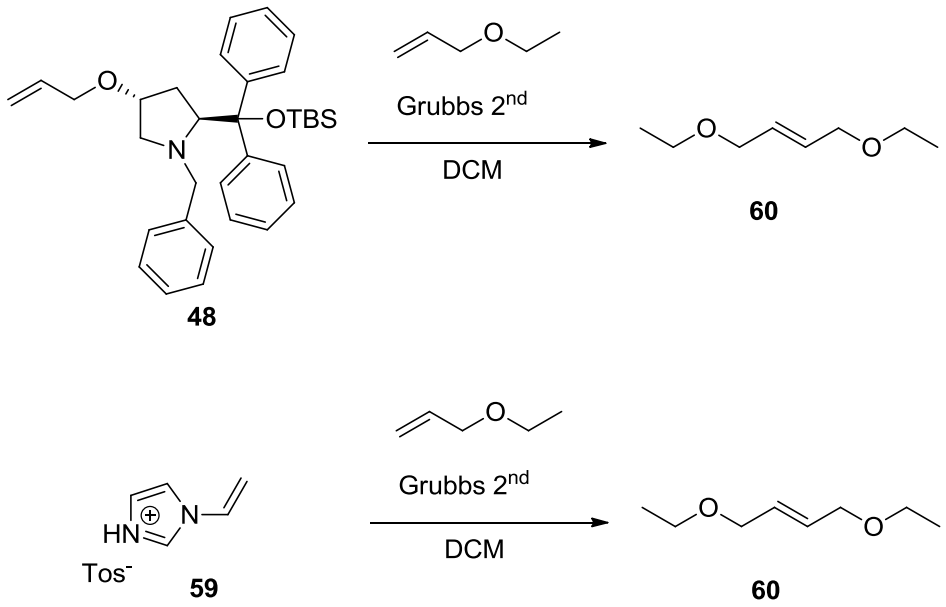


Scheme 38: Synthetic approach *via* olefin metathesis

Unfortunately a metathesis reaction between an excess of the vinyl imidazolium salt **59** and allyl ether **48** again showed no conversion to the desired cross metathesis product in the presence of Grubbs 1st and 2nd generation catalyst. On the contrary, a fivefold excess of allyl ethyl ether yielded quantitative amounts of the ethyl allylether

[203] Chatterjee, A.K.; Choi, T.L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc*. **2003**, *125*, 11360.
[204] Diver, S.T. *Coordination Chemistry Reviews*, **2007**, *251*, 671.

homo metathesis product **60** when converted in the presence of Grubbs catalysts with either vinyl imidazolium salt **59** or silylated allyl ether **48**. These results showed that both compounds **48** and **59** were no suitable substrates for olefin metathesis with either Grubbs 1st or 2nd generation catalysts.



Scheme 39: Olefin metathesis giving undesired homo metathesis product

Quaternisation with methyl imidazole

According to NMR spectroscopy, no quaternisation of bromide **53** with methyl imidazole under the following conditions was observed:

- equimolar amounts of bromide and methyl imidazole in benzene at 40 °C
- equimolar amounts of bromide and methyl imidazole neat at rt over a period of 48 h
- equimolar amounts of bromide and methyl imidazole neat at 60 °C over a period of 24 h

Equimolar amounts of bromide and methyl imidazole neat at 60 °C over a period of 48 h lead to a partial conversion, confirmed by ^{1}H NMR spectroscopy and TLC-MS. Signals of quaternised methyl imidazole at 8.38 and 10.46 ppm could be observed and one spot on TLC measured in the positive mode of MS with a mass of 596.5 was detected, which matches the methyl imidazolium cation of **54**. Although both results

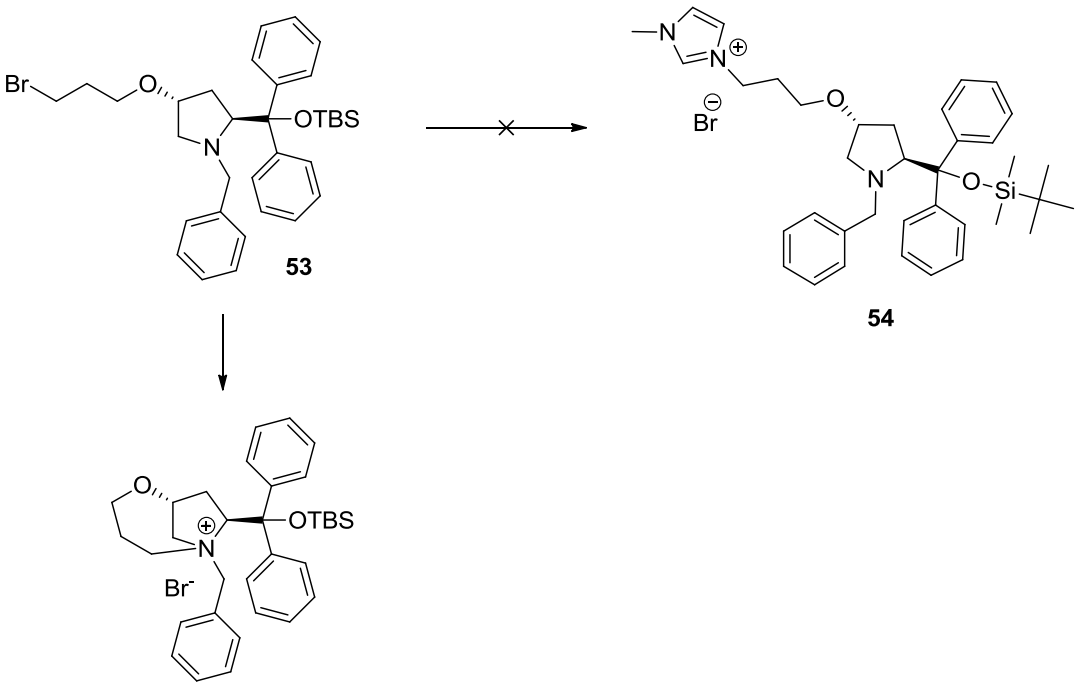
indicated formation of the desired ionic liquid, ^{1}H NMR clearly showed decomposition of the substance.

Bromide **53** inherently proved to be rather unstable. Even short time storage in $CDCl_3$ or solvent evaporation at 40 °C led to partial decomposition observed by shifted NMR signals and an additional spot on TLC with a lower rf-value. TLC/MS identified a mass of 594.2 of the second spot and the mass spectra showed the classical isotope ratio for one bromo atom present in the structure. Additionally mass spectra showed signals with higher masses, indicating oligomers.[205]

Similar results were obtained when bromide **53** was treated with methyl imidazole to alkylate the imidazole and end up with an ionic liquid.

These signs of decomposition together with the fact of only partial quaternisation indicated an unwanted side reaction during alkylation conditions. An intramolecular reaction between the bromide and the tertiary N of the proline ring is assumed. Bromides are known to be suitable substrates for alkylation of tertiary amines and formation of a seven membered ring would be energetically favoured. Such an intramolecular ring closure would explain the instability of the bromide **53** as well as the impossibility to quaternise methyl imidazole. Intermolecular alkylation between bromide and tertiary amines leading to oligomers are possible as well.

[205] ^{1}H NMR spectrum showed new signals at 4.88, 4.56, 3.50 and 2.44 ppm. A slight intensity decrease of signals at 2.15, 3.06 and 3.19 ppm was observed. ^{13}C NMR spectrum showed upfield shifts of the signals of the benzylic CH_2 carbon and the CH_2 carbon of the proline ring. The signal of the $BrCH_2$ group was shifted.



Scheme 40: Presumed intramolecular ring closure of bromide **53**

3.2 Application of ionic liquid catalysts in C-C bond forming reactions

3.2.1 Asymmetric Henry reaction

The asymmetric version of Henry reaction is catalysed with copper salts in combination with moderately basic ligands.[46, 51, 206] As especially β-amino alcohols are among the best catalysts allowing the Henry reaction in good yields and high enantiomeric excess,[53, 207] this reaction was a good example to apply our amino alcohol based chiral ionic liquids.

Due to simplicity the misleading notation "ligand" and "ionic liquid", will be used for catalyst labelling in this chapter. Of course, both ligands and ionic liquids function as ligands in Henry reaction and coordinate to the transition metal, the latter as charged ligands.

Some of our chiral ligands (**18**, **20**, **21**) containing a pyridinium moiety substituted in position 3 already proved to be successful as bidentate ligands in diethyl zinc alkylation of aromatic aldehydes, where *ee* values up to 99% could be obtained.[189] Representatives of these pyridinium-3 substituted ligands, derived from valine **18**, phenylalanine, **16** and ephedrine, **20** and another set of ligands with a pyridinium moiety substituted in position 2 and the corresponding chiral ionic liquids were examined concerning their application in enantioselective Henry reaction (Figure 17). The pyridinium nitrogen in a distance of three bond lengths instead of 4 is supposed to allow different coordination behavior to the transition metal.

In combination with Cu(II) these catalytic systems shown in Figure 24 and Figure 25 were screened on their performance in asymmetric Henry reaction as an example for a C-C bond forming reaction.

[206] Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org.Lett*. **2007**, *9*, 2151; Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2006**, *17*, 2046.
[207] Lai, G.; Wang, S.; Wang, Z. *Tetrahedron:Asymmetry*. **2008**, 19, 1813. Steurer, M.; Bolm, C. *J.Org.Chem*. **2010**, *75*, 3301.

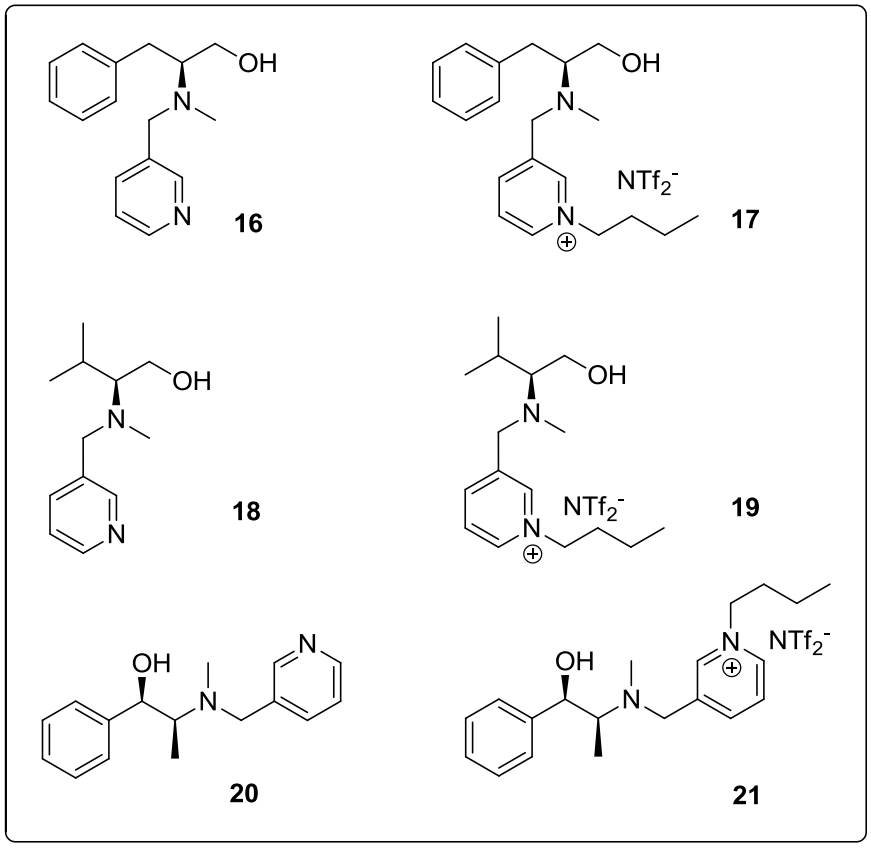


Figure 24: Ligands and coordinating ionic liquid catalysts derived from pyridin-3-carbaldehyde

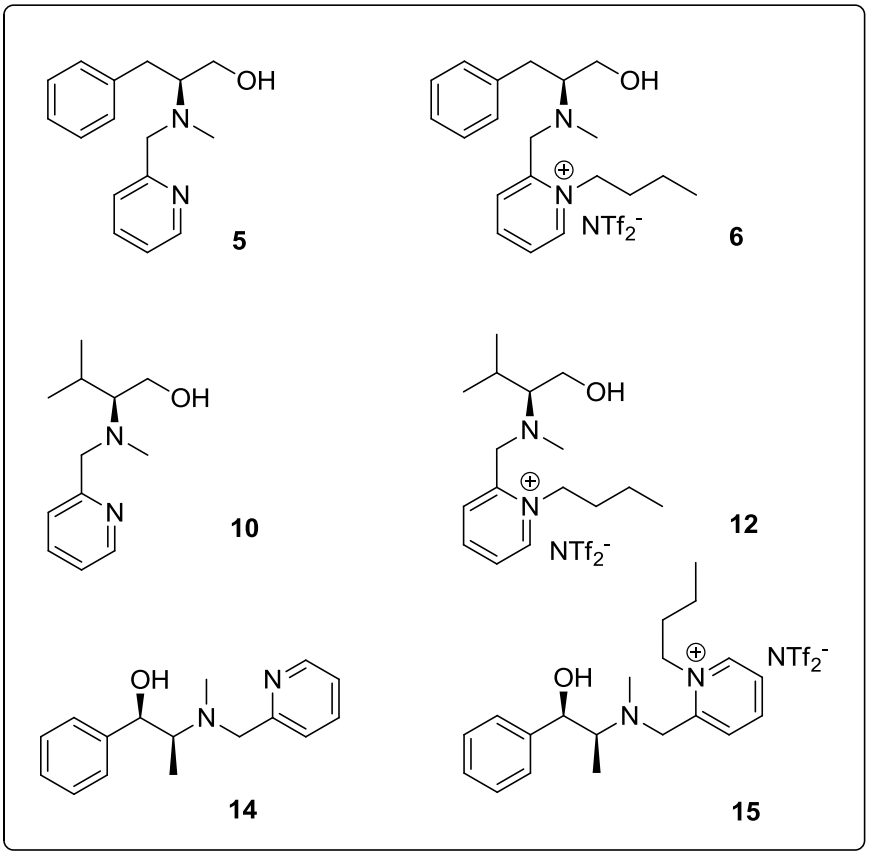
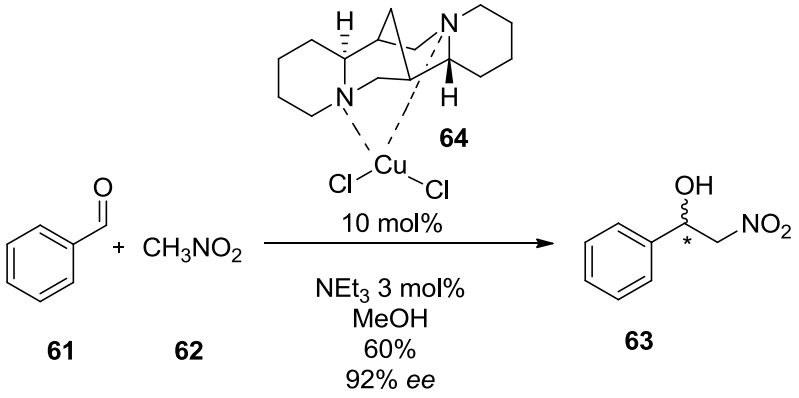


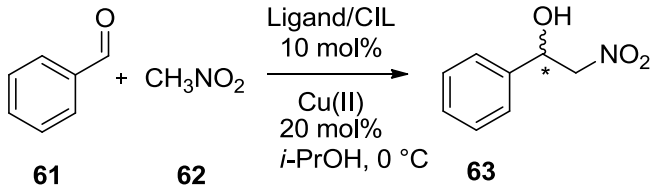
Figure 25: Ligands and coordinating ionic liquid catalysts derived from pyridin-2-carbaldehyde

At the beginning of our study a Cu(II) spartein complex **64** was synthesised according to a procedure published by Maheswaran.[63] Henry reaction of benzaldehyde catalysed with this Cu(II) complex led to the desired product in 60% yield and an enantioselectivity of more than 90% *ee* which is according to literature (Scheme 41).



Scheme 41: Asymmetric Henry reaction of benzaldehyde **61** catalysed with dichloro [(-)-spartein-N,N']Cu(II) **64** according to Maheswaran

In Scheme 42 the model reaction for the preliminary Henry screening also using benzaldehyde **61** as substrate is presented. This model reaction was used to establish suitable reaction conditions for Henry reaction catalysed with our set of ligands and ionic liquids.

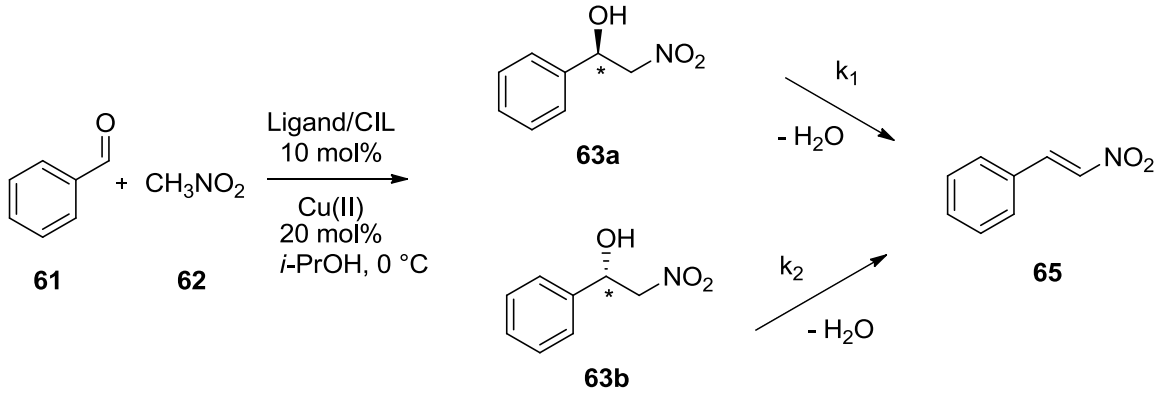


Scheme 42: Asymmetric Henry reaction of benzaldehyde **61**

To secure for reproducibility, stock solutions of chiral catalysts and copper salt ensuring a constant ratio between chiral catalyst and copper source were used. To prepare stock solutions, chiral catalyst and Cu-salts were dried in high vacuum for 12 hours and the amount for 10 experiments 10 portions was weighted into a volumetric flask. The appropriate quantity of nitro methane was added and the flask was filled up to the mark with an appropriate solvent.

Optimisation of reaction conditions started with a screening of solvents and different reaction temperatures. In these preliminary studies 10 mol% of phenylalanine derived tridentate ligand **16** and several Cu(II) salts or solvents were used and *i*-PrOH proved to be the superior solvent compared to MeOH, EtOH and THF (Table 8). First screenings at room temperature clearly showed the superiority of alcohols concerning yield. Independently from the used Cu(II) salt all reactions carried out in EtOH, MeOH or *i*-PrOH showed better conversion than reactions in THF (Table 8, entry 1-9 or entry 13). Taking a glance at *ee* values of these first reactions, *i*-PrOH showed better performance than sterically less demanding MeOH or EtOH, especially in combination with $Cu(OAc)_2$ as source of copper. These results could be confirmed in reactions using CIL **15** as a representative ionic liquid catalyst for chiral induction (Table 8, entry 13-15). Unfortunately the obtained enantioselectivities of our preliminary screenings were lower than those reported in many publications for other ligands (Table 3).

As preliminary results showed small amounts of ω–nitro styrene **65** as byproduct formed during the reaction, we were interested whether the lower *ee* values are resulting from kinetic resolution effects of this side reaction. If one enantiomer of the formed hydroxy nitro compound **63** could eliminate and racemise faster under the reaction conditions, an excess of the less favoured enantiomer would be observed.



Scheme 43: Elimination of water forming nitro styrene as side product during Henry reaction

Kinetic resolution in general is known to be the achievement of partial or complete resolution by virtue of unequal rates k_1 and k_2 of reaction of the enantiomers in a racemate or enantiomeric enriched substrate with a chiral agent. In case of kinetic resolution of the known side reaction of Henry reaction a lower or higher enantioselectivity than originally induced by the chiral catalyst could be observed, depending on whether the reaction rate of the favoured or the disfavoured enantiomer is higher. The comparable low *ee* values obtained with our catalyst set necessitated the examination whether the reaction rate of both enantiomers of the desired Henry product to the elimination product was the same ($k_1 = k_2$) or a kind of kinetic resolution takes place ($k_1 < \text{or} > k_2$) under certain conditions. Several experiments with racemic 2-nitro-1-phenylethanol **63** were done. In the beginning racemic 2-nitro-1-phenylethanol was stirred with 10 mol% of **16** and 10 mol% of Cu(II) salt in EtOH. After 24 h, 96 h and 144 h, respectively, samples were taken and after standard workup *ee* values were measured again on chiral HPLC. They showed no significant difference in enantiomeric excess, indicating that no kinetic resolution took place when byproduct is formed. To ensure that also remaining nitro methane had no influence, additional experiments were done. Racemic product was stirred

under standard Henry conditions and every 24 h a small sample was taken and analysed after workup, giving *ee* values lower 2% after 24 h, 48 h, 72 h and 96 h and therefore confirming the upper results. According to these results kinetic resolution of product may be excluded under chosen conditions.

Table 8: Asymmetric Henry reaction of benzaldehyde **61**; variation of Cu(II) salts and solvents

entry	catalyst	Cu(II) salt	solvent	T [°C]	yield [%][a]	*ee* [%][b]
1	**16**	$Cu(OTf)_2$	EtOH	25	40	rac
2	**16**	$Cu(OAc)_2$	EtOH	25	36	15 (*R*)
3	**16**	$Cu(BF_4)_2$	EtOH	25	40	10 (*S*)
4	**16**	$CuCl_2$	EtOH	25	7	rac
5	**16**	$CuBr_2$	EtOH	25	16	rac
6	**16**	$Cu(OAc)_2$	THF	25	20	16 (*R*)
7	**16**	Cu(OAc)2	MeOH	25	55	6 (*R*)
8	**16**	$Cu(BF_4)$	MeOH	25	1	10
9	**16**	$Cu(OAc)_2$	*i*-PrOH	25	43	20 (*R*)
10	**16**	$Cu(OAc)_2$	*i*-PrOH	0	33	24 (*R*)
11	**16**	$CuCl_2$	*i*-PrOH	0	1	7 (*S*)
12	**16**	$CuBr_2$	*i*-PrOH	0	1	rac
13	**17**	$Cu(OAc)_2$	THF	25	3	20 (*S*)
14	**17**	$Cu(OAc)_2$	*i*-PrOH	25	50	32 (*S*)
15	**17**	$Cu(OAc)_2$	*i*-PrOH	0	26	49 (*S*)

All reactions were performed with 1 mmol benzaldehyde, 10 mmol nitro methane and 0.1 mmol catalyst for 72 hrs. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H or IA column. Absolute configuration determined by comparison with literature values.

The results shown in Table 8 give indications of a strong influence of reaction temperature. Therefore an additional screening at different reaction temperatures with $Cu(OAc)_2$ in *i*-PrOH was performed, which results are shown in Table 9.

Table 9: Asymmetric Henry reaction of benzaldehyde **61** at various temperatures and conditions

entry	catalyst	duration [d]	T [°C]	NEt_3 [mol%]	yield [%][a]	*ee* [%][b]
1	**16**	3	25	-	43	20 (*R*)
2	**16**	3	0	-	51	24 (*R*)
3	**16**	3	-10	-	23	25 (*R*)
4	**17**	3	25	-	50	32 (*R*)
5	**17**	3	0	-	26	49 (*S*)
6	**17**	3	-10	-	6	55 (*S*)
7	**17**	6	0	-	12	46 (*S*)
8	**16**	3	0	1	47	21 (*R*)
9	**16**	3	0	5	73	15 (*R*)
10	**16**	3	-10	1	38	22 (*R*)
11	**17**	3	0	1	22	31 (*S*)
12	**17**	3	0	5	52	38 (*S*)
13	**17**	3	-10	1	26	33 (*S*)

All reactions were performed with 1 mmol benzaldehyde, 10 mmol nitro methane, 0.1 mmol $Cu(OAc)_2$ and 0.1 mmol catalyst at different temperatures for 72 or 144 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H or IA column. Absolute configuration determined by comparison with literature values.

Concerning the yield, reactions carried out at room temperature showed good performance but on the other hand *ee* values were much higher, when reactions were performed at lower temperatures. Decreasing temperature led to lower reaction rates and as a consequence to better chiral induction. Test reactions were performed at 0 °C as well as at -10 °C. While yield was extremely decreasing at temperatures below 0 °C, enantioselectivities were higher under these conditions. Especially when ionic liquid **17** was used as catalyst, *ee* values increased with decreasing temperature. Even a prolongation of reaction time from three days to six days did not significantly improve yield (Table 9, entry 5 vs. 7). Considering reaction temperatures, reactions reported in literature showed promising results with EtOH at room temperature[51, 57] as well as *i*-PrOH at 0 °C.[208] To improve yield in our test reactions, 1 to 5 mol% NEt_3 as base was added to the reaction mixture. There are many interesting examples in publications dealing with increasing yields with constant *ee* values, when DIPEA or NEt_3 where added.[48, 52] Kowalczyk reported improved yields up to 80% with reactions performed in *i*-PrOH at -30 °C and 2-7 mol% DIPEA.[209]

With additional 5 mol% NEt_3 we were able to enhance yield from 51% to 73% or from 26% to 52%, respectively, even at lower temperatures (Table 9, entry 2 vs. entry 9, entry 5 vs. 12). Unfortunately in all our reactions with additional base *ee* values were lower than in analogous reactions without base. Decreasing the amount of added base to 1 mol% gave comparable results. The best compromise between yield and enantiomeric excess for the pyridinium catalyst set appeared to be 0 °C without any addition of base. Different amounts of solvent or nitro methane did not show any influence in reaction performance. Standard test reactions were performed for three days. Enhancing reaction time to six days led to no significant higher yields with constant *ee* values.

To check reproducibility of the reaction, experiments were performed three times under exact the same conditions using **16** and **17**, respectively (Table 10). Obtained

[208] Bandini, M.; Cabiddu, S.; Cadoni, E.; Olivelli, P.; Sinisi, R.; Umani-Ronchi, A.;Usai M. *Chirality*. **2009**, *21*, 239. Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org.Lett*. **2007**, *9*, 2151. Zielinska-Blajet, M.; Skarzewski, J. *Tetrahedron:Asymmetry*. **2009**, *20*, 1992.
[209] Kowalczyk, R.; Skarzewski, J. *Tetrahedron:Asymmetry*. **2009**, *20*, 2467.

results were satisfying. Phenylalanine derived ligand **16** gave both an *ee* value of 25 (+/- 10_{rel}%) and a calculated yield of 42 (+/- 10_{rel}%), whereas phenylalanine derived IL **17** showed good reproducible *ee* values (52 (+/- 10_{rel}%)) and an acceptable statistical scatter of yields (Table 10, entry 1-6). Due to the known hygroscopy of ionic liquids, the influence of water content was checked. Although stock solutions were used for the screenings it was interesting to know whether water content of catalyst had an influence on reaction performance. For this purpose, reactions with 24 h high vacuum dried catalysts, stock solutions and stock solutions with added water have been carried out under standard reaction conditions. Variations of yields and enantioselectivities of all reaction were within the 10_{rel}% mark. These results clearly indicated no significant influence of water content of catalysts. Furthermore we were interested whether enantioselectivity or yield could be improved when the ratio of ligand in comparison to copper was enhanced. Therefore 20 mol% of chiral catalyst was used instead of 10 mol% (Table 10, entry 11, 12). While the yield remained constant and within observed fluctuation, a slight decline of enantiomeric excess was noticed both with ligand and corresponding ILs. Henry reaction catalysed with sole $Cu(OAc)_2$ without any chiral induction not only showed no enantioselectivity, but also no conversion.[210]

Table 10, entry 14 shows an experiment where reaction was catalysed only by ligand **20**. The poor yield obtained here indicates that the basicity of the amino alcohol ligand is not sufficient for deprotonation of nitro methane and actually a combination of ligand and Lewis acidic transition metal salt is required.

[210] TLC showed no product spot after three days under standard reaction conditions. The recorded NMR spectrum of the isolated raw material showed no product signals as well but a mixture of applied benzaldehyde and benzoic acid as an oxidation product.

Table 10: Asymmetric Henry reaction of benzaldehyde **61** catalysed with various Cu(II)salts

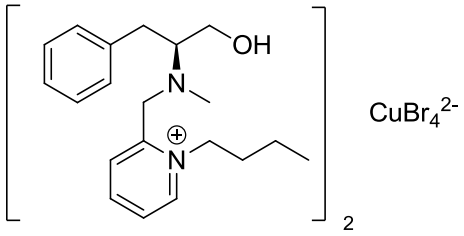
entry	chiral catalyst	amount of chiral catalyst [mol%]	comment	yield [%][a]	*ee* [%][b]
1	**16**	10	-	41	24 (*R*)
2	**16**	10	-	39	29 (*R*)
3	**16**	10	-	46	22 (*R*)
4	**16**	10	-	11	49 (*S*)
5	**16**	10	-	7	47 (*S*)
6	**16**	10	-	5	58 (*S*)
7	**16**	10	vacuum dried	30	30 (*R*)
8	**16**	9	1 mol% water	35	26 (*R*)
9	**17**	10	vacuum dried	8	41 (*S*)
10	**17**	9	1 mol% water	6	41 (*S*)
11	**16**	20	-	30	15 (*R*)
12	**17**	20	-	7	26 (*S*)
13 [c]	-	-	only Cu(II)	0	nd
14[d]	**20**	10	only chiral lig.	3	rac

All reactions were performed with 1 mmol benzaldehyde, 18 mmol nitro methane, $Cu(OAc)_2$ chiral catalyst at 0 °C for 72 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H column. Absolute configuration determined by comparison with literature values [c] Reaction carried out without chiral catalyst. [d] Reaction performed without copper source.

With the optimised conditions in hand, asymmetric Henry reaction of benzaldehyde **61** in the presence of various Cu(II) salts was investigated. Commonly in Henry reactions used Cu(II) salts were screened.[48, 58] Initial experiments at 0 °C in *i*-PrOH for

72 hours with $Cu(OAc)_2$ using tridentate ligand **16** gave a yield of 40% and enantioselectivity of 15% *ee* (Table 11, entry 2), whereas other Cu(II) salts showed less conversion and significant lower *ee* values. A screening of various copper salts as Cu(II) source clearly indicated the superiority of $Cu(OAc)_2$ in comparison to $Cu(BF_4)_2$ and especially copper halides. Using $CuCl_2$ or $CuBr_2$ as metal salt a significant drop in yield and enantioselectivity of test reactions was observed, shown in Table 11. Copper halides completely failed to catalyse the reaction (Table 11, entry 4, 5). An original concept of the thesis was to use bifunctional catalysts with two catalytic active sites. Therefore the plan was to integrate the Cu(II) into the anion of the ionic liquid as CuX_4^{2-} to get bifunctional catalysts shown in Scheme 44. Starting from ionic liquid bromides it would be possible to synthesise copper bearing ILs by simple adding an ethanolic solution of $CuBr_2$ to a solution of IL in dry ethanol and stirring at rt.

Not only experiments with ligands and halides (Table 11, entry 4, 5) but also initial experiments with $[C_4mim]_2CuBr_4$ (entry 10) did not work satisfactoring. Including other copper(II) salts would be challenging, as synthesis of such ILs would lead to mixed anions and there are no useful analytical methods to analyse exact amount and nature of mixed IL anions. Therefore concept was changed and CILs were used as sole ligands.



Scheme 44: Phenylalanine IL as example for a bifunctional CIL with Cu(II) containing anion

The results in Table 11 clearly indicate the superiority of $Cu(OAc)_2$ as source of Cu(II). Considering all initially screened Cu-salts, $Cu(OAc)_2$ gave the best overall performance and was therefore chosen for further Henry screenings.

Furthermore we were interested whether enantioselectivity or yield could be improved when the ratio of copper with respect to the ligand was changed.

The influence of the ratio between ligand and $Cu(OAc)_2$ was investigated next (Table 12). Adding 0.2 eq. of Cu-salt instead of 0.1 eq. slightly improved yield and enantiomeric excess in all cases, indicating the participation of this second equivalent of copper salt in the catalytic active species (Table 11, entry 6, 7,). This observation could be affirmed by the work of Constable.[42] He synthesised copper complexes with diimino or diamino ligands. Structural data of the complexes showed a cavity, able to bind a metal centre, which is already structurally confirmed in other complexes.[211] They looked at the effects of adding equimolar amounts of metal(II) acetate with respect to the amount of complex to the reactions and observed higher yields.

Important to mention was the occurrence of the opposite enantiomer when ligand **16** was used in combination with $Cu(OAc)_2$ to catalyse the reaction instead of other copper salts. This indicated an influence of the anion during formation of the catalytic active complex. X-ray suitable crystals of the catalyst would be highly appreciated to confirm the structures of complexes but could not be obtained until now.

Table 11: Asymmetric Henry reaction of benzaldehyde **61** catalysed with various Cu(II)salts

entry	Cu(II) salt	amount of Cu-salt [mol%]	yield [%][a]	*ee* [%][b]
1	$Cu(OTf)_2$	10	1	8 (*S*)
2	$Cu(OAc)_2$	10	32	20 (*R*)
3	$Cu(BF_4)_2$	10	4	9 (*S*)
4	$CuCl_2$	10	1	7 (*S*)
5	$CuBr_2$	10	2	rac
6	$Cu(OAc)_2$	20	40	20 (*R*)
7	$Cu(BF_4)_2$	20	3	13 (*S*)

[211] Salmon, L.; Theury, P.; Ephritikhine, M. *Polyhedron*, **2007**, *26*, 645

entry	Cu(II) salt	amount of Cu-salt [mol%]	yield [%][a]	*ee* [%][b]
8	$CuCl_2$	20	7	nd
9	$CuBr_2$	20	5	6
10[c]	$[C_4mim]_2CuCl_4$	10	1	rac
11[d]	$Cu(OAc)_2$	10	32	18 (*R*)
12 [d]	$Cu(OAc)_2$	10	27	20 (*R*)

All reactions were performed with 1 mmol benzaldehyde, 18 mmol nitro methane and 0.1 mmol ligand **16** at 0 °C for 72 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H or IA column. Absolute configuration determined by comparison with literature values [c] Reaction carried out in EtOH. [d] Reactions performed with 10 eq. of nitro methane.

Henry reactions of benzaldehyde **61** with ligands **16**, **18**, **20** and CILs **17**, **19**, **21**, respectively, and additionally 10, 15 and 20 mol% of $Cu(OAc)_2$ proved our prior observations, that a second equivalent of Cu-salt increased yield as well as *ee*-values, when the pyridinium moiety is substituted in position 3 (Table 12). These results were in accordance to Constable´s observation, that the addition of a second copper(II) centre significantly enhances the performance of the catalyst.[42]

Increasing the amount of Cu-salt showed significant higher yields with all complexes initially screened on their catalytic performance on Henry reaction of benzaldehyde (Table 12, entry 1 versus 2 or 3, entry 6 versus 7 or 8, entry 11 versus 12 or 13). Selectivity as well could be slightly improved by adding the double amount of Cu-salt. When using CILs as catalysts we obtained good to excellent enantioselectivities, however, only poor yields were observed. On the other hand yields could be enhanced by adding more Cu-salt even in the case of CIL catalysts. As already mentioned before, addition of 1-5 mol% NEt_3 improved yields, but on the contrary when base was added to the reaction enantioselectivity dropped significantly (Table 12, entry 4, 7).

The ligand and CIL set with the pyridinium residue substituted in position 2, ligands **8**, **11**, **13** and CILs **9, 12**, **14** gave - with comparable yield - slightly higher

enantioselectivity values when both - chiral catalyst and $Cu(OAc)_2$ - were applied in 10 mol% amounts instead of the double amount of copper salt for the systems with substituents in position 3 of the pyridinium residue (Table 12, entry 18 vs. 19, entry 20 vs. 21, entry 22 vs. 23). The shorter distance of three bond lengths instead of four between the two N coordination sites of these ligands and CILs offered different coordinating abilities to the metal. The catalytic active species with ligands and ILs seemed to involve the second Cu atom into the transition state when the distance to the pyridinium N was four bond lengths (pyridinium 3 derived catalyst set). Our results indicated no participation of the second equivalent of Cu salt in the catalytic active species of the pyridinium-2 catalyst set.

Table 12: Asymmetric Henry reaction of benzaldehyde **61** with various amounts of Cu(II) acetate

entry	catalyst	amount of Cu-salt [mol%]	yield [%][a]	*ee* [%][b]
1	**16**	10	30	19 (*R*)
2	**16**	15	40, 38[d]	20 (*R*)
3	**16**	20	40	22 (*R*)
4[c]	**16**	10	73	15 (*R*)
5	**17**	10	5	42 (*S*)
6	**17**	20	6	52 (*S*)
7[c]	**17**	10	52	38 (S)
8	**18**	10	40	30 (*R*)
9	**18**	15	47	30 (*R*)
10	**18**	20	68	33 (*R*)
11	**19**	10	3	35 (S)

entry	catalyst	amount of Cu-salt [mol%]	yield [%][a]	*ee* [%][b]
12	**19**	20	5	31 (*S*)
13	**20**	10	39	55 (*R*)
14	**20**	15	50	75 (*R*)
15	**20**	20	57, 51[d]	77 (*R*)
16	**21**	10	10	77 (*S*)
17	**21**	20	12	80 (*S*)
18	**5**	10	27	21 (*R*)
19	**5**	20	28	15 (*R*)
20	**11**	10	22	31 (*R*)
21	**11**	20	26	18 (*R*)
22	**15**	10	10	58 (*S*)
23	**15**	20	6	43 (*S*)

All reactions were performed with 1 mmol benzaldehyde, 18 mmol nitro methane and 0.1 mmol chiral catalyst at 0 °C for 72 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H column. Absolute configuration determined by comparison with literature values. [c] 5 mol% NEt_3 were added. [d] Isolated yield after chromatography.

Surprisingly a reverse of selectivity was observed when CILs were used to catalyse the reaction instead of ligands. Whereas CILs in combination with $Cu(OAc)_2$ gave an excess of the (*S*)-enantiomer, $Cu(OAc)_2$ in combination with tridentate ligands induced the formation of the (*R*)-enriched product. These facts indicate different coordination abilities depending on the alkylation of the pyridinium N and a different catalytically active species.

Due to the alkylated pyridinium nitrogen, CILs only have two coordination sites which can interact with the metal ion, while the ligands offer three nucleophilic centres in the reasonable distance of 3 and 4 bond length that are available for direct interaction with coordinating metals or substrates. This may be the reason for differences in structure of complexes. The experimentally observed differences in catalytic activity and stereochemical induction in asymmetric Henry reaction may thus be partly explained. Similar differences in selectivity of (-)-spartein complexes with $Cu(OAc)_2$ and $CuCl_2$ were observed by Maheswaran. Here the acetate complex completely failed to induce chirality to the nitro aldol product whereas the $CuCl_2$-spartein was extremely successful. Different relative orientation of the counter anion and consequently different bond angles and torsion angles were supposed to be responsible.[63] It is well known that ligands with various metal salts can form different structures of complexes. Seleem examined phenolic quinolin hydrazones with various Cu(II)-salts and observed dimeric, binuclear and mononuclear complexes depending on the type of the anion.[212] Going back and calling Table 11 in mind, we observed a reverse enantioselectivity of the complexes of **16** in dependency on the anion of the copper salt, similar to the reverse of chiral induction observed with ligands and CILs. While ligands and $Cu(OAc)_2$ favoured the formation of the (*R*)-enantiomer, in comparison the (*S*)-enriched nitro alcohol was formed with the other copper salts (halides, triflate and BF_4, respectively) in combination with tridentate ligands (Table 11, entry 2 vs. 4).

The resulting structural diversity and different modes of bonding depending on the anion could also explain the formation of the opposite enantiomer with coordinating ILs used in our Henry reaction. The Cu-halide bond is much stronger than the Cu-coordination with N, which is again stronger than the Cu-O coordination. While in case of the copper acetate system the Cu prefers to coordinate with the pyridinium N instead of the O of the acetate, it can´t coordinate when Cu halides are used to form the complex. That means that in case of Cu(II) halides we have a similar situation to complexes with CILs, where due to the alkylated pyridinium no coordination is

[212] Seleem, H.S.; El-Inary, G.; El-Shetary, B.A.; Mousa, M.A. *Chemistry Central Journal*, **2011**, 5:2

possible to the pyridinium N. This fact could explain the observed results. When the pyridine N is not coordinating to the copper, the carbonyl oxygen of the aldehyde is coordinating in such a manner that the phenyl ring is positioned in front of the paper plane. As a consequence, the coordinated nitro methane is attacking the planar aldehyde from the *Re face*, leading to the (*S*)-enantiomer. On the contrary, a coordination of the pyridine N in ligands probably leads to a *Si face* attack of the nucleophile and to the (*R*)-enantiomer.

Next step was getting more insight into possible structure of our complexes. Because of the paramagnetic copper(II) it was not possible to get useful NMR spectra, not even with only 10 mol% of copper salt in the NMR samples.[213]

To confirm structural diversity of our catalysts IR spectra of the free amino alcohol ligands and the corresponding ILs of the pyridinium-3 set and its complexes with various Cu(II) salts were recorded. Comparison of the IR spectra are shown in Table 13 and revealed the following:

Free ligands **16** and **20** showed broad bands of O-H stretch vibrations, which were shifted to higher wavenumbers indicating coordination via the O-atom. The C-H deformation vibrations resulting from the methyl group of the aliphatic tertiary amine, occurring at wavenumbers 1450 and 1425 cm^{-1} in free ligands are weaker in all complexes and shifted to lower wavenumbers. This indicates coordination of the amine N with the copper, confirmed by bands in the range of 460-420 cm^{-1} which have been assigned to the ν(Cu-N) band.[214] This fact together with the similar shift of O-H stretch vibrations suggests the participation of the OH-group and the tertiary amine functionality in complexation of all screened Cu(II) salts.

On the other hand the typical vibrations of a 3-substituted pyridine ring showed different bands in spectra of different complexes: The strong bands at 1028 cm^{-1}

[213] Copper is one of the two exceptions of transition metals to the writing of electron configurations. Instead of the expected s^2d^9 configuration, one electron is borrowed from the 4s orbital to completely fill the 3d orbitals. Due to the unpaired electron in the 4s orbital, copper metal is therefore paramagnetic. In contrast to the diamagnetic Cu(I), in oxidation state +II copper is paramagnetic, as the Cu^{+2} ion with its $4s^03d^9$ configuration again possesses an unpaired electron.

[214] Joseph, M.; Kuriakose, M.; Kurup, M.R.P.; Suresh, E.; Kishore, A.; Bhat, S.G. *Polyhedron*, **2006**, *25*, 61. Hosny, N.M.; El-Dossoki, F.I.; Mostafa, M.M. *Phosphorus, Sulphur and Silicon and the Related Elements*, **2010**, *185:2*, 402.

observed in the spectra of free tridentate ligands resulting from C-H deformation vibrations (compare band at 1025 cm^{-1} Table 13entry 1) are shifted to higher wavenumbers in the corresponding CILs **17** and **21** due to the alkylated pyridinium N. N-Alkylation in ILs is also indicated by the bands in range 3300-2280 cm^{-1}. The band at 1028 cm^{-1} is clearly weaker in the $Cu(OAc)_2$ complexes of **16** and **20** whereas the $CuBr_2$-complex of ligand **5** showed no band in this range. In case of $Cu(BF_4)_2$ complexes the strong broad band of the BF_4^{2-} anion interfered in this area. Bands at 1580 and 1600 cm^{-1} were observed in ligands **16** and **20**, respectively, indicating pyridinium ring stretching vibrations. The absence of these bands in CILs **17** and **21** and complexes of **17** with $CuBr_2$ or $Cu(BF_4)_2$ is assigned to a different coordination behavior depending on the alkylation of the pyridinium N and the anion of the complex. In $Cu(OAc)_2$ complexes the bands undergo a shift to higher wavenumbers but partially interfere with strong acetate vibrations. Bands in the fingerprint range of about 700 cm^{-1} resulting from C-H ring vibrations in 3-substituted pyridines could be observed in all recorded spectra, but at different wavenumbers.

Table 13: IR spectral assignments [cm^{-1}] of ligands, CILs and the Cu(II) complexes

Entry	compound	O-H stretch	C-H stretch aromatic	Ring stretch 3-subst Py	C-H def tert N	C-N (N^+) stretch	C-H def 3-subst Py	C-H ring 3-subst Py	Cu-N
1	β-picoline		3030	1579			1025	785, 711	
2	**16**	3340	2937	1600, 1580	1450, 1430		1029	699	
3	**20**	3190	2850	1590, 1580	1450, 1430		1027	704	
4	**17**	3565	2930		1350, 1330	1180, 1130	1054	690	
5	**21**	3534	2960		1350, 1330	1180, 1130	1050	690	
6	**16**-$Cu(OAc)_2$	3400	2927	1621	interference		1027[a]	700	435
7	**20**-$Cu(OAc)_2$	3380	2940	1620	interference		1032[a]	680	451
8	**20**-$CuBr_2$	3423	2990		1455,1434[a]			701	420
9	**20**-$Cu(BF_4)_2$	3530	3160		1440,1430[a]		interference	702	461
10	**17**-$Cu(OAc)_2$	3480, 3387	2940		1348, 1332	1180, 1130	1050	690[b]	457

[a] IR band weaker than in the corresponding free ligand [b] IR band stronger than in the corresponding free CIL

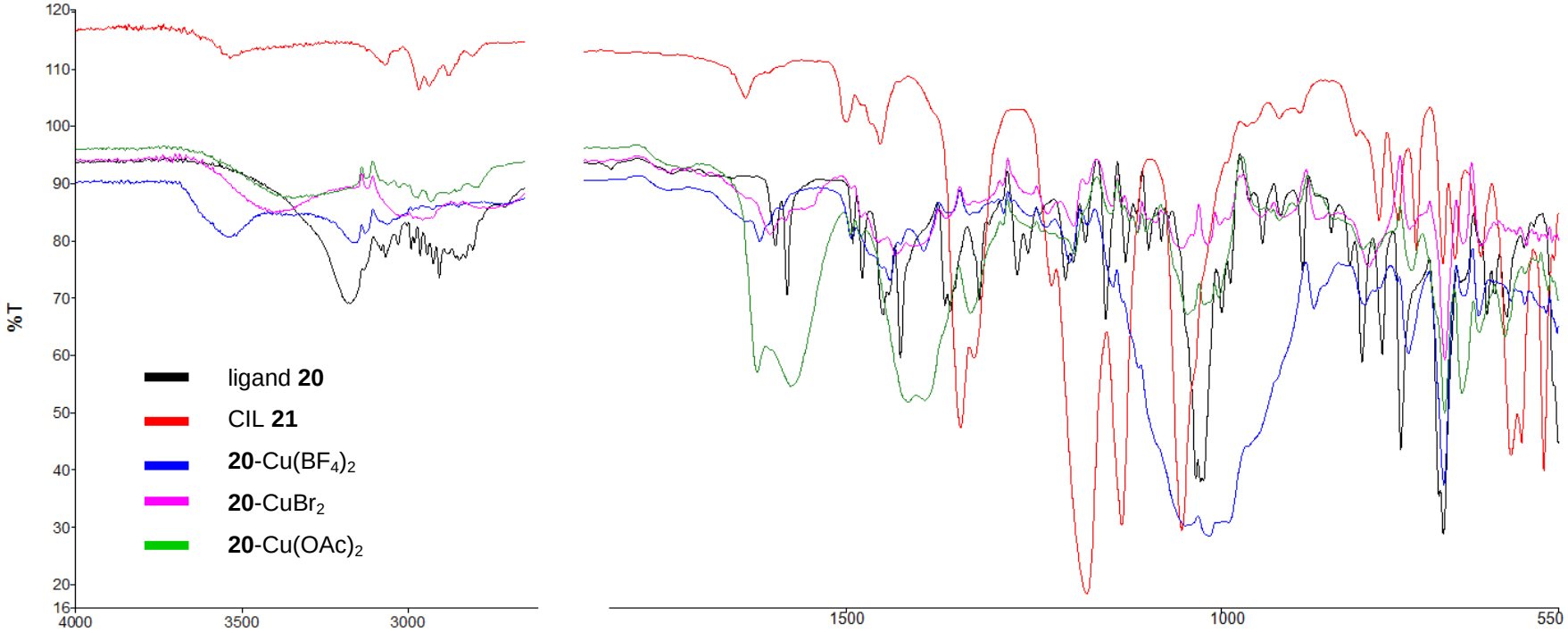


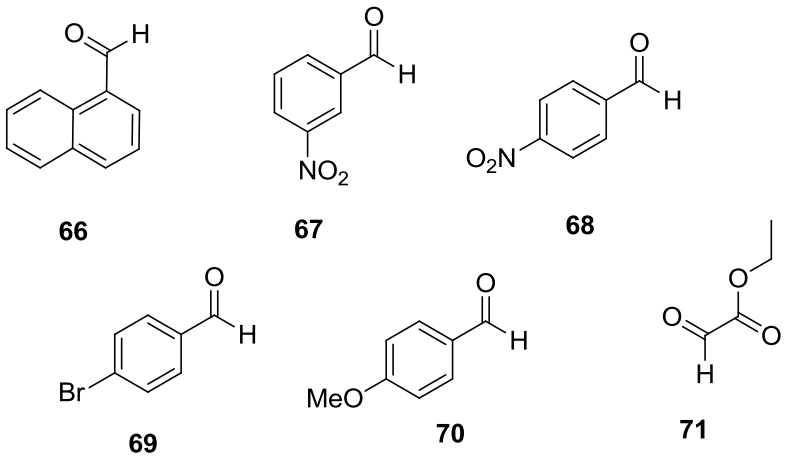
Figure 26: IR spectra of Cu(II) complexes of **20** and coordinating CIL **21**.

Shift of O-H stretch vibrations (ν 3400-3000 cm^{-1}) and shift of C-H deformation vibrations resulting from the methyl group of the aliphatic tertiary amine (ν 1450-1425 cm^{-1}) to lower wavenumbers clearly indicate coordination to the Cu(II) in our complexes. Missing or shifted bands resulting from 3-substituded pyridines (ν 1580 and 1028 cm^{-1}) are assigned to a different coordination behavior at the pyridine-N depending on the anion of the complex. This can partly explain the occurrence of the opposite enantiomer, when complexes with $Cu(OAc)_2$ are used as catalysts.

The obtained and discussed results with ligands and coordinating ionic liquids can be rationalised by the following considerations, using ligand **5** and the corresponding CIL **6**. Depending on a tridentate coordination in case of ligand **5** a more rigid and steric demanding complex is formed, while the ionic liquid **6** is not able to coordinate to the copper with the quaternised pyridinium N. Therefore rotation of the pyridine moiety is still possible.

Reaction may involve dual activation of both the nitro methane and the aldehyde.[44] In the more rigid complex with the ligand, the nucleophilic carbon of the nitro methane favorably attacks the aldehyde from the *Si face* to afford the (*R)*-enantiomer as major product. When CIL are used to catalyse the reaction, a *Re face* attack takes place yielding an excess of the (*S)*-enantiomer.

To get an impression of the scope of our asymmetric Henry reaction we screened all ligands and corresponding CILs not only with benzaldehyde **61** but also with various aromatic aldehydes shown in Scheme 45. Results are summarised inTable 14 and Table 15.



Scheme 45: Aldehydes used for Henry screening

Table 14: Asymmetric Henry reaction of various aldehydes under optimised conditions

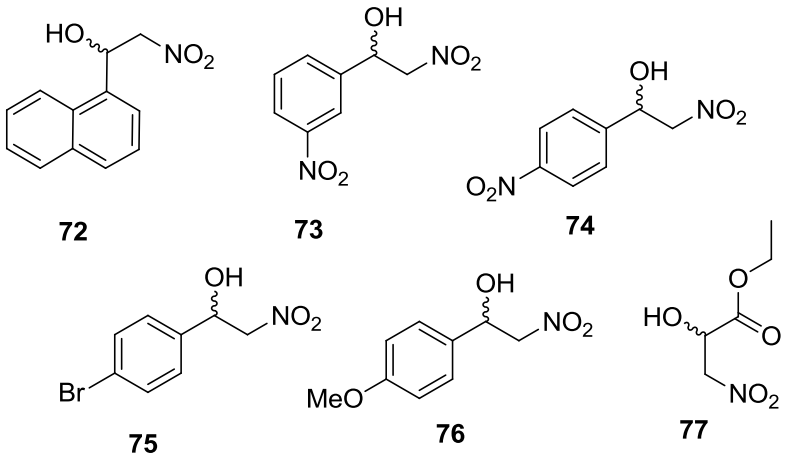
entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
1	**66**	**16**	36	23 (*R*)
2	**66**	**18**	57	20 (*R*)
3	**66**	**20**	79	35 (*R*)
4[c]	**66**	**17**	47	44 (*S*)
5	**66**	**19**	11	24 (*S*)
6	**66**	**21**	63, 57[d]	80 (*S*)
7[c]	**67**	**16**	41	< 6
8	**67**	**18**	57	18 (*R*)
9	**67**	**20**	51	49 (*R*)
10	**67**	**17**	3	50 (*S*)
11	**67**	**19**	<1	64 (*S*)
12	**67**	**21**	13	44 (*S*)
13	**68**	**16**	35	13 (*R*)
14	**68**	**18**	36	14 (*R*)
15	**68**	**20**	50	26 (*R*)
16	**68**	**17**	<1	nd
17	**68**	**19**	<1	nd
18	**68**	**21**	66	72 (*S*)

entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
19	**69**	**16**	30	10 (*R*)
20	**69**	**18**	38	15 (*R*)
21	**69**	**20**	6	48 (*R*)
22	**69**	**17**	5	15 (*S*)
23	**69**	**19**	2	14 (*S*)
24	**69**	**21**	39	81 (*S*)
25	**70**	**16**	11	39 (*R*)
26	**70**	**18**	11	55 (*R*)
27	**70**	**20**	4	73 (*R*)
28	**70**	**17**	3	51 (*S*)
29	**70**	**19**	2	35 (*S*)
30	**70**	**21**	27	91 (*S*)
31	**70**	**16**	<3	67
32	**71**	**18**	<3	40
33	**71**	**20**	<3	58
34	**71**	**17**	<3	35
35	**71**	**19**	<3	37
36	**71**	**21**	<3	57
37[c]	**71**	**16**	18	12

entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
38[c]	**71**	**18**	24	7
39[c]	**71**	**20**	8	18
40[c]	**71**	**17**	9	rac
41[c]	**71**	**19**	9	< 6
42[c]	**71**	**21**	<1	33

Catalysts bearing a 3-substituted pyridinium moiety were used. All reactions were performed with 1 mmol aldehyde, 18 mmol nitro methane 0.2 mmol $Cu(OAc)_2$ and 0.1 mmol chiral catalyst at 0 °C for 72 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H or IA column [c] Reactions carried out at rt. [d] Isolated yield after chromatography.

Using the first set of catalysts containing the 3-substituted pyridinium, the results of the screening of several aromatic aldehydes are summarised in Table 14. The efficiency of ligand **20** and CIL **21** was proved since the appropriate products were obtained with good selectivity. The results were able to confirm what initial experiments with benzaldehyde had already shown. Tridentate ligands as catalysts gave the (*R*)-enantiomer of nitro aldol product (Scheme 46), whereas CILs induced the formation of the (*S*)-enantiomer. In all cases yields were significant higher when ligands were used to catalyse the reactions instead of CILs. The best yields could be obtained using ephedrine derived ligand **20**, which gave 79% yield with unsubstituted naphthaldehyde (Table 14, entry 3). Aldehydes with electron withdrawing substituents in 3 or 4 positions yielded the nitro aldol product in more than 50% (Table 14, entry 9, 15). However, aromatic aldehydes with higher electronic density showed comparatively less conversion when ligands catalysed the reaction (Table 14, entry 19-21 and 25-27). Although only poor yields could be observed using ligand **20** in reactions on aldehydes with +M substituents (Table 14, entry 21, 27), a strong +M effect in para position led to comparatively high enantioselectivities up to 73% *ee* (Table 14, entry 27).



Scheme 46: Henry products

The different selectivity compared to literature known ligands like the bisoxazoline ligands synthesised by Ginotra[58] or bis(sulphonamide)diamine ligands[215] suggested that ligand architecture plays an important role in chiral induction of Henry reaction. Reactivity and enantioselectivity should be dependent upon both number of chiral centres and character of substituents on the side chain. In this context Evans assumes an impact of the Jahn Teller effect on Cu(II) coordination. He suggested that the most reactive transition state of a bidentate ligand affords a complex positioning the two cis-oriented sites in the ligand plane.[51] The highest reactivity is suggested for those complexes where the transition state positions the nucleophile (Nuc) perpendular to the ligand plane. For maximal activation the electrophile (El) should be positioned in one of the more Lewis acidic equatorial sites in the ligand plane, as shown in Figure 27. Comparison of our ligands showed that the more steric demanding ligand **16** succeeded over ligand **18.** In all screened examples the ligand with two asymmetric carbon atoms derived from ephedrine, **20** gave products with higher *ee* values.

[215] Jin , W.; Li, X; Huang, Y.; Wu, F.; Wan, B. *Chem.Eur.J*. **2010**, *16*, 8259.

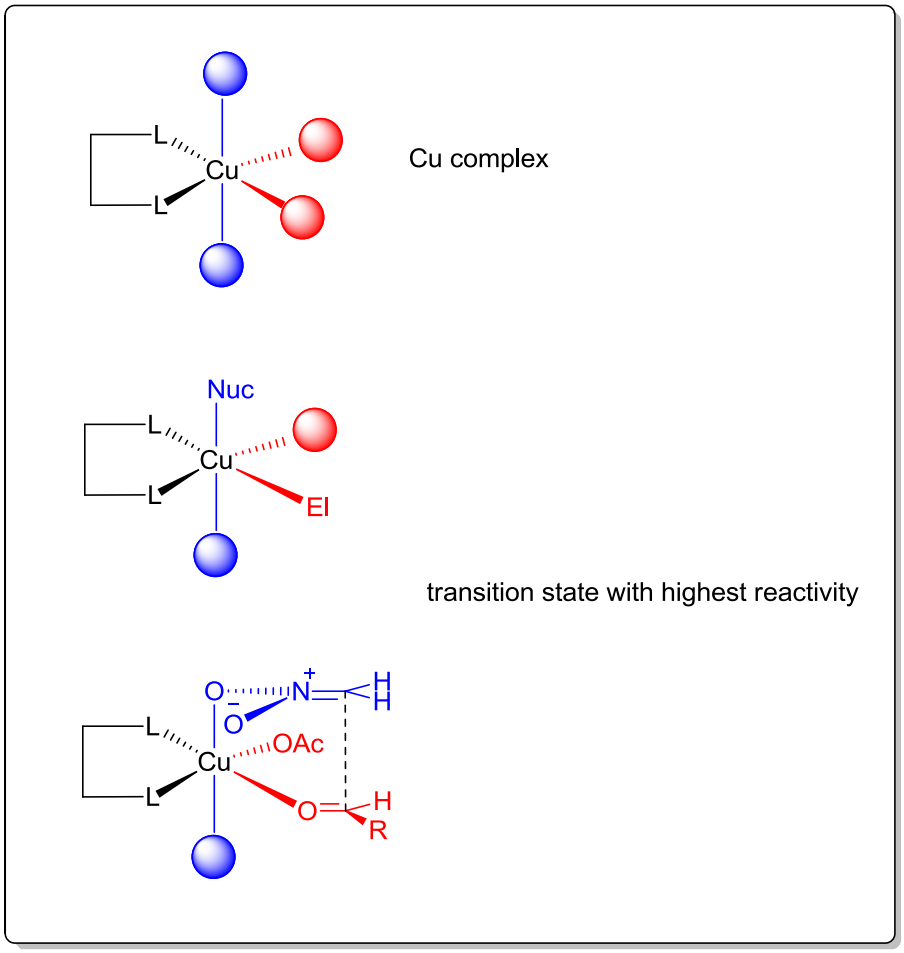


Figure 27: Plausible transition structures for Henry reaction according to Evans

On the contrary, when CILs were used as chiral catalysts, *ee* values increased. Especially CIL **21** improved selectivity to *ee* values up to 91% (Table 14, entry 6, 18, 24, 27). Unfortunately only poor yields could be obtained here. Particularly the phenylalanine and valine derived ILs showed disappointing performances. A possible explanation for the reduced catalytic activity of ionic liquids could be the interaction of the transition metal with the associated bistriflimide present in the ionic liquid so that the ionic liquid interfered with the catalytic activity of the copper. Garcia proposed a similar explanation for lower enantioselectivities obtained with ionic liquid catalysts in cyano silylation.[216]

In case of 4-nitro benzaldehyde **70**, CILs **17** and **19** completely failed to catalyse the reaction (Table 14, entry 16, 17). Even in Henry reaction of ethyl-2-oxoacetate **71**, our

[216] Baleizao, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron: asymmetry*, **2004**, *60*, 10461.

representative for aliphatic aldehydes, not only CILs but also ligands gave yields under 3% but good enantioselectivities up to 67% (Table 14, entry 31-36). Raising temperature to room temperature to improve conversion led to slightly better yields but a decrease in selectivity was observed with all catalysts (Table 14, entry 37-49).

Table 15: Asymmetric Henry reaction of various aldehydes under optimised conditions

entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
1	**66**	**5**	18	27 (*R*)
2	**66**	**11**	11	41 (*R*)
3	**66**	**14**	13	43 (*R*)
4	**66**	**6**	4	8 (*S*)
5	**66**	**12**	1	8 (*S*)
6	**66**	**15**	1	< 6
7	**67**	**5**	59	< 6
8	**67**	**11**	59	8 (*R*)
9	**67**	**14**	52	14 (*R*)
10	**67**	**6**	27	< 6
11	**67**	**12**	7	< 6
12	**67**	**15**	8	13 (*S*)
13	**68**	**5**	53	6 (*R*)
14	**68**	**11**	80	8 (*R*)
15	**68**	**14**	50	12 (*R*)

entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
16	**68**	**6**	32	< 6
17	**68**	**12**	8	< 6
18	**68**	**15**	1	22 (*S*)
19	**69**	**5**	34	18 (*R*)
20	**69**	**11**	38	24 (*R*)
21	**69**	**14**	29	34 (*R*)
22	**69**	**6**	12	< 6
23	**69**	**12**	3	< 6
24	**69**	**15**	3	30 (*S*)
25	**70**	**5**	5	21 (*S*)
26	**70**	**11**	4	37 (*S*)
27	**70**	**14**	7	17 (*R*)
28	**70**	**6**	8	6 (*R*)
29	**70**	**12**	6	34 (*R*)
30	**70**	**15**	4	50 (*R*)
31	**71**	**5**	87	< 6
32	**71**	**11**	75	< 6
33	**71**	**14**	52	< 6
34	**71**	**6**	3	< 6

entry	aldehyde	catalyst	yield [%][a]	*ee* [%][b]
35	**71**	**12**	12	23
36	**71**	**15**	2	35
37	**61**	**5**	27	21 (*R*)
38	**61**	**11**	22	31 (*R*)
39	**61**	**14**	24	46 (*R*)
40	**61**	**6**	18	< 6
41	**61**	**12**	4	< 6
42	**61**	**15**	10	58 (*S*)

Catalysts bearing a 2-substituted pyridinium moiety were used. All reactions were performed with 1 mmol aldehyde, 18 mmol nitro methane 0.1 mmol $Cu(OAc)_2$ and 0.1 mmol chiral catalyst at 0 °C for 72 hrs in *i*-PrOH. [a] Yield determined via NMR-quantification with toluene as ISTD. [b] Determined by HPLC using a DAICEL Chiralpak AS-H or IA column.

In comparison to the 3 substituted pyridinium catalysts, the second set of ligands **5**, **11**, **14** and CILs **6**, **12**, **15**, containing a pyridinium moiety substituted in 2 position, showed different performance. As already mentioned above, these catalysts gave slightly higher *ee* values, when chiral catalyst and $Cu(OAc)_2$ were used equimolar. All obtained results using the adapted protocol are summarised in Table 15. Although yield dropped with most tested aldehydes, electron poor aromatic aldehydes with NO_2 groups in 3 or 4 position showed significant better conversion than with the corresponding catalysts incorporating the pyridinium moiety substituted in position 3, especially when ligands were used to catalyse the reaction. Yields up to 80% could be obtained (Table 15, entry 14).

Unfortunately enantioselectivity dropped using the pyridinium set substituted in position 2: for example from 49% with ligand **5** to 14% with ligand **13**, which only differ in the position of the pyridinium N. While ligands **16, 18, 20** and CILs **17, 19, 21** failed to catalyse the reaction with the aliphatic ethyl glyoxalate at 0 °C (Table 14,

entry 31-36), the pyridinium ligands with substituents in position 2 **5**, **11**, **14** yielded the desired chiral product in up to 87% but low *ee* (Table 15, entry 31-33). CILs **6**, **12** and **15** showed less conversion in Henry reaction with ethyl glyoxalate. These data clearly show the overall observation that especially in reactions, where reaction rate is fast and high conversion could be observed, *ee* values are comparable low and *vice versa*. The already mentioned reverse of selectivity when CILs were used to catalyse the reaction instead of ligands was also observed with this set of catalysts in which the pyridinium was substituted in position 2. CILs in combination with $Cu(OAc)_2$ gave an excess of the (*S*)-enantiomer, $Cu(OAc)_2$ in combination with tridentate ligands induced the formation of the (*R*)-enriched product. Interesting to mention is the behaviour of 4-methoxy benzaldehyde **70**. Although only poor yields could be obtained with that electron rich aromatic aldehyde, here another reverse of selectivity was observed. While all other screened aromatic aldehydes gave the (*R*)-enantiomer with ligands as catalysts and the (*S*)–enantiomer with CILs, 4-methoxy benzaldehyde gave an excess of the (*S*)-enantiomer with ligands and CILs yielded the (*R*)-enriched product (Table 15, entry 25-30).

In conclusion, the prepared set of tridentate chiral catalysts and their corresponding chiral ionic liquids is working effective in enantioselective Henry reaction, although yields remained low when CILs catalysed the reaction. That is presumed by interference of the catalytic activity of the copper by the ionic liquid.

Our catalysts are easily prepared starting from cheap and chiral pool derived amino alcohols. They work at moderate temperatures and can be applied as catalysts for various aromatic aldehydes. With a catalyst loading of 10 mol% they give chiral nitro alcohols in good yields and *ee* values up to 81 %. Although yield and selectivity of our new catalysts for asymmetric Henry reaction were lower compared to literature known ligands, the observed reverse of selectivity was unexpected and fascinating. The only difference in coordination behaviour of neutral and charged ligands is the quaternised pyridinium N of the ionic liquids which cannot coordinate to the copper. The fact that such structurally similar catalysts gave an excess of the other enantiomer when CILs were used to catalyse the reaction instead of ligands is very

interesting and seldom observed. At the moment efforts are done to get X-ray suitable crystals of any ligand or IL containing Cu(II) complexes to gain more insight in structures of catalytic active species and to give an explanation of this observed reverse of selectivity.

3.2.2 Asymmetric cyclopropanation

The intention was to use our set of amino alcohol based ionic liquids in another important C-C forming reaction, the asymmetric cyclopropanation.

Although the asymmetric catalytic conversion of olefins into cyclopropanes by means of a carbene insertion using diazo compounds has been extensively developed, the control of diastereoselectivity has resulted elusive. The number of systems inducing a high level of diastereoselection towards one or another diastereoisomer is still low, particularly when using ethyl diazoacetate **85** as the diazo compound.[87] There is still demand of novel, both regio- and enantioselective catalysts for cycopropanations and fine tuning of ligands or complexes to improve catalytic properties is inevitable.

The set of tridentate pyridinium ligands, substituted in position 2, derived from valine, phenylalanine and ephedrine **5**, **11**, **14** and the corresponding chiral ionic liquids **6**, **12**, **15** were examined concerning their application as ligands in enantioselective cyclopropanation reaction (Figure 28). In combination with various copper salts these novel catalytic systems were screened on their performance in reaction of styrene **78** with ethyl diazoacetate **79** (Scheme 47).

Analogous to the notation "ligand" and "ionic liquid" used in the chapter of Henry reaction, these a little bit misleading labelling will be retained in the following chapter. Of course, both ligands and ionic liquids function as ligands in cyclopropanation reactions and coordinate to the transition metal, the latter as charged ligands (Figure 28).

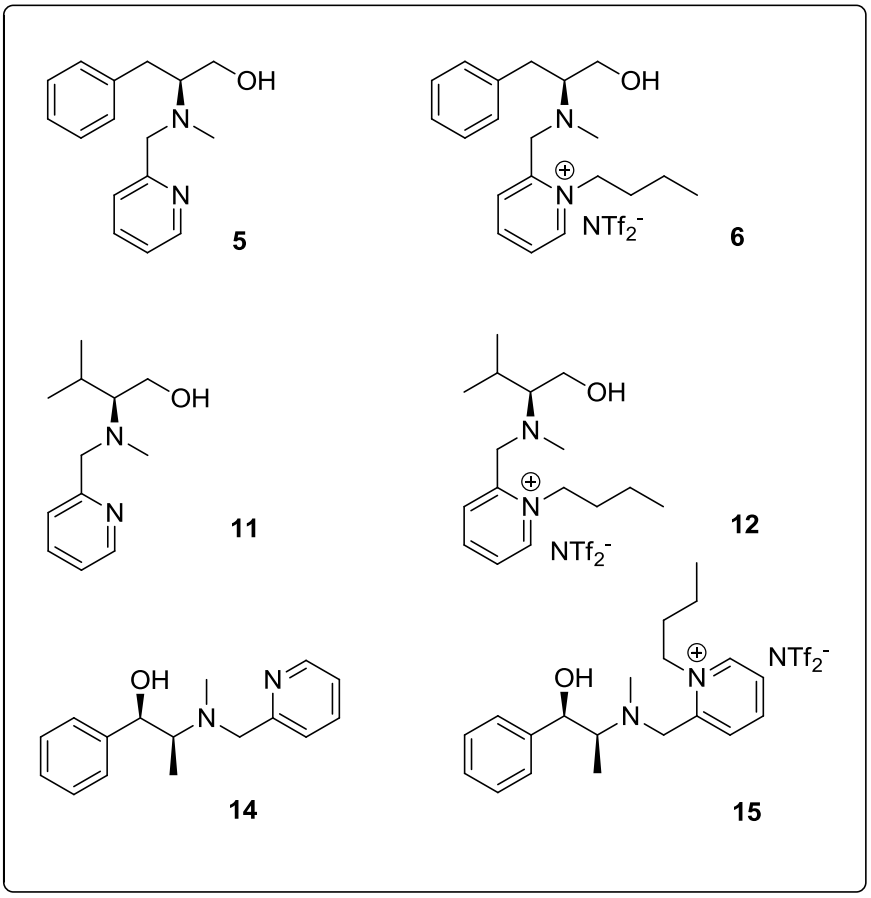
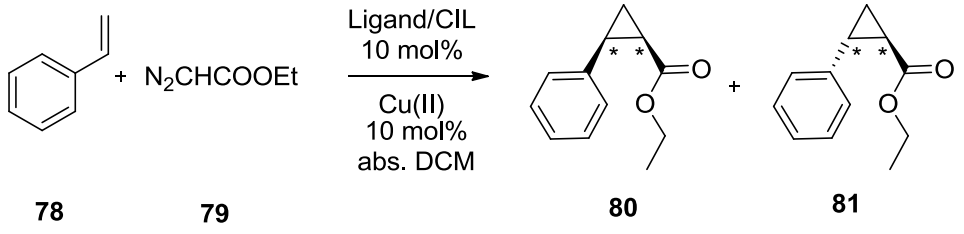


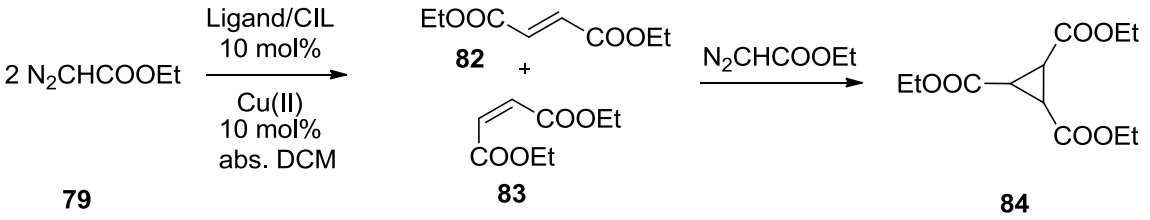
Figure 28: Neutral and charged ligands used as catalysts for cyclopropanation reactions

A racemic version of cyclopropanation reaction with $Cu(OAc)_2$ and triphenyl phosphine as catalyst was investigated to optimise reaction conditions (Scheme 47). In a first experiment to a stirred solution of 1.5 mmol freshly distilled styrene in DCM containing catalyst, 10 mmol ethyl diazoacetate were added *via* a syringe and the reaction was stirred for 24 h.[101] Unfortunately this experiment yielded basically in a mixture of diethyl fumarate and diethyl maleinate, which are both common by-products of cyclopropanations because of dimerisation of the carbenoid species.[106] Only 10% of the desired product could be obtained with a ratio of diastereoisomers **80** (*cis*) and **81** (*trans*) 31:69.



Scheme 47: Asymmetric cyclopropanation of styrene with ethyl diazoacetate

Changing reaction conditions according to Iglesias[103] using an excess of styrene and one eq. of ethyl diazoacetate, added by means of a syringe pump, yielded the mixture of desired isomers in 54% as well as 25% of by-products **82** and **83**. The *cis:trans* ratio of diastereoisomers **80** and **81** was found to be 28:72.



Scheme 48: Formation of by-products in cyclopropanations

Byproducts are formed as the catalytic active species of the reaction, a copper carbene complex, formed from the copper complex and an equivalent of ethyl diazoacetate has in principle the possibility to undergo two reactions: the desired one with styrene to form cyclopropanes or, unfavoured, with another equivalent to form diethyl fumarate **82** and maleinate **83** as by-products which subsequently can react with another EDA to the cyclic triester **84** (see also Scheme 48).

Yields up to 75% and *cis* **80** and *trans* **81** products in a ratio of 40:60 are typical for cyclopropanations using ethyl diazoacetate.[106] When bulkier diazo compounds such as ethyl 2-phenyl diazoacetate or *t*-butyl diazoacetate are employed, diastereoselection commonly is higher. Sterically demanding diazoacetates such as 2,6 dimethylphenyl are reported to increase diastereoselectivity without affecting the enantioselection, documenting the influence of diazo ester on *cis/trans* selectivity in an impressive way.[217]

A complete chromatographical separation of diastereomers **80** and **81** was not possible. Therefore stereoisomers were isolated together and the ratio was determined via GC/MS and NMR spectroscopy, respectively. Values were in agreement to each other.

[217] Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M. *J. Am. Chem. Soc*. **1991**, *113*, 726.

For further improvement of yield in following experiments the solution of ethyl diazoacetate was added by means of a syringe pump over a period of 6 h to suppress side reaction.

To catalyse the reaction, stock solutions of equimolar amounts of $Cu(OAc)_2$ and ligands **5, 11, 14** (Table 16, entry 1, 3, 5) as well as corresponding ionic liquids **6, 12, 15** (Table 16, entry 2, 4, 6) were added to a solution of styrene **78** in dry dichloromethane. After a reaction time of overall 24 h, mixture was filtered over silica and evaporated. Crude product was taken to determine the diastereomeric ratio *via* GC/MS and NMR as well as *ee* values *via* chiral GC. Flash chromatography yielded a pure mixture of both isomers. Results of asymmetric cyclopropanations are summarised in Table 16.

Table 16: Asymmetric cyclopropanation catalysed with ionic liquids

entry	catalyst	Cu-salt	ratio c/t [%][a]	yield [%][b]	*ee* [%][c]	
					cis	***trans***
1	**14**	$Cu(OAc)_2$	28/72	51	14	9
2	**15**	$Cu(OAc)_2$	31/69	61	2	6
3	**11**	$Cu(OAc)_2$	20/80	45	0	5
4	**12**	$Cu(OAc)_2$	29/71	76	0	1
5	**5**	$Cu(OAc)_2$	16/84	41	5	4
6	**6**	$Cu(OAc)_2$	27/73	57	4	4
7	**15**	$Cu(OTf)_2$	41/59	51	0	4
8	**14**	$Cu(OTf)_2$	32/68	77	2	12
9	**12**	$Cu(OTf)_2$	41/59	59	2	0
10	**11**	$Cu(OTf)_2$	31/69	81	1	2

entry	catalyst	Cu-salt	ratio c/t [%][a]	yield [%][b]	*ee* [%][c]	
					cis	***trans***
11[d]	**12**	Cu(OAc)	38/62	53	1	1
12[d]	**12**	Cu(OTf)	40/60	64	2	2
13[d]	**11**	Cu(OAc)	27/73	57	3	6
14[e]	**12**	$Cu(OAc)_2$	33/67	12	1	3
15[e]	**15**	$Cu(OAc)_2$	33/67	29	0	6

All reactions were performed with 1 mmol ethyl diazoacetate, 1mL styrene and 0.1 mmol catalyst and Cu salt in abs. DCM under Ar for 24 hrs. [a] *Cis/trans* ratio determined via chiral GC, GC/MS and NMR respectively. Values are in agreement. [b] Isolated yield of both isomers after chromatographic purification (LP:EA 50:1). [c] Determined *via* chiral GC. [d] Cu(II) salt was *in situ* reduced with phenyl hydrazine. [e] Reaction carried out at 0 °C for 5 days.

All experiments with $Cu(OAc)_2$ showed comparable *cis:trans* ratios of 20:80 which was slightly better than averaged reported in literature.[91] Ligands showed better *trans* selectivity than the corresponding ionic liquids (Table 16, entry 1 vs. 2, entry 3 vs. 4, entry 5 vs. 6). On the other hand, when ligands where used to catalyse the reaction dimerisation of the carbene intermediate took place, forming fumarate and maleinate which reacted again with a carbene to give the cyclic triester **84** as by-product, identified both with NMR spectroscopy and GC/MS (Scheme 48). Therefore the overall yield of desired product was higher when CILs were used for chiral induction. The fact that no by-product was obtained when CILs were used to catalyse the reaction indicated different coordination behaviour of ligands and CILs due to the quaternary pyridinium N, already discussed in chapter 3.2.1. The different coordination is presumed to be responsible for the favoured reaction of the catalytically active species with styrene.

Results were different than expected and low enantioselectivity was observed with $Cu(OAc)_2$ as copper source and our ligands and CILs, respectively.

In order to improve enantioselectivity and to examine the influence of the Cu(II) salt on enantioselectivity of the reaction another screening with the valine and ephedrine derived ligands **11**, **14** and corresponding ILs **12**, **15** using $Cu(OTf)_2$ was carried out. $Cu(OTf)_2$ already showed good performance when used as copper source in enantioselective cyclopropanations. Burguete for example achieved *trans/cis* selectivities of 60:40 and *ee* values from 18% to 80% with silica supported $Cu(OTf)_2$ complexes.[218]

Our experiments with $Cu(OTf)_2$ also gave an excess of the *trans* isomer, but showed lower diastereoselectivity than comparable experiments with $Cu(OAc)_2$ (Table 16, entry 7-10). Especially reactions catalysed with CILs showed a significant drop in diastereoselectivity (Table 16, entry7 vs. 2, entry 9 vs. 4). Interesting to mention is that all experiments running with $Cu(OTf)_2$ as copper source showed no fumarate or maleinate or triester **84** as by-product, which led to enhanced yields when ligands were used (Table 16, entry 8 vs1, entry 10 vs. 3). Although formation of unwanted side products could be suppressed by changing the source of Cu(II), unfortunately no improvement of enantioselectivity could be observed. To check whether reaction conditions are responsible for the unsatisfying enantioselectivity, experiments were repeated at 0 °C running 5 days. Besides a significant drop of yield lower temperature did not improve enantioselectivity, while *cis/trans* ratio was comparable with former results (Table 16, entry 14, 15).

As a consequence, the source of copper was changed again. Phenyl hydrazine was added to the reaction and the mixture was allowed to stir for 10 minutes to reduce the Cu(II) *in situ* to Cu(I) prior the addition of styrene **78** and diazoacetate **79**. The reduction of the Cu was clearly seen because of a colour change of the green blue complexes to yellow. According to Reiser´s representative asymmetric cyclopropanation experiment,[98] $Cu(OTf)_2$ and chiral catalyst were weighted under Ar and dissolved in 1 mL dry DCM. A 10% solution of one equivalent phenyl hydrazine was added and the mixture was allowed to stir until the colour change from green

[218] Burguete, M.I.; Fraile, J.M.; Garcia, J.I., Garcia-Verdugo, E.; Herrerias, C.I.; Luis, S.V. Mayoral, J.A. *J. Org. Chem.* **2001**, *66*, 8893.

blue to yellow was observed. The Cu(I) experiments again showed no formation of any by-product, even when Cu(OAc) in combination with valine derived ligand **11** was used to catalyse the reaction (Table 16, entry 13). While diastereoselectivity with Cu(OTf) was comparable to values obtained with $Cu(OTf)_2$ (Table 16, entry 12 vs. 9), diastereoselectivity slightly decreased when Cu(I) acetate was used instead of Cu(II) acetate (Table 16 entry 11, 13 vs. 4, 3).

Even a change of oxidation state did not lead to any improvement of enantioselectivity of the reaction. Comparison with results reported in literature indicated that the design of ligands played again an important role for satisfying enantioselectivities in that kind of reaction.[82, 91] There were examples for both Cu(II) and Cu(I) systems with different ligands or complexes reported to give good yields and *ee* values, whereat C_2-symmetric ligands showed better performances. [219] While Gao reported enantioselectivities up to 89% with symmetrical ephedrine derived amino alcohols,[101] cyclopropanation results with unsymmetrical Schiff base Cu(II) complexes as catalysts suggested that the square planar structure and the lack of steric crowding around the metal prohibited sufficient stereochemical induction.[103] Iglesias published synthesis and application of several non symmetrical chiral Schiff base complexes in asymmetric cyclopropanations under various conditions with poor enantioselectivities.[103]

All results of the cyclopropanation screening presented in this thesis obtained with the set of unsymmetrical amino alcohol ligands and CILs are summarised in Table 16. As a consequence of low enantioselectivities further cyclopropanation experiments with the amino alcohol ionic liquids were not done.

3.2.3 Iron catalysed asymmetric hydroxymethylation

The tendency of 1,3-dicarbonyl compounds to form iron(III) ato complexes (Figure 29) with iron(III) species can be used for the activation in position 2 for alkylation or other reactions. An example is shown in Scheme 49.

[219] Ito, K.; Katsuki, T. *Chem. Lett*. **1994**, 1857.

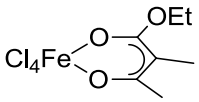
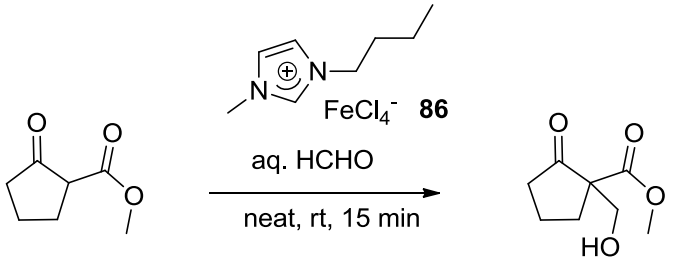


Figure 29: Iron(III) ato complex with ketoester



Scheme 49: Iron catalysed hydroxymethylation

According to previous work of Katharina Bica in the present thesis iron catalysed hydroxymethylation reactions were carried out using ionic liquid catalysts bearing not only Lewis acidic iron salts as transition metal catalyst but also a chiral secondary amine (Figure 30).[37] We were interested whether there was an impact of the chiral proline part of the molecule.

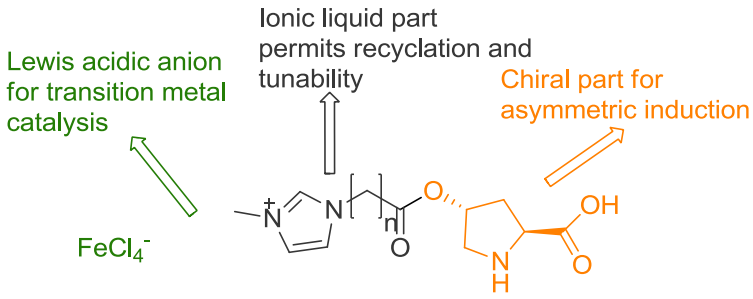


Figure 30: Bifunctional ionic liquid catalyst

The proximity of two stereo centres to the catalytically active transition metal is proposed to introduce chirality to the product. To examine this effect on hydroxymethylation, various iron-containing chiral ionic liquids can be used. Starting from proline **22** and *trans*-4-hydroxyproline **25** a set of iron containing chiral catalysts shown in Figure 31 was designed and synthesised.

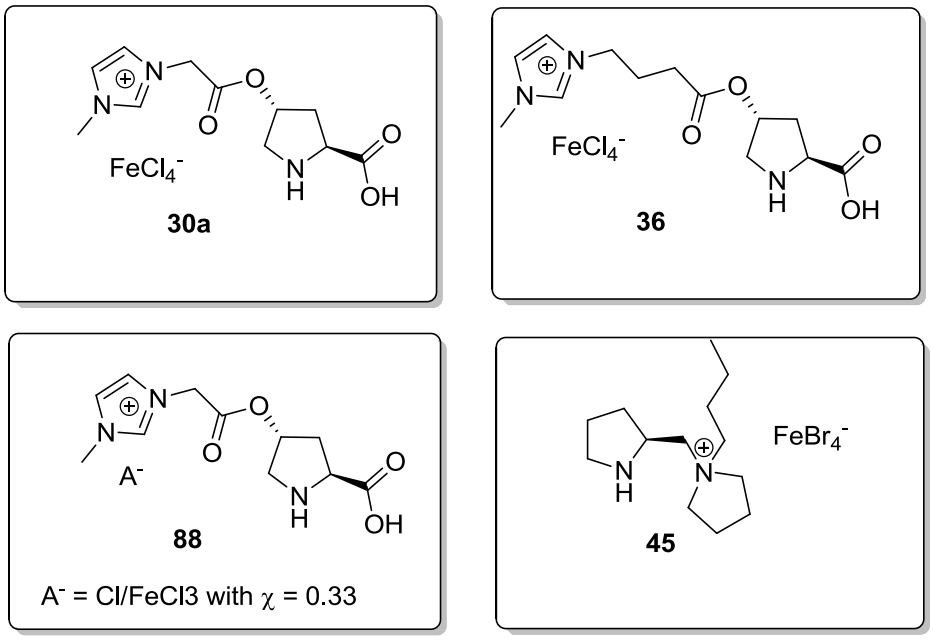
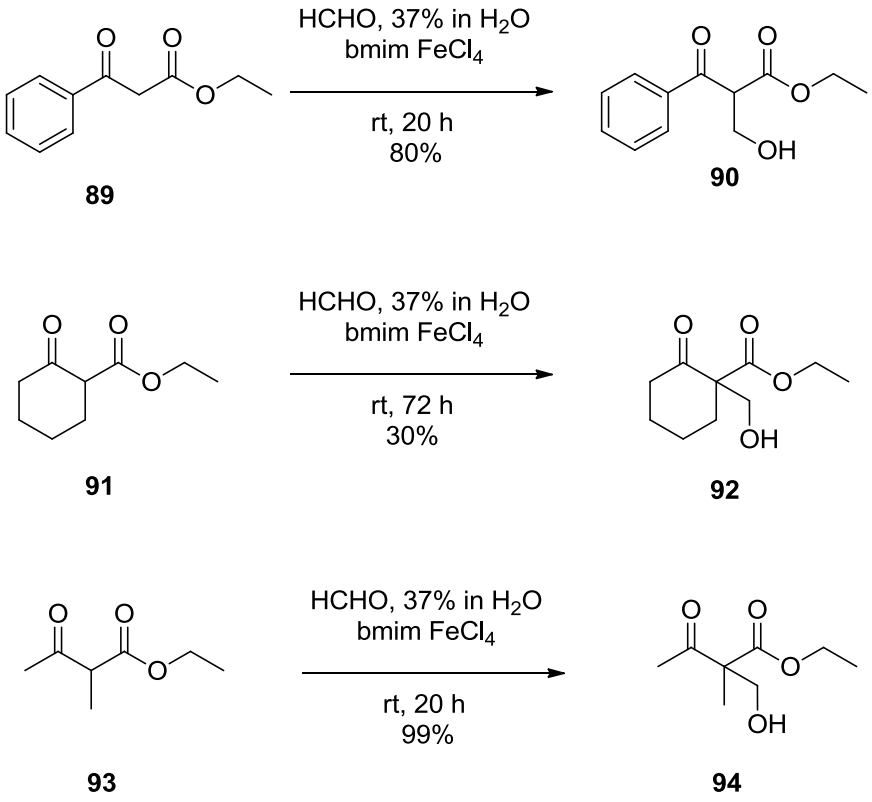


Figure 31: Iron containing CIL catalysts

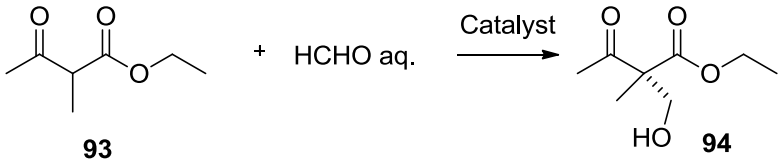
The designed CILs can induce chirality with the cationic part, whereas the metal containing anion can act as transition metal catalyst.

At the beginning of this study a racemic version of hydroxymethylation using [C4mim]FeCl4 as catalyst was investigated to find a suitable substrate for further investigations and to optimise reaction conditions (Scheme 50).



Scheme 50: Racemic hydroxymethylations with various substrates

Ketoester **93** showed best conversion and was used for further investigations. The metal containing CILs depicted in Figure 31 were used as catalysts in 1 mol% and 5 mol%, respectively.



Scheme 51: Enantioselective hydroxymethylation

Immediately after addition of the catalyst to the substrate the dark red colour of the Fe(III)-ato complex occurred. Complete conversion could be easily recognised by a colour change from dark purple to a clear yellow solution that was caused by the alkylated species and the Fe(III) salt. Reactions worked extremely satisfying with respect to yield. With 1 mol% catalyst, yields between 87% and 98% were obtained, whereas 5 mol% FeCIL gave over 98% of the product in all experiments.

Table 17: Asymmetric hydroxymethylation catalysed with bifunctional CILs

entry	catalyst	conditions	yield [%] [a]	ee [%] [b]
1	**30a**	1 mol% catalyst, rt, 18 h, ketoester first	87	3
2	**36**	1 mol% catalyst, rt, 18 h, ketoester first	86	2
3	**45**	1 mol% catalyst, rt, 18 h, ketoester first	82	2
4	**30a**	5 mol% catalyst, rt, 18 h, ketoester first	99	3
5	**36**	5 mol% catalyst, rt, 18 h, ketoester first	98	3
6	**45**	5 mol% catalyst, rt, 18 h, ketoester first	97	3
7	**36**	1 mol% catalyst, rt, 18 h, HCHO first	81	4
8	**36**	1 mol% catalyst, 0 °C, 18 h, HCHO first	68	4
9	**36**	1 mol% catalyst, 0 °C, 60 h, 5 eq HCHO	81	3
10	**36**	1 mol% catalyst, 0 °C, 18 h, ketoester first	70	4
11	**36**	1 mol% catalyst, rt, 18 h, HCHO first	100	3
12	**36**	1 mol% catalyst, rt, 18 h, 0.5 mL dioxane	94	3
13	**36**	1 mol% catalyst, rt, 48 h, 0.5 mL toluene	99	6
14	**36**	1 mol% catalyst, rt, 48 h, 0.5 mL DIPE	100	2
15	**36**	1 mol% catalyst, 0 °C, 18 h, 0.5 mL dioxane	65	2
16	**36**	1 mol% catalyst, 0 °C, 48 h, 0.5 mL toluene	99	3
17	**36**	1 mol% catalyst, 0 °C, 48 h, 0.5 mL DIPE	59	4

All reactions were performed with 1 mmol ketoester **93**, 0.1 mmol catalyst, 6 eq. HCHO at rt or 0 °C for 18 hrs. [a] Isolated yield of **94** after chromatographic purification (LP:Et_2O 1:1). [b] Determined *via* chiral GC.

Table 17 shows obtained results. No enantioselectivities could be observed with any applied catalytic system. Increasing the amount of IL did slightly improve yield without having any effect on enantioselectivity (Table 17, entry 4-6). Decreasing reaction temperature from rt to 0 °C had a negative effect on yield which dropped to 70% because of a slower reaction rate (Table 17, entry 8, 10). Enhancing reaction time from 18 h to 60 h could compensate this fact (Table 17, entry 9). Regrettable in all experiments no influence on enantioselectivity could be observed. Modifying reaction conditions by adding formaldehyde solution first to facilitate better interaction of the proline N and the carbonyl of the aldehyde also showed no significant effect on enantioselectivity. According to literature,[71] toluene, DIPE or dioxane as cosolvent was added, but addition of organic solvent to the reaction mixture to improve solubility of ketoester did not show significant impact on chiral induction to the product formation. With water immiscible toluene and DIPE had a negative influence on reaction time and yield, but as already mentioned no effect on enantioselectivity.

Obtained results soon led to the presumption that no influence of the chiral part of the catalyst took place in the reaction. Using $FeCl_3$ and proline **22** in different ratios or CILs with substoichiometric amount of $FeCl_3$ **88** should answer the question, whether there is a domineering effect. Results are summarised in Table 18.

Table 18: Hydroxymethylations with different ratios of Fe-salt and chiral catalyst

entry	catalyst	amount of catalyst	yield % [a]	ee % [b]
1	$FeCl_3$, **25**	10 mol% each	81	2
2	$FeCl_3$, **25**	5 mol% Fe salt 10 mol% proline	79	3
3	$FeCl_3$, **22**	10 mol% each	99	4
4	$FeCl_3$, **22**	5 mol% Fe salt 10 mol% proline	99	4
5	**88**	10 mol%	75	4

entry	catalyst	amount of catalyst	yield % [a]	ee % [b]
6	**88**	20 mol%	80	4
7[c]	**30b**	10 mol%	57	3
8[c]	**29**	20 mol%	35	5

All reactions were performed with 1 mmol ketoester **93**, 0.1 mmol catalyst, 6 eq. HCHO at rt for 18 hrs. [a] Isolated yield of **94** after chromatographic purification (LP:Et_2O 1:1). [b] Determined *via* chiral GC. [c] Reaction time was 60 h.

Equimolar amounts of $FeCl_3$ and proline **22** respectively hydroxyproline **25** as expected led to the same results as described above – excellent yield and poor enantioselectivity, showing the catalytic activation *via* the ato complex but no chiral induction. A bisection of the amount of iron salt with an unchanged amount of chiral catalyst gave similar results (Table 18, entry 2, 4). As expected, the same fact was noticed when CILs with a substoichiometric iron content **88** where synthesised and applied as catalyst. All these results confirmed that there is no impact of the chiral part of the molecule during the reaction.

It is supposed that after formation of the Fe(III)-ato complex the formaldehyde is activated by the Lewis acid. Lewis acidic activation also functions with other transition metals. When the metal was changed from iron to copper (**30b,** Table 18, entry 7), yield dropped to 57% without any effect on enantioselectivity indicating again no impact of the cationic part of the catalyst.

Results and proposed mechanism soon clarified that our concept of an additional impact of the chiral part of the catalyst did not lead to the requested results in asymmetric hydroxymethylation. Due to the fact that there was no effect of the chiral cation of CILs observed, it was desisted from further investigations with iron containing ILs and the proline derived precursor ILs **29** and **36** were used in other asymmetric reactions.

3.2.4 Asymmetric α-alkylation of aldehydes – combination of transition metal catalysis and organocatalysis

An aspect of this thesis was the combination of organocatalysis and transition metal catalysis using chiral ionic liquids to introduce chirality to the product. During the last years, challenging synthetic problems could be solved by the fusion of these two catalytic concepts. Inspired by the double catalytic cycle of the reaction described in literature[130] and some promising results of enantioselective test reactions by the authors, this kind of alkylation was chosen to prove the scope of our proline derived chiral ionic liquids synthesised so far. Although chiral ionic liquids gained ground in a great variety of organocatalytic reactions by taking advantage of the intrinsic properties of ionic liquids, only few examples using ILs in alkylations have been reported up to now.[220] While the combination of the two powerful concepts of electrophilicity and nucleophilicity with enamine catalysis was successfully used in alkylation reaction with $InBr_3$ as co-catalyst,[221] we restricted our approach to the use of $Pd(PPh_3)_4$ as metal source. According to literature[130] the described double catalytic reaction started with an *in situ* generation of an enamine intermediate. Ibrahem and Cordova suggested in their mechanism of the reaction that this enamine intermediate performs a subsequent attack on the catalytically generated electrophilic Pd-π-complex of the allyl species to form a C-C bond.[130] Reductive elimination and hydrolysis regenerates the Pd^0 as well as the organocatalyst to give the α-alkylated product of the aldehyde. A scheme of the suggested mechanism of the reaction according to Cordova is shown in Figure 32.[130] The transition metal catalytic cycle starts down to the right with the Pd^0 species marked with an arrow. Addition of allyl acetate forms an electrophilic Pd-π-allyl complex **I**. On the other hand, organocatalysis starts top left with *in situ* enamine **II** formation. The enamine intermediate attacks the π-allylic system to give an iminium intermediate **III** which releases the α-alkylated aldehyde **IV** and regenerates after reductive elimination and

[220] Zhang, L.; Cui, L.; Li, X.; Li, J.; Luo, S.; Cheng, J.P. *Eur. J. Org. Chem.* **2010**, 4876.
[221] Capdevilla, M.G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P.G. *Chem. Eur. J.* **2010**, *16*, 11237.

hydrolysis the Pd^0 as well as the organocatalyst, now available for the next catalytic cycle.

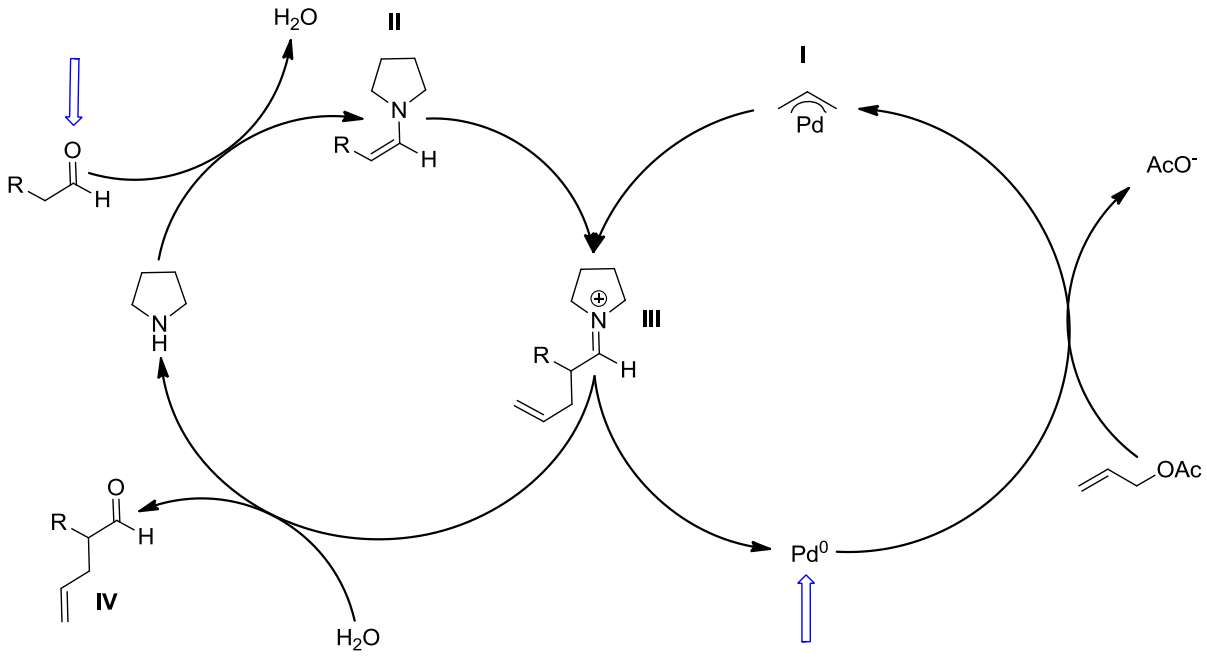


Figure 32: Reaction mechanism of double catalysed alkylation of aldehydes

Achiral experiments with pyrrolidine as organocatalyst showed extremely satisfying results.[130] Encouraged by recently published results of the Cordova group[135] we decided to go one step further and to use proline derived CILs not only to catalyse the reaction but also to introduce chirality to the product. Chiral secondary amines provide an asymmetric surrounding and therefore favour the formation of one enantiomer.

An advantage of CILs could be once more the recyclability of ionic liquids. Phenylacetaldehyde **95** was used as model substance. To optimise the reaction conditions, pyrrolidine was used as organocatalyst and $DMSO_{d6}$ was used as solvent. The reaction mixture was monitored *via* NMR spectroscopy. Reactions were carried out under inert atmosphere in water free solvent. After addition of all reagents the mixture was stirred for 30 minutes at room temperature until a clear solution was obtained, and then NMR measurement was sterted. As the aldehyde **95** was applied in threefold excess, the protons of the allyl acetate **96** were used to monitor conversion. NMR monitoring of the reaction catalysed with pyrrolidine clearly showed partial conversion after the first 30 min. and full conversion after 18 hours as

shown in Figure 33. When alkylation of the α-position of the aldehyde occurred, upfield shift of olefinic protons from 6-5.5 ppm in allyl acetate to 5.5 -5 ppm in alkylated aldehyde **97** can be observed. Simultaneously the strong upfield shift of the doublet of CH_2 protons of allyl acetate from 4.5 ppm to 2.3 gives a clear indication of reaction conversion.

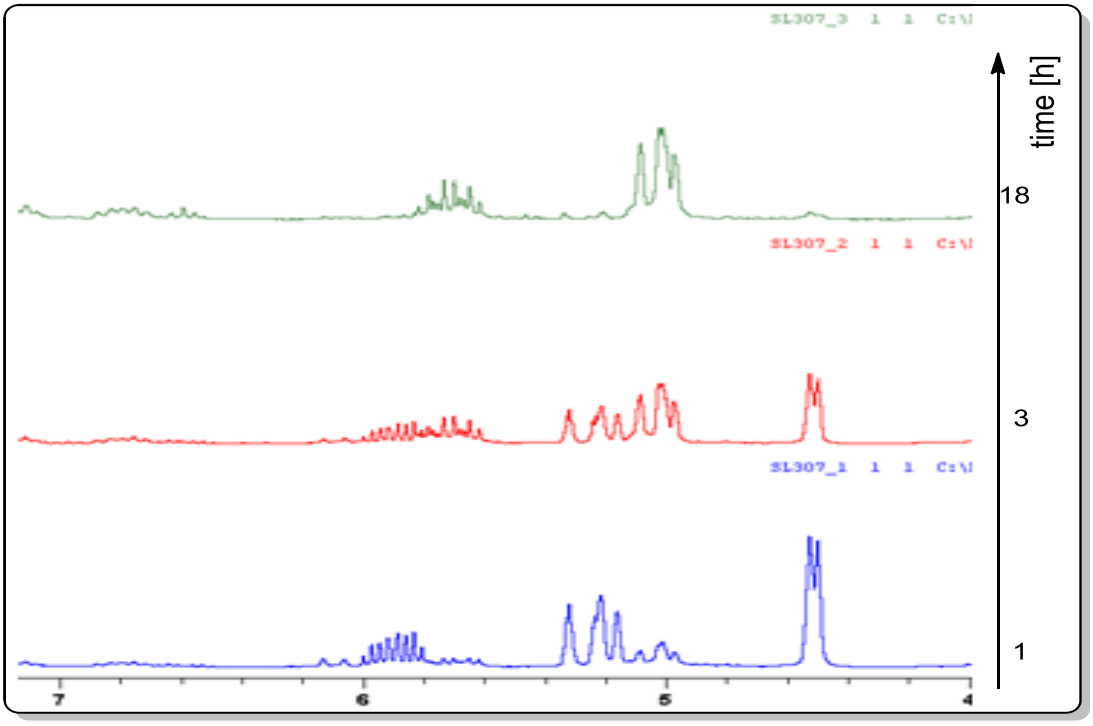


Figure 33: Reaction progress of an achiral α-alkylation of an aldehyde with allyl acetate **96**. The spectrum at the bottom shows the reaction mixture 30 minutes after addition of allyl acetate. The spectrum on the top shows full conversion.

To prevent racemisation of the enolizable product **97** a subsequent reduction with $NaBH_4$ to the corresponding alcohol **98**, shown in Figure 34, was attached before workup.

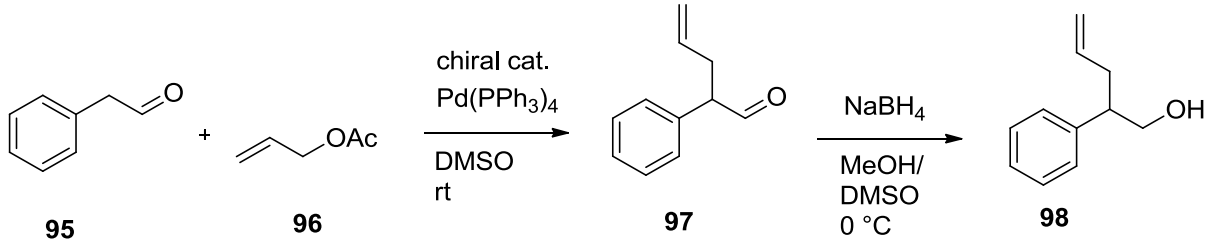


Figure 34: α-Alkylation of phenylacetaldehyde **95** with subsequent reduction

Preliminary experiments with pyrrolidine showed extremely satisfying results encouraging us to try the reaction with our ionic liquids. Cordova reported the asymmetric alkylation of phenyl propane aldehyde catalysed with proline derivatives in moderate yields and moderate enantioselectivities.[130]

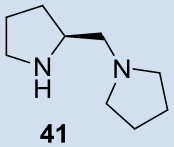
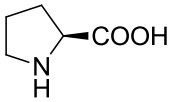
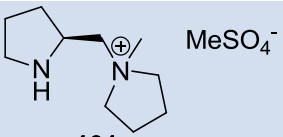
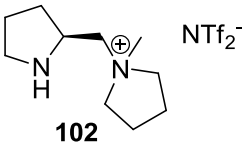
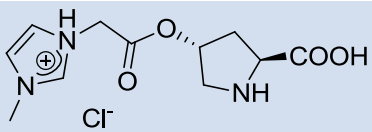
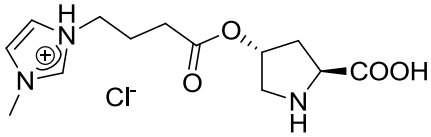
Although pyrrolidine catalysed reactions showed full conversion within 18 h, no significant conversion was observed with several chiral ionic liquids within 60 h (Table 19, entry 5-10). Additionally the obtained products after reduction with $NaBH_4$ showed no enantioselectivity. In addition to the synthesised organocatalytic ionic liquids **29** and **36**, other chiral organocatalytic active ionic liquids provided by M. Vasiloiu **99-102**[196] were applied showing again no catalytic activity in alkylation reaction. To test whether the disappointing conversion was due to the ionic liquid functionality of the catalysts, experiments with IL precursors **22** and **41** were performed. *L*-proline and (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine as catalysts again showed conversions over 90% within 18 h, but enantioselectivity remained low. These results indicated that the charged groups of the ionic liquids could be responsible for the low catalytic activity in the reaction – they supposable interfere with the catalytic activity of the Pd^0 preventing formation of the Pd-π-allyl complex. All obtained results were depicted in Table 19.

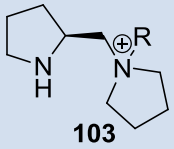
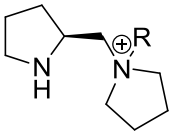
The disappointing enantioselectivity of all experiments could be an indication for a strong electrophilicity of the Pd-π-allyl complex, which can not only be attacked by an enamine but by an enol as well. In that case the transition metal catalysis would have a stronger impact on the reaction mechanism and enantioselectivity remains low under the chosen conditions.

In a recently published work the Cordova group modified former reaction conditions to improve enantioselectivity.[135] Solvent seemed to have a great influence on the reported α-alkylation. The highest reactivity was achieved in DMSO, whereas the highest enantioselectivity was obtained in DMF. Whith optimised conditions (DMSO:DMF 1:1) they were able to enhance enantioselectivity of the α-alkylation catalysed with diaryl prolinol derivatives.

Due to disappointing chiral induction with our CIL precursors **22** and **41** (Table 19, entry 3, 4) and the fact that CILs were not suitable to catalyse the reaction at all, resulting in yields clearly lower than 10% which was unlike than anticipated, it was desisted from further investigations on the reaction with the designed catalytic systems.

Table 19: Asymmetric α-alkylation of 2-phenylacetaldehyde **95**

entry	catalyst	conversion [%][a]	*ee* [%][b]
1	pyrrolidine	>90%, 45%[c]	-
2	pyrrolidine	>90%, 68%[c]	-
3	 **41**	>90%, 80%[c]	rac
4	 **22**	>90%	rac
5[d]	 **101**	<10%	rac
6[d]	 **102**	<10%	rac
7[d]	 **29**	<10%	n.d.
8[d]	 **36**	<10%	rac

entry	catalyst	conversion [%][a]	*ee* [%][b]
9[d]	 **103**	<10%	rac
10[d]	 **104**	<10%	rac

All reactions were performed with 0.5 mmol allyl acetate **96**, 1.5 mmol phenylacetaldehyde **95**, 0.025 mmol $Pd(PPh_3)_4$, 0.05 mmol pyrrolidine or 0.1 mmol chiral catalyst in 2 mL DMSO d_6 for 24 hrs. [a] Conversion determined via NMR-quantification. [b] Determined by HPLC using a DAICEL Chiralpak IB column. [c] Isolated yield of alcohol after reduction with $NaBH_4$, standard workup and flash chromatography (LP:EA 7:1). [d] Reaction time was 60 h.

4 Summary and Conclusion

4.1 Chiral coordinating ionic liquid – synthesis and application

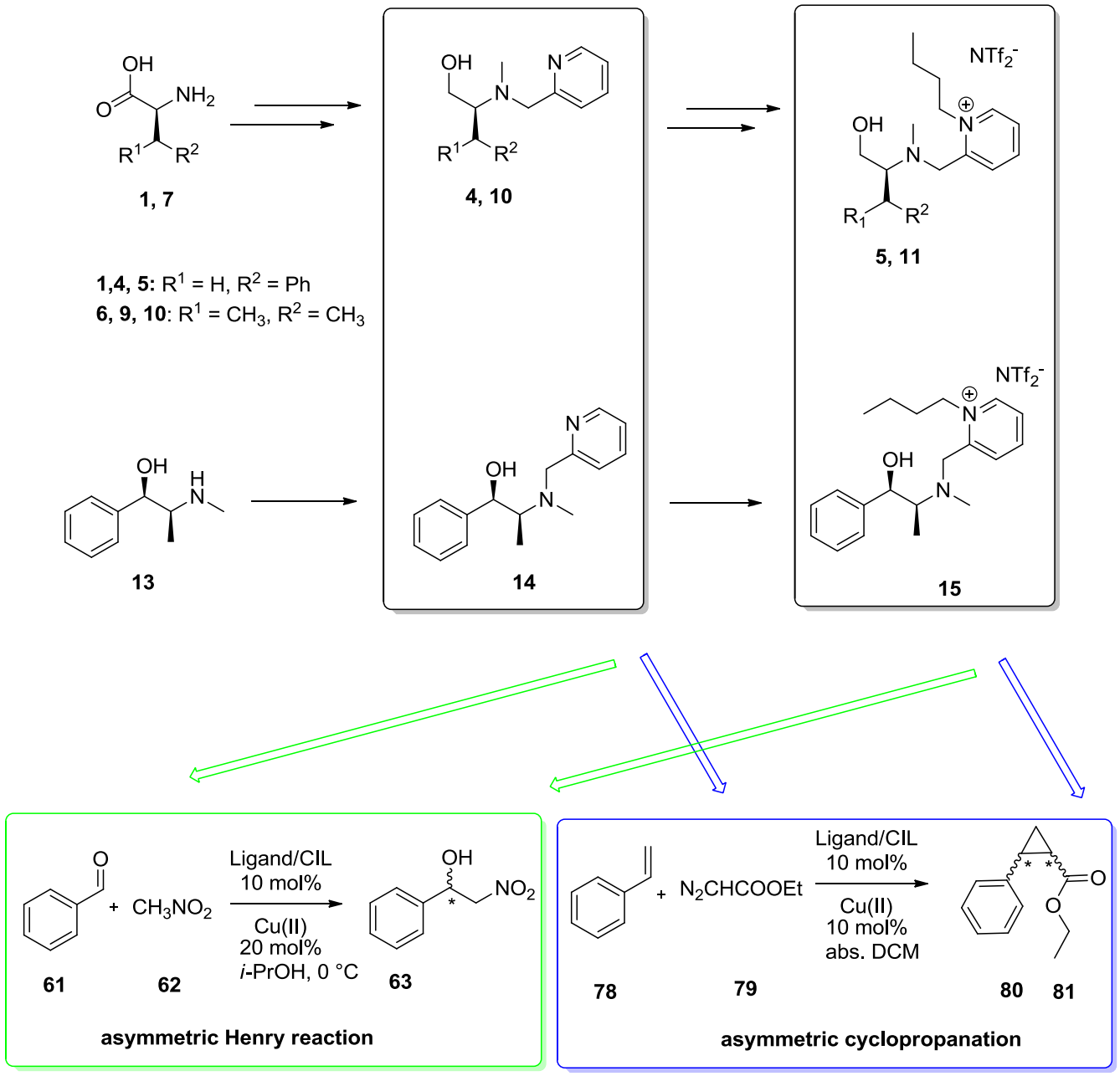


Figure 35: Amino alcohol functionalised ionic liquids and their application

A set of 12 chiral catalysts, six tridentate ligands and their corresponding ionic liquids derived from valine, phenylalanine and ephedrine containing an amino alcohol functionality in combination with a pyridinium residue substituted in position 2 or -3 were synthesised and fully characterised. The application of these

chiral amino alcohol catalysts in asymmetric C-C bond forming reactions was investigated and results were discussed.

4.1.1 Summarising asymmetric Henry reaction

The chiral amino alcohol functionalised ligands and ionic liquids worked as catalysts in asymmetric Henry reaction. In single reactions good yields and enantioselectivities up to 80% could be obtained.

Extensive optimisation of reaction conditions including solvent effects, kinetic resolution or the influence of added base had been carried out. In preliminary experiments $Cu(OAc)_2$ as source of copper succeeded concerning both yield and enantioselectivity. Furthermore it could be presented that the amount of $Cu(OAc)_2$ with respective to the amount of chiral catalyst had an influence on the reaction. While in reactions catalysed with ligands or ionic liquids containing a substituent in position 2 of the pyridine equimolar amounts of catalyst and copper succeeded, in reaction with catalysts containing a in position 3 substituted pyridine the double amount of copper showed better performance and led to enhanced yields and enantioselectivities in all cases. This indicates an incorporation of the second equivalent of copper into the catalytically active species, which exact structure has not been confirmed yet.

Different absolute configurations of Henry products were obtained with ligands on the one hand or ionic liquids on the other hand. This reverse of selectivity is seldom observed and indicates different catalytically active species in the transition state - depending on, whether chiral amino alcohol functionalised ligands or ionic liquids were used to catalyse the reaction. Low yields obtained with our chiral ionic liquid catalysts could be explained by an interference of the catalytic activity of the copper by the ionic liquid.

Summing up all results, novel chiral catalysts were synthesised, suitable in asymmetric Henry reaction to introduce chirality; although *ee* values in single reactions remained lower than reported in literature. Great efforts are made to obtain

crystal structures of the complexes to get more insight in the structure of the transition state and to explain all interesting observations.

Due to limitations of ionic liquid catalysts resulting in low yields the further use of coordinating ionic liquids in combination with Cu(II) is not to be followed for Henry reaction in the future. At least, successful recovering of the ionic liquid catalyst should be ensured to be beneficial.

4.1.2 Summarising asymmetric cyclopropanation

The chiral amino alcohol functionalised ligands and ionic liquids worked as catalysts in asymmetric cyclopropanation. Obtained diastereoselectivities with both, $Cu(OAc)_2$ and $Cu(OTf)_2$ as source of copper were comparable to literature values. Ratios between *cis* and *trans* isomers of 30:70 could be obtained. Yields were good to excellent in all screened reactions. Interesting to mention is the fact that unwanted side reactions did not occur when chiral ionic liquids were used to catalyse the reaction. While the combination of $Cu(OTf)_2$ and ligands also showed no by-product, a cyclic triester **84** was formed when ligands in combination with $Cu(OAc)_2$ were applied as catalyst, resulting in lower yields.

Unfortunately enantioselectivity in all reactions was rather low.

A change of the oxidation state of the copper from Cu(II) to Cu(I) using phenyl hydrazine as *in situ* reducing agent and a decrease of temperature to 0 °C did not improve enantioselectivity. The synthesised amino alcohol functionalised catalysts showing good results in diethyl zinc alkylation[37] and Henry reaction were not suitable to introduce chirality in cyclopropanation. Therefore the application of these ligands and ionic liquids will not be followed in the future.

Summing up, the obtained results show again that there is no universal catalyst and each reaction needs a proper, well designed catalyst, which is also true for ionic liquid catalysts.

4.2 Chiral organocatalytic ionic liquids – synthesis and application

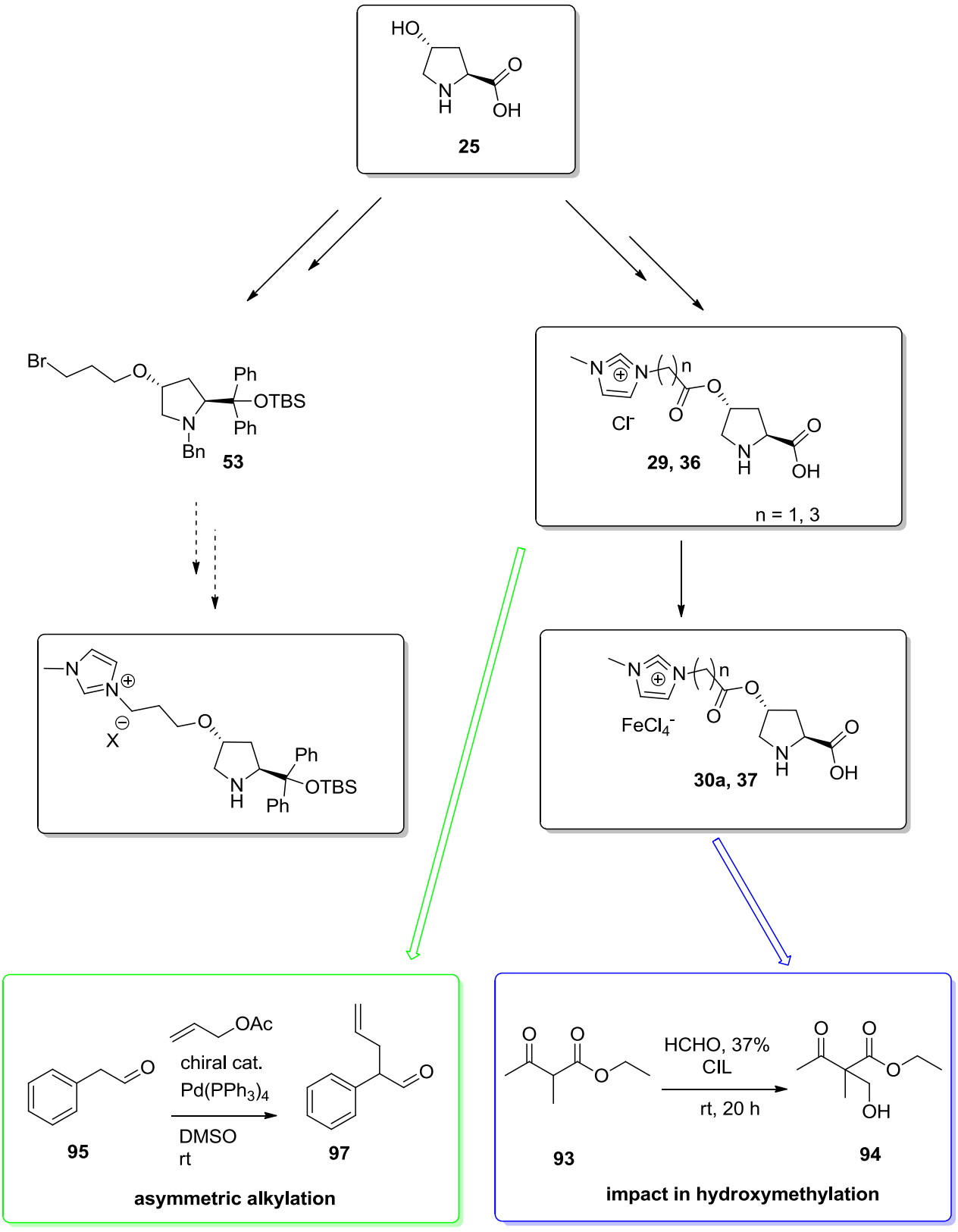


Figure 36: Synthesis and application of organocatalytic ionic liquids starting from *trans*-4-hydroxyproline

Starting from chiral pool derived *trans*-4-hydroxyproline, chiral ionic liquids bearing a secondary amine for imine-enamine activation were designed and synthesised. The chiral part of the molecule was connected *via* an ester or an ether spacer to an imidazolium moiety. While the chiral secondary amine should promote chiral discrimination during the reaction, the ionic liquid part offers the possibility for recyclation. The designed chiral ionic liquids should function as organocatalysts in asymmetric alkylation reactions:

- Ionic liquid precursor *L*-proline showed quantitative conversion in asymmetric α-alkylation and product could be obtained in 80% yield – but in a racemic form. All screened ionic liquids showed no catalytic activity in this reaction resulting in conversions below 10%, even when reaction time was increased to 72 h and more. It is presumed that the ionic liquids interfered with the catalytic activity of the transition metal. Therefore further optimisation to enhance enantioselectivity rendered pointless.
- Furthermore the ionic liquids **29** and **36** as well as their corresponding tetrachloro-ferrates were applied in hydroxymethylation to examine a possible impact of the chiral part. The presented results clearly showed no significant chiral induction indicating no activation of the aldehyde *via* the chiral secondary amine. On the contrary it is supposed that after formation of the Fe(III)-ato complex an exchange of ligands leads to a coordination of the formaldehyde to the Fe and even if there were an activation of the formaldehyde by the amine, this species had no influence on the catalytic cycle of the reaction.
- An ionic liquid was designed to catalyse asymmetric Michael addition *via* an organocatalytic imine-enamine activation of the Michael acceptor. Additionally a basic anion should enhance nucleophilicity of the Michael donor. What was planned as a straight forward five-step synthesis turned out to be challenging in some points and the whole synthetic approach has been adapted twice, finally ending up in a 10 step synthetic strategy to obtain the desired ionic liquid. Due to this fact and the resulting lack of time the synthesis could not be completed yet, although being in an advanced stage.

5 Outlook

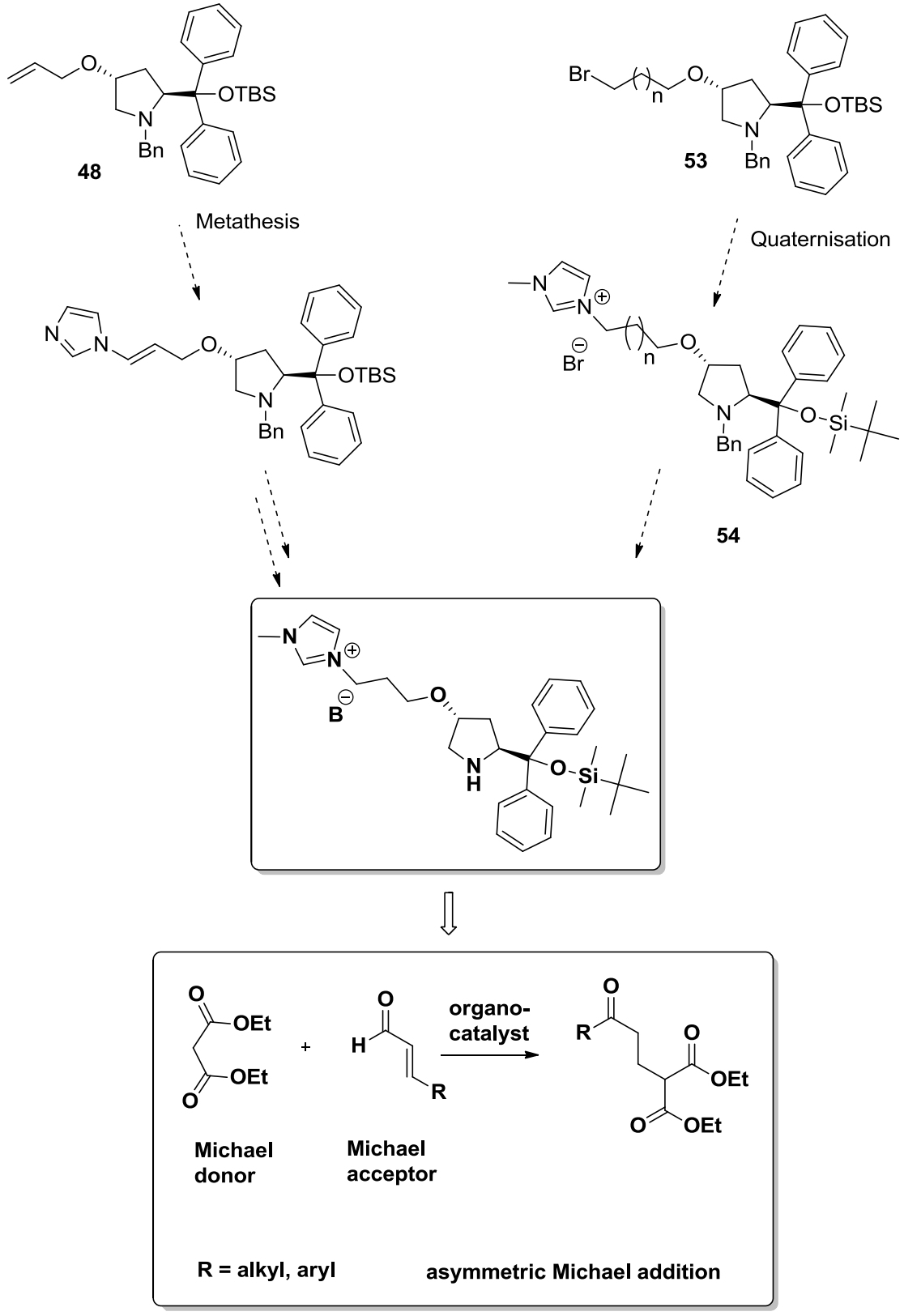
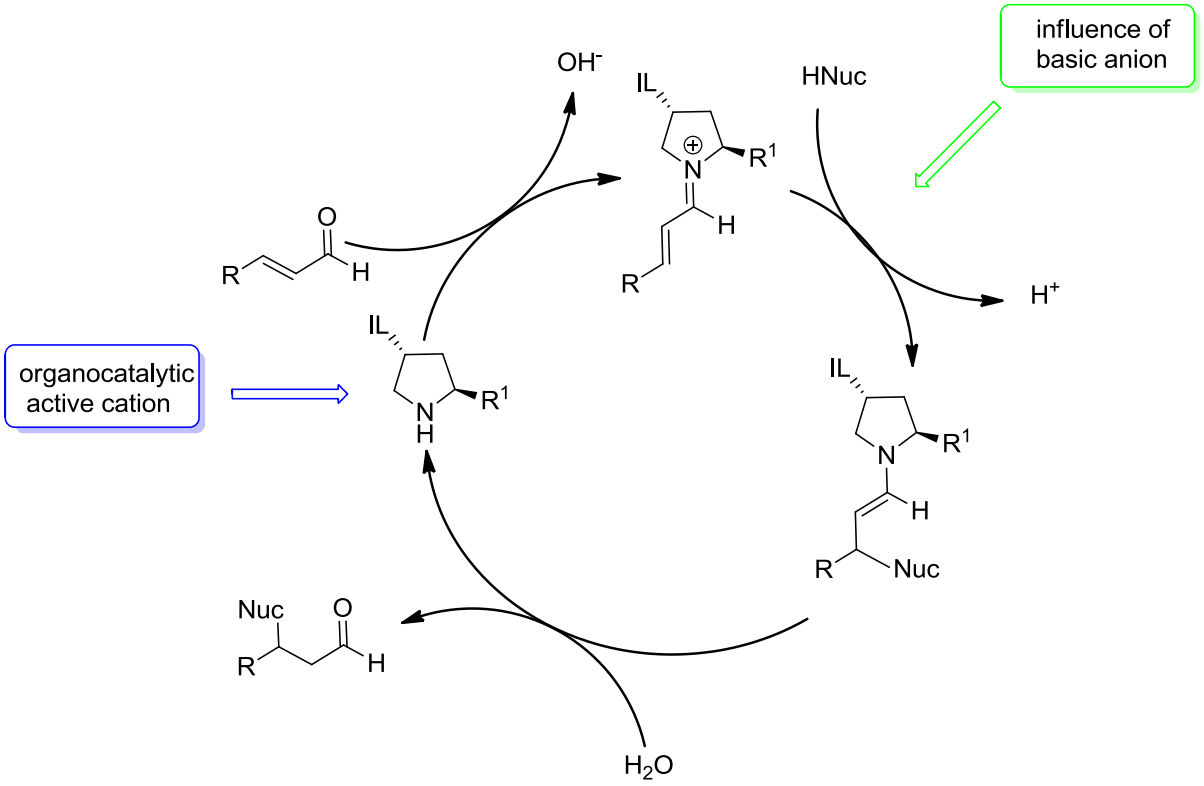


Figure 37: Synthetic approach to organocatalytic CIL and application in asymmetric Michael addition

Completion of the synthesis of bifunctional ionic liquid would be interesting. The possibilities and catalysts for olefin metathesis have not been exhausted yet and there are many unexploited alternatives, which lack of time rendered impossible in this thesis. Otherwise an introduction of a longer spacer chain to prevent intramolecular ring closure would be a possibility to achieve classical quaternisation of the bromide.

The desired ionic liquid with its basic anion would be able to work as bifunctional organocatalyst in asymmetric Michael addition, promoting formation of a nucleophile from a malonic ester on the one hand and introducing chirality *via* an organocatalytic imine-enamine activation of the Michael acceptor.

The carefully designed structure of the ionic liquid should facilitate outstanding results in Michael addition. The introduction of a siloxy group into the proline structure should lead to an increase in catalytic activity and the sterically demanding phenyl rings are reported to enhance enantioselectivity in similar reactions.



Scheme 52: Imine enamine catalytic cycle of organocatalysed Michael addition

6 Experimental part

6.1 Materials and methods

General: Commercially available reagents and solvents were used as received from the supplier unless otherwise specified. Diethyl ether, light petrol (60-80 °C fraction), ethyl acetate and dichloromethane were distilled prior to use. If reactions were carried out under argon atmosphere, all glassware was either flame-dried or oven-dried at 110°C and assembled while still hot.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz or on a Bruker AC 400 at 400 and 100 MHz, resp., using the solvent peak or TMS as reference. ^{13}C NMR spectra were run in proton-decoupled mode and multiplicities from APT were referred as s (singlet), d (doublet), t (triplet) and q (quartet). Multiplicities of ^{1}H signals were referred to as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

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

TLC-analysis was done with precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck). Compounds were visualised by submerging in a basic potassium peroxide solution and heating or by submerging in an acidic phosphomolybdic acid/ceric sulphate solution and heating. Vacuum flash chromatography (VFC) was carried out with silica gel Merck 60.

Melting points of crystalline compounds were determined with a Kofler hot-stage apparatus or an automated melting point system OPTI MELT of Stanford Research Systems and are uncorrected.

Specific rotations were measured on an Anton Parr MCP 500 polarimeter.

Elemental analysis was carried out at Vienna University, Department of Physicochemistry - Laboratory for Microanalysis, Währinger Str. 42, A-1090 Vienna.

HPLC analysis was performed on Thermo Finnigan Surveyor chromatograph with a PDA plus detector (190-360 nm). DAICEL Chiralpak AS-H column (250 × 4.60 mm) or DAICEL Chiralpak IA column (250 × 4.60 mm) or DAICEL Chiralpak IB column

(250 × 4.60 mm) was used as stationary phase with *n*-heptane/*i*-propanol as solvent and a flow of 0.5 -1.0 ml/min; PDA detection at 230 and 210 nm.

GC–MS analyses were conducted on a VOYAGER Quadrupol (Thermo Finnigan) directly interfaced to a GC 8000 TOP gas chromatograph using a BGB-5 (30 m × 0.32 mm i.d., 1.0 μm 5 film thickness) cross-bonded dimethyl polysiloxane capillary column. The oven program temperature was 80 °C (2 min)//10 °C/min//280 °C (3 min). Source and transfer line temperatures were set at 200 and 280 °C, resp.

TLC/MS analyses were analysed on a Bruker Esquire HTC ion trap mass spectrometer equipped with a camag TLC-MS interface.

HPLC-HR/MS were measured at Vienna University of Technology, Institute of Chemical Technology and Analytics by Prof. Erwin Rosenberg. Samples were dissolved in CH_3CN or CH_3OH and measured with a LC-IT-TOF-MS, EI, APCI in positive- and negative-ion-mode.

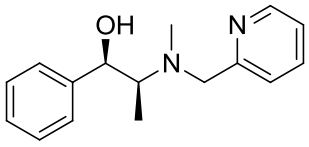
Shimadzu Prominence HPLC, equipped with DGU-20 A3, 2 x LC-20AD, SIL-20A, CTO-20AC, CBM-20A, SPD-M20A. MS System: Shimadzu IT-TOF-MS with Electrospray-Interface. Chromatographic parameters: Short_Col_MS_PI_NI_12 min.lcm: Phenomenex Kinetex ODS (3), 30 mm x 4.6 mm, 2.6 μm Core Shell-Particle. *MS* parameters: auto tune, 100-1000 amu for MS (PI und NI)-detection. ES ionisation. Cycle time <0.6 s. CDL-Temp.: 200°C. Heating block Temp.: 200°C. DAD parameters: 200-400 nm, datarate: 1.5 Hz.

Thermo gravimetrical Analysis (TGA): thermal stabilities were conducted on a Netzsch TGA/DSC in a range of -100 to 150 °C with a heating rate of 5 °C/min.

6.3 Coordinating amino alcohol functionalised ionic liquids

6.3.1 (1*R*,2*S*)-2-[Methyl[(pyridin-2-yl)methyl]amino]-1phenylpropan-1-ol

To a suspension of commercial available (1*R*,2*S*)-ephedrine **13** (9.78 g, 59,6 mmol) and freshly activated molecular sieve 4 Å (22 g) in 220 mL abs. MeOH pyridine-2-carboxaldehyde (6.38 g, 59.6 mmol) was added drop wise. The reaction mixture was refluxed for 3 or 4 days until TLC showed complete conversion. The mixture was filtrated over celite to remove the molecular sieve and acetic acid (18 g, 300 mmol) and $NaCNBH_3$ (11.34 g, 180 mmol) were added to the solution of the oxazolidine intermediate. The mixture was again stirred over night at room temperature. Solid $NaHCO_3$ (40 g) was added and the mixture was allowed to rest for 2 hours. Methanol was removed under reduced pressure and EA 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 flash chromatography (CH_2Cl_2 : MeOH 20:1 + Et_3N) to yield 9.03 g (35.2 mmol, 59%) light yellow oil.



14

$C_{16}H_{20}N_2O$
256.34 g/mol

r_f = 0.35 (CH_2Cl_2:MeOH 20 : 1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = -36.474 (CH_2Cl_2, c = 0.38)

IR: ν = 3059 cm^{-1}, 2971 cm^{-1}, 2324 cm^{-1}, 2171 cm^{-1}, 1737 cm^{-1}, 1594 cm^{-1}, 1475 cm^{-1}, 1449 cm^{-1}, 1435 cm^{-1}, 1366 cm^{-1}, 1120 cm^{-1}, 1045 cm^{-1}, 892 cm^{-1}, 756 cm^{-1}

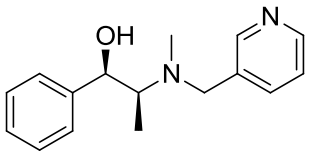
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.45 (d, 1H, *J* = 4.86 Hz), 7.53 (t, 1H, *J* = 7.63 Hz), 7.34-7.01 (m, 7H), 4.83 (d, 1H, *J* = 4.18 Hz), 4.67 (bs, 1H, OH), 3.56 (q, 2H, *J* 0 14.15 Hz), 2.91 (m, 1H), 2.22 (s, 3H), 0.93 (d, 3H, *J* = 6.65 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.1 (d), 142.8 (s), 136.7 (d), 133.5 (s), 127.9 8d, 2C), 126.8 (d), 126.2 (d, 2C), 122.9 (d), 122.1 (d), 73.9 (d), 64.3 (d), 59.6 (t), 39.8 (q), 9.5 (q)

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.63, H, 7.55, N, 10.92

6.3.2 (1*R*,2*S*)-2-[Methyl[(pyridin-3-yl)methyl]amino]-1-phenylpropan-1-ol

According to procedure 6.3.1, pyridine-3-carboxaldehyd (0.49 g, 4.5 mmol) was added to a suspension of (1*R*,2*S*)-ephedrine **13** (0.76 g, 4,6 mmol) and activated 4 Å molecular sieve (2 g) in 20 mL abs. MeOH. The obtained raw product was recrystallized from EA/*n*-pentane to give colourless crystals (0.85 g, 3.35 mmol, 73%).



20

$C_{16}H_{20}N_2O$
256.34 g/mol

r_f = 0.24 (CH_2Cl_2:MeOH 20 : 1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = -20.51 (CH_2Cl_2, c = 0.135)

mp = 106-108 °C (hexane/EA)

IR: ν = 3190 cm^{-1}, 2850 cm^{-1}, 1590 cm^{-1}, 1580 cm^{-1}, 1450 cm^{-1}, 1430 cm^{-1}, 1027 cm^{-1}, 704 cm^{-1}

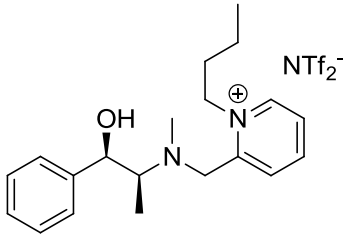
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.43 (dd, 1H, *J* = 4.69 Hz, *J* = 1.56 Hz), 8.35 (d, 1H), 7.43 (d, 1H, *J* = 7.82 Hz), 7.32 (m, 5H), 7.17 (dd, 1H), 4.83 (d, 1H, *J* = 5.28 Hz), 3.67 (br s, 1H, OH), 3.59 (s, 2H), 2.92 (quin., 1H, *J* = 3.02 Hz), 2.19 (s, 3H), 1.08 (d, 3H, *J* = 6.85 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.6 (d), 148.0 (d), 143.3(s), 136.2 (d), 135.0 (s), 127.9 (d), 126.9(d), 126.2 (d), 123.2 (d), 74.4 (d), 63.6 (d), 55.9 (t), 38.1 (q), 14.6 (q)

Analytical data were in accordance to literature.[222]

6.3.3 1-Butyl-2-((((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)-amino)methyl)pyridin-1-ium bis(trifluoromethansulfonyl)imid

14 (0.769 g, 3.00 mmol) and freshly distilled *n*-butyl bromide (0.615 g, 4.5 mmol) were weighted in a round bottom flask and stirred for 20 hours at 60 °C. The excess of *n*-butyl bromide was removed on a rotary evaporator and the brown residue was washed with abs. Et_2O. Remaining solvents were removed in high vacuum to yield 1.17 g (2.97 mmol) ionic liquid as brown oil which was directly used for the anionic exchange step. The bromide was dissolved in 3 mL deionised water and 3 mL acetonitrile. The solution was stirred at rt and a solution of $Li[N(CF_3SO_2)_2]$ (0.86 g, 3.00 mmol) in 2 mL deionised water was added. Immediately a second layer occurred. After 30 minutes stirring at room temperature the reaction mixture was extracted with dichloromethane. Combined organic layers were washed repeatedly with deionised water until the washing water was free of halides, which was checked by using an aqueous $AgNO_3$ solution. Organic layer was extracted with brine, dried over Na_2SO_4, filtrated and the solvent was removed under reduced pressure. Further volatiles were removed in high vacuum to give 1.57g (2.64mmol, 89%) orange brown ionic liquid.



15

$C_{22}H_{29}F_6N_3O_5S_2$
593.60 g/mol

[α]$_{589}^{20}$ = -0.743 (CH_2Cl_2, c = 0.525)

IR: ν = 2968 cm^{-1}, 1737 cm^{-1}, 1629 cm^{-1}, 1595 cm^{-1}, 1453 cm^{-1}, 1348 cm^{-1}, 1380 cm^{-1}, 1182 cm^{-1}, 1133 cm^{-1}, 1053 cm^{-1}, 895 cm^{-1}

[222] Bica, K. *PhD Thesis*, Vienna University of Technology, **2007**.

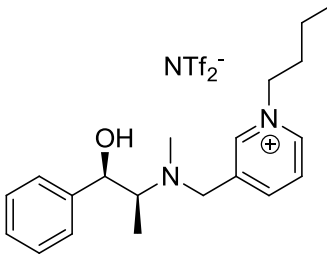
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.35 (d, 1H, *J* = 5.28 Hz), 7.92 (m, 1H), 7.69 (d, 1H, *J* = 7.4 Hz), 7.34 (d, 1H, *J* = 7.6 Hz), 7.24 (m, 5H), 4.68 (d, 1H, *J* = 6.45 Hz), 4.39-3.85 (m, 3H), 3.45 (bs, 1H, OH), 2.83 (m, 1H), 2.47 (s, 2H), 2.28 (s, 3H), 1.67 (m, 1H), 1.28 (m, 2H), 1.13 (t, 3H, *J* = 6.36 Hz), 0.89 (t, 3H, *J* = 7.24 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 152.2 (s), 149.3 (d), 144.9 (d), 143.4 (s), 137.9 (d), 129.1 (d), 128.5 (d), 127.9 (d), 127.8 (d), 126.6 (d), 125.7 (d), 119.3 (q), 75.7 (d), 64.2 (q), 57.2 (t), 54.9 (t), 38.5 (q), 32.6 (t), 19.6 (t), 13.5 (d), 9.2 (q)

Anal. Calcd. for $C_{22}H_{29}F_6N_3O_5S_2$: C, 44.51; H, 4.92; N, 7.08. Found: C, 45.18, H, 4.98, N, 7.12

6.3.4 1-Butyl-3-((((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)-amino)methyl)pyridin-1-ium bis(trifluoromethansulfonyl)imid

According to procedure 6.3.3, **20** (0.290 g, 1.10 mmol) and *n*-butyl bromide (0.3 g, 2.2 mmol) were stirred for 20 h. Removal of excessive butyl bromide gave the ionic liquid bromide as orange oil which was dissolved in water and treated with a solution of $Li[N(CF_3SO_2)_2]$ (0.47 g, 1.62 mmol) to obtain 0.56 g (0.95 mmol, 86%) light orange liquid.



21

$C_{22}H_{29}F_6N_3O_5S_2$
593.60 g/mol

[α]$_{589}^{20}$ = --14.482 (EtOH, c = 1.03)

IR: ν = 3534 cm^{-1}, 2960 cm^{-1}, 1350 cm^{-1}, 1330 cm^{-1}, 1180 cm^{-1}, 1130 cm^{-1}, 1050 cm^{-1}, 690 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.49 (d, 1H, *J* = 6.06 Hz), 7.90 (m, 2H), 7.71 (dd, J_1 = 7.53 Hz, J_2 = 6.36 Hz, 1H), 7.30 (m, 5H), 4.62 (d, 1H, *J* = 7.43 Hz), 4.29 (t, 2H, *J* = 7.63

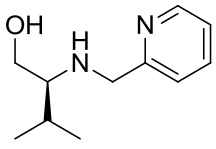
Hz), 3.79/3.77 (2d, 2H, *J* = 15.85 Hz), 2.90 (m, 1H), 2.67 (br s, 1H, OH), 2.15 (s, 3H), 1.79 (quin, 1H, *J* = 7.83 Hz), 1.28 (sext, 2H, *J* = 7.83 Hz), 1.17 (d, 3H, *J* = 6.65), 0.93 (t, 3H, *J* = 7.34 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 144.7 (d),142.9 (d), 143.8 (s), 143.1 (s), 142.3 (d), 128.3 (d), 127.7 (d), 127.4 (d), 126.7 (d), 119.5 (q), 76.0 (d), 64.3 (d), 61.9 (t), 54.7 (t), 37.6 (q), 33.2 (t), 19.1, (t), 13.2 (q), 9.4 (t)

Analytical data were in accordance to literature.[223]

6.3.5 (*S*)-3-Methyl-2-((pyridin-2-ylmethyl) amino)butan-1-ol

Valinol **8** (7.00 g, 67.8 mmol) and 20 g freshly activated molecular sieve 4Å were suspended in abs. MeOH. Using a syringe, pyridine-2-carbaldehyde (7.21 g, 67.8 mmol) was added drop wise and the reaction mixture was refluxed for 24 hours, until TLC showed complete conversion. The mixture was cooled to 0 °C followed by addition of $NaBH_4$ (2.56 g, 67.8 mmol) and stirred for one hour. Reaction was allowed to warm up to room temperature and hydrolyzed with deionised water. After addition of solid Na_2SO_4 the mixture was filtrated over celite to remove remaining molecular sieve and Na_2SO_4. Solvent was removed under reduced pressure. The obtained yellowish liquid (13.17 g, 67.6 mmol) could be used directly in the next step without further purification.



9

$C_{11}H_{18}N_2O$
194.14 g/mol

r_f = 0.09 (CH_2Cl_2:MeOH 20 : 1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = 26.358 (CH_2Cl_2, c = 1.285)

IR: ν = 3287 cm^{-1}, 2955 cm^{-1}, 1871 cm^{-1}, 1738 cm^{-1}, 1655 cm^{-1}, 1593 cm^{-1}, 1570 cm^{-1}, 1472 cm^{-1}, 1434 cm^{-1}, 1366 cm^{-1}, 1212 cm^{-1}, 1047 cm^{-1}, 895 cm^{-1}

[223] Bica, K. *PhD Thesis*, Vienna University of Technology, **2007**.

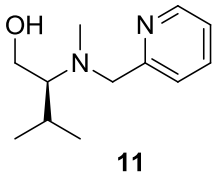
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.48 (d, 1H, *J* = 5.28 Hz), 7.58 (t, 1H, *J* = 7.63 Hz), 7.13 (d, 1H, *J* = 7.63 Hz), 6.95 (t, 1H, *J* = 6.06 Hz), 3.95 (s, 2H), 3.72, (dd, 1H), 3.38 (m, 1H), 2.89 (bs, 1H), 2.41 (q, 1H, *J* = 2.44 Hz), 1.91 (m, 1H), 0.96 (t, 6H, *J* = 7.24 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.9 (s), 151.2 (d), 139.1 (d), 125.6 (d), 125.0 (d), 66.7 (s), 63.6 (d), 54.7 (d), 31.2 (s), 21.3 (t), 20.5 (t)

Anal. Calcd. for $C_{11}H_{18}N_2O$: C, 68.01, H, 9.34, N, 14.42. Found: C, 67.53, H, 9.32, N, 13.67.

6.3.6 (*S*)-3-Methyl-2-(methyl(pyridin-2-ylmethyl)amino)butan-1-ol

Compound **9** (13 g, 68 mmol) was dissolved in 120 mL HCOOH and stirred at rt for one hour, followed by addition of 90 mL 37% aqueous HCHO-solution. The reaction mixture was refluxed over night and after complete conversion the excess of HCHO was removed under reduced pressure. The mixture was neutralised with 4 N NaOH and stirred further for three hours at rt. Workup started by extracting with CH_2Cl_2 for 3 times. Combined organic layers were extracted with saturated NaCl-solution, dried over Na_2SO_4 and remaining solvent was removed on a rotary evaporator. Chromatographical purification (CH_2Cl_2 : MeOH 15:1 + 0.2% NEt_3) of the raw material yielded yellowish oil (11.33 g, 54.4 mmol, 80%).



11

$C_{12}H_{20}N_2O$
208.30 g/mol

r_f = 0.31 (CH_2Cl_2:MeOH 20 : 1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = +2.667 (CH_2Cl_2, c = 0.38)

IR: ν = 3276 cm^{-1}, 2954 cm^{-1}, 2870 cm^{-1}, 1738 cm^{-1}, 1592 cm^{-1}, 1570 cm^{-1}, 1472 cm^{-1}, 1434 cm^{-1}, 1364 cm^{-1}, 1216 cm^{-1}, 1048 cm^{-1}, 1002 cm^{-1}, 755 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.49 (d, 1H, *J* = 4.11 Hz), 7.59 (dt, 1H, J_1 = 7.63 Hz, J_2 = 1.76 Hz), 7.13 (m, 2H), 4.95 (bs, 1H, OH), 3.89 (m, 2H), 3.61 (dd, 1H, *J* = 10.95 Hz, *J* =

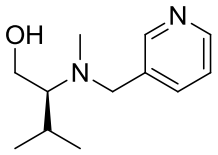
5.28 Hz), 3.32 (t, 1H, *J* = 10.56 Hz), 2.45 (m, 1H), 2.30 s, 3H), 1.80 (m, 1H), 0.98 (d, 3H, *J* = 6.65 Hz), 0,84 (d, 3H, *J* = 6.65 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 160.2 (s), 149.2 (d), 136.6 (d), 122.4 (d), 122.0 (d), 71,8 (d), 60.7 (t), 37.9 (q), 28.7 (d), 21.9 (q), 20.0 (q)

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.53, H, 9.32, N, 13.67

6.3.7 (*S*)-3-Methyl-2-(methyl(pyridin-2-ylmethyl)amino)butan-1-ol

According to procedure 6.3.5 and 6.3.6, valinol **8** (1.63 g, 15.8 mmol) was treated with pyridine-3-carbaldehyde and $NaBH_4$ and subsequently with HCHO. Chromatographical purification (CH_2Cl_2 : MeOH 30:1 + NEt_3) of the raw material yielded light yellow oil (2.27 g, 10.9 mmol, 69%).



18

$C_{12}H_{20}N_2O$
208.30 g/mol

r_f = 0.17 (CH_2Cl_2:MeOH 30 : 1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = - 19.64 (EtOH, c = 1.00)

IR: ν = 3277 cm^{-1}, 2953 cm^{-1}, 2870 cm^{-1}, 1738 cm^{-1}, 1578 cm^{-1}, 1467 cm^{-1}, 1427 cm^{-1}, 1364 cm^{-1}, 1286 cm^{-1}, 1217 cm^{-1}, 1050 cm^{-1}, 1028 cm^{-1}, 938 cm^{-1}, 836 cm^{-1}, 713 cm^{-1}

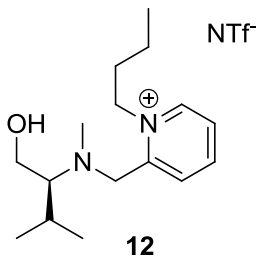
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.51 (s, 2H), 7.63 (td, 1H, *J* = 8.02 Hz, *J* = 1.85 Hz), 7.27 (dd, 4.16 Hz, 1H), 3.75 (q, 2H, *J* = 13.17 Hz), 3.62 (dd, 1H), 3.35 (t, 1H, *J* = 10.23 Hz), 2.52 (m, 1H), 2.27 (s, 3H), 1.93 (m, 1H), 1.09 (d, 3H, *J* = 6.63 Hz), 0.82 (d, 3H, *J* = 6.84 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 149.8 (d), 148.3 (d), 136.2 (d), 135.2 (s), 123.4 (d), 70.7 (d), 59.4 (t), 58.9 (t), 35.9 (q), 27.8 (d), 22.1 (q), 19.8 (q)

Analytical data were in accordance to literature.[224]

6.3.8 (*S*)-1-Butyl-2-(((1-hydroxy-3-methylbutan-2-yl)(methyl)amino)-methyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide

Ligand **11** (3.87 g, 18.45 mmol) was converted with 1.8 equivalents of *n*-butyl bromide (4.51 g, 33.26 mmol) for 20 h at 80 °C and stirred. Remaining butyl bromide was removed under reduced pressure and the glassy solid was washed twice with diethylether to give brown, viscose oil in 90% yield (5.71 g, 16.53 mmol). To change the anion, IL bromide was dissolved in 20 mL deionised water and 20 mL acetonitrile according procedure 6.3.3. The solution was stirred at rt and a solution of $Li[N(CF_3SO_2)_2]$ (4.93 g, 17.18 mmol) in 20 mL deionised water was added drop wise.. Volatiles were removed in high vacuum to give orange brown ionic liquid (8.29 g, 15.21 mmol, 93%).



12

$C_{18}H_{29}F_6N_3O_5S_2$
545.56 g/mol

$[\alpha]_{589}^{20}$ = - 5.265 (CH_2Cl_2, c = 1.67)

IR: ν = 3550 cm^{-1}, 2967 cm^{-1}, 2878 cm^{-1}, 1738 cm^{-1}, 1630 cm^{-1}, 1581 cm^{-1}, 1468 cm^{-1}, 1350 cm^{-1}, 1187 cm^{-1}, 1155 cm^{-1}, 1055 cm^{-1}, 739 cm^{-1}, 654 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.66 (d, 1H, *J* = 6.26 Hz), 8.32 (t, 1H, *J* = 8.02 Hz), 8.18 (d, 1H, *J* = 8.02 Hz), 7.82 (t, 1H, *J* = 6.84 Hz), 4.55 (m, 2H), 4.28 (s, 2H), 4.04 (q, 1H, *J* = 2.41 Hz), 3.89-3.65 (m, 2H), 2.27 (m, 4H), 1.91-1.58 (m, 3H), 1.39 (sext., 2H, *J* = 4.53 Hz), 0.99-0.76 (m, 9H)

[224] Bica, K. *PhD Thesis*, Vienna University of Technology, **2007**.

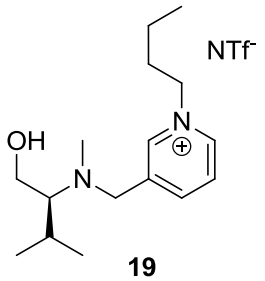
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 157.1 (s), 145.0 (d), 129.1 (d), 126.5 (d), 123.0 (s), 116.6 (s), 71.3 (d), 60.0 (t), 57.5 (t), 57.3 (t), 36.4 (q), 32.9 (t), 28.0 (d), 21.5 (q), 20.3 (q), 19.6 (t), 13.4 (q)

Anal. Calcd. for $C_{16}H_{29}F_6N_3O_5S_2$: C, 39.63; H, 5.36; N, 7.70. Found: C, 39.49, H, 5.03, N, 7.61

6.3.9 (*S*)-1-Butyl-3-(((1-hydroxy-3-methylbutan-2-yl)(methyl)amino)-methyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide

According to procedure 6.3.8, ligand **18** (0.28 g, 1.39 mmol) was converted with *n*-butyl bromide to orange, viscose IL bromide which was directly used in the next step.

To change the anion, IL bromide (0.48 g, 1.38 mmol) was dissolved in deionised water and acetonitrile according to procedure 6.3.3. A solution of $Li[N(CF_3SO_2)_2]$ (0.42 g, 1.45 mmol) was added drop wise. After extraction with DCM and workup volatiles were removed in high vacuum to give orange ionic liquid (0.72 g, 1.31 mmol, 95%).



19

$C_{18}H_{29}F_6N_3O_5S_2$
545.56 g/mol

[α]$_{589}^{20}$ = -3.922 (EtOH, c = 1.00)

IR: ν = 3552 cm^{-1}, 3073 cm^{-1}, 2964 cm^{-1}, 2878 cm^{-1}, 1737 cm^{-1}, 1634 cm^{-1}, 1503 cm^{-1}, 1469 cm^{-1}, 1348 cm^{-1}, 1183 cm^{-1}, 1134 cm^{-1}, 1054 cm^{-1}, 740 cm^{-1}, 690 cm^{-1}

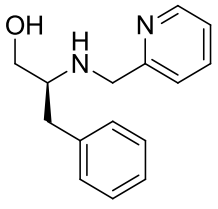
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.72 (s, 1H), 8.59 (d, 1H, *J* = 5.87 Hz), 8.37 (d, 1H, *J* = 7.83 Hz), 7.91 (m, 1H), 4.51 (t, 2H, *J* = 7.53 Hz), 4.05 (s, 2H), 3.67 (M, 2H), 2.37 (dt, 1H), 2.28 (s, 3H), 1.99-1.69 (m, 3H), 1.32 (sext, 2H, *J* = 6.26 Hz), 1.19 (t, 3H, *J* = 4.01 Hz), 0.89 (m, 6H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 145.08 (d), 143.69 (d), 143.24 (s), 142.66 (d), 128.05 (d), 122.90 (s), 116.51 (s), 71.14 (d), 62.21 (t), 60.27 (t), 56.26 (t), 36.48 (q), 33.25 (t), 27.80 (d), 21.59 (q), 20.06 (q), 19.21 (t), 13.17 (q)

Anal. Calcd. for $C_{16}H_{29}F_6N_3O_5S_2$: C, 39.63; H, 5.36; N, 7.70. Found: C, 39.43; H, 5.03; N, 7.45.

6.3.10 (*S*)-3-Phenyl-2-((pyridin-2-ylmethyl)amino)propan-1-ol

According to 6.3.5, phenylalaninol **2** (8.00 g, 52.9 mmol) and 15 g freshly activated molecular sieve 4 Å were suspended in abs. MeOH. After 15 minutes stirring, pyridine-2-carbaldehyde (5.66 g, 52.9 mmol) was added drop wise using a syringe. The reaction mixture was allowed to stir 24 hours at reflux temperature, until TLC showed complete conversion. The mixture was cooled to 0 °C and $NaBH_4$ (2.00 g, 52.9 mmol) was added. After two hours stirring, the mixture was allowed to warm to rt and then hydrolysed with a small amount of water. Solid Na_2SO_4 was added and subsequently the suspension was filtrated over celite to remove molecular sieve and Na_2SO_4. Solvent was removed under reduced pressure and after drying in high vacuum, yellowish solid (12.78 g, 52.8 mmol, >99%) was obtained which could be directly used in the next reaction step without further purification.



3
$C_{15}H_{18}N_2O$
242.32 g/mol

r_f = 0.21 (CH_2Cl_2:MeOH 25:1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = -7.050 (CH_2Cl_2, c = 0.99)

mp = 36-38 °C

IR: ν = 3294 cm^{-1}, 3022 cm^{-1}, 2971 cm^{-1}, 2853 cm^{-1}, 1946 cm^{-1}, 1738 cm^{-1}, 1590 cm^{-1}, 1567 cm^{-1}, 1376 cm^{-1}, 1229 cm^{-1}, 1115 cm^{-1} 1036 cm^{-1}, 857 cm^{-1}, 742 cm^{-1}, 696 cm^{-1}

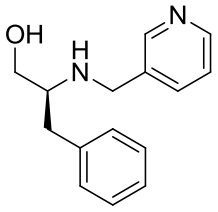
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.45 (d, 1H, *J* = 4.49 Hz), 7,53 (td, 1H, *J* = 6.85 Hz, *J* = 1.76 Hz), 7.29-7.03 (m, 7H), 3.86 (q, 2H, *J* = 12.45 Hz), 3.57 (dd, 1H, *J* = 11.15 Hz, *J* = 4.49 Hz), 3.34 (dd, 1H, *J* = 11.15 Hz, *J* = 5.61 Hz), 2.95 (m, 3H), 2.73 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.1 (s), 149.2 (d), 138.8 (s), 129.2 (d, 2C), 128.5 (d, 2C), 126.3 (d), 122,1 (d), 62.6 (t), 60.5 (d), 52.0 (t), 38.4 (t)

Anal. Calcd.: for $C_{15}H_{18}N_2O$: 0.1 H_2O: C, 73.80; H, 7.51; N, 11.48. Found: C, 73.73; H, 7.67; N, 10.60

6.3.11 (*S*)-3-Phenyl-2-((pyridin-2-ylmethyl)amino)propan-1-ol

According to procedure 6.3.5, phenylalaninol **2** (3.00 g, 19.8 mmol) was converted with pyridine-3-carbaldehyde (2.02 g, 18.8 mmol). The iminium intermediate was reduced with $NaBH_4$ (0.71 g, 18.8 mmol). After workup and recrystalization of the raw material from EA/*n* hexane colourless crystals were obtained (3.17 g, 13.07 mmol 66%).



4

$C_{15}H_{18}N_2O$

242.32 g/mol

r_f = 0.22 (CH_2Cl_2:MeOH 30:1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = -14.026 (EtOH, c = 0.07)

mp = 67-68 °C

IR: ν = 3255 cm^{-1}, 3015 cm^{-1}, 2919 cm^{-1}, 2828 cm^{-1}, 1942 cm^{-1}, 1737 cm^{-1}, 1653 cm^{-1}, 1575 cm^{-1}, 1452 cm^{-1}, 1343 cm^{-1}, 1229 cm^{-1}, 1105 cm^{-1}, 1055 cm^{-1}, 1025 cm^{-1}, 892 cm^{-1}, 857 cm^{-1}, 697 cm^{-1}

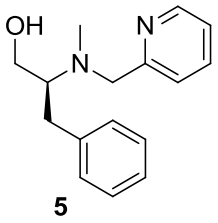
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.41 (m, 2H), 7.46 (d, 1H, *J* = 7.82 Hz), 7.29-7.05 (m, 6H), 3.72 (s, 2H), 3.60 (dd, 1H, J_1 = 10.76 Hz, J_2 = 3.72 Hz), 3.32 (dd, 1H, J_1 = 10.76 Hz, J_2 = 3.72 Hz), 2.88 (m, 1H), 2.75 (s, 1H), 2.71 (d, 1H), 1.92 (bs, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.6 (d), 148.6 (d), 138.2 (s), 135.7 (d), 135.2 (s), 129.1 (2d), 128.6 (2d), 126.7 (d), 123.6 (d), 62.7 (d), 59.6 (d), 48.6 (t), 37.9 (t)

Anal. Calcd. for $C_{15}H_{18}N_2O$: 0.1 H_2O: C, 73.80; H, 7.51; N, 11.48. Found: C, 73.88; H, 6.91; N, 11.32

6.3.12 (*S*)-2-(Methyl(pyridin-2-ylmethyl)amino)-3-phenylpropan-1-ol

Ligand **3** (10 g, 41.3 mmol) was further converted with HCHO according to procedure 6.3.6. Purification via flash chromatography (CH_2Cl_2 : MeOH 15:1 + NEt_3) gave the product as colourless oil (8.09 g, 31.58 mmol) in 76% yield.



5

$C_{16}H_{20}N_2O$
256.16 g/mol

r_f = 0.4 (CH_2Cl_2:MeOH 15:1 + 0.2% NEt_3).

$[\alpha]_{589}^{20}$ = -3.304 (CH_2Cl_2, c = 0.58)

IR: ν = 3309 cm^{-1}, 3025 cm^{-1}, 2930 cm^{-1}, 2849 cm^{-1}, 1736 cm^{-1}, 1672 cm^{-1}, 1591 cm^{-1}, 1434 cm^{-1}, 1354 cm^{-1}, 1196 cm^{-1}, 1147 cm^{-1}, 1036 cm^{-1}, 941 cm^{-1}, 747 cm^{-1}, 700 cm^{-1}

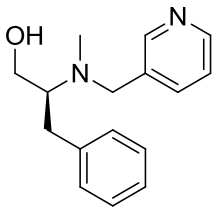
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.50 (d, 1H, *J* = 4.89 Hz), 7,56, (dt, 1H, J_1 = 7.63 Hz, J_2 = 1.76 Hz), 7.26-7.04 (m, 7H), 3.86 (d, 1H, *J* = 14.28 Hz), 3.60 (d, 1H, *J* = 14.28 Hz), 3.40 (m, 2H), 2.89 (m, 2H), 2.38 (m, 1H), 2.30 (s, 3H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 159.5 (s), 149.3 (d), 139.3 (d), 136.6 (d), 129.0 (d, 2C), 128.5 (d, 2C), 126.1 (d), 122.7 (d), 122.2 (d), 66.5 (d), 61.1 (t), 58.5 (t), 37,3 (q), 32.2 (t)

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.21; H, 7.69; N, 10.97

6.3.13 (*S*)-2-(Methyl(pyridin-3-ylmethyl)amino)-3-phenylpropan-1-ol

Ligand **4** (6.99 g, 28.68 mmol) was treated with HCHO solution in HCOOH according to procedure 6.3.6 and isolated as light yellow oil (4.11 g, 16.06 mmol, 56%) after flash chromatography (CH_2Cl_2 : MeOH 20:1 + NEt_3).



16
$C_{16}H_{20}N_2O$
256.16g/mol

$\mathbf{r_f}$ = 0.16 (CH_2Cl_2:MeOH 20:1 + 0.2% NEt_3).

$\mathbf{[\alpha]_{589}^{20}}$ = -16.60 ($CHCl_3$, c = 1.05).

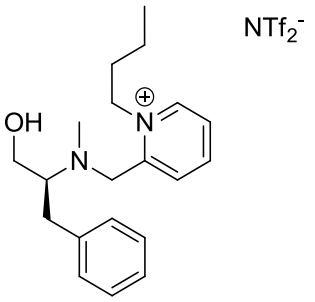
IR: ν = 3340 cm^{-1}, 2937 cm^{-1}, 1600 cm^{-1}, 1580 cm^{-1}, 1450 cm^{-1}, 1430 cm^{-1}, 1029 cm^{-1}, 699 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.42 (m, 2H), 7,55 (d, J = 9.6 Hz, 1H), 7.28-7.20 (m, 6H), 3.74-3.45 (dd, J_1 = 33.5 Hz, J_2 = 13.4 Hz, 2H), 3.38 (m, 2H), 3.08-2.75 (m, 3H), 2.36 (dd, J_1 = 13.0 Hz, J_2 = 8.9 Hz, 1H), 2.21 (s, 3H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 150.1 (d), 148.7 (d), 139.0 (s), 136.5 (d), 134.4 (s), 129.1 (2d), 128.6 (2d), 126.3 (d), 123.6 (d), 65.8 (d), 60.6 (t), 55.7 (t), 35.8 (q), 31.6 (t)
Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.88; H, 7.62; N, 10.80

6.3.14 (*S*)-1-Butyl-2-(((1-hydroxy-3-phenylpropan-2-yl)(methyl)-amino)methyl)pyridin-1-ium bis((trifluoromethyl) sulfonyl)amide

According to procedure 6.3.3 compound **5** (0.61 g, 2.39 mmol) was stirred with *n*-butyl bromide (0.59 g, 4.30 mmol) for 20 h at 80 °C. To change the anion, IL bromide was dissolved in deionised water and acetonitrile. A solution of $Li[N(CF_3SO_2)_2]$ (2.41 mmol) was added drop wise. After extraction with DCM and workup, volatiles were removed in high vacuum to give orange ionic liquid (1.36 g, 2.29 mmol, 96%).



6
$C_{22}H_{29}F_6N_2O_5S$
593.36 g/mol

$[\alpha]_{589}^{20}$ = -10.184 (CH_2Cl_2, c = 0.65)

IR: ν = 2937 cm^{-1}, 2852 cm^{-1}, 1738 cm^{-1}, 1629 cm^{-1}, 1496 cm^{-1}, 1455 cm^{-1}, 1349 cm^{-1}, 1181 cm^{-1}, 1133 cm^{-1}, 1053 cm^{-1}, 739 cm^{-1}, 702 cm^{-1}

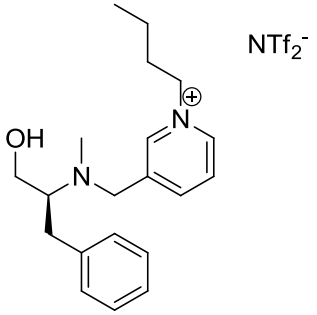
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.43 (d, 1H), 8.06 (t, 1H, *J* = 7.8 Hz), 7.67 (m, 2H), 7.30-7.03 (m, 5H), 4.31-3.47 (m, 6H), 2.94 (m, 1H), 2.59 (d, 2H *J* = 7.43 Hz), 2.37 (s, 3H), 1.63 (m, 2H), 1.28 (sext., 2H, *J* = 6.85 Hz), 0.87 (t, 3H, *J* = 7.23 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 156.1 (s), 144.9 (d), 139.6 (s), 129.4 (d), 129.1 (d, 2C), 128.8 (d), 128.6 (d, 2C), 126.4 (d), 123.0 (d), 116.6 (s), 66.2 (d), 62.6 (t), 57.3 (t), 56.7 (t), 35.3 (q), 34.3 (t), 32.7 (t), 19.6 (t), 13.3 (q)

Anal. Calcd. for $C_{22}H_{29}F_6N_3O_5S$: C; 44.51; H, 4.92; N, 7.08 Found: C, 44.50; H, 4.55; N, 6.71.

6.3.15 (*S*)-1-Butyl-3-(((1-hydroxy-3-phenylpropan-2-yl) (methyl)-amino)methyl)pyridin-1-ium bis((trifluoromethyl) sulfonyl)amide

According to procedure 6.3.3, **16** (1.28 g, 5.0 mmol) was stirred with *n*-butyl bromide for 20 h at 80 °C bath temperature. Excess butyl bromide was removed under reduced pressure and the remaining brown oil was washed twice with diethylether. Removal of volatiles in high vacuum gave the ionic liquid as orange oil in quantitative yield. IL bromide (1.92 g, 4.89 mmol) was converted into its bistriflimide. to give orange ionic liquid (2.89 g, 4.89 mmol, 98%).



17
$C_{22}H_{29}F_6N_2O_5S$
593.36 g/mol

$[\alpha]_{589}^{20}$ = -14.29 (EtOH, c = 0.96)

IR: ν = 2921 cm^{-1}, 2852 cm^{-1}, 1738 cm^{-1}, 1633 cm^{-1}, 1497 cm^{-1}, 1456 cm^{-1}, 1349 cm^{-1}, 1178 cm^{-1}, 1132 cm^{-1}, 1052 cm^{-1}, 739 cm^{-1}, 687 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 6.1 Hz, 1H), 8.26 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.75 (m, 1H), 7.31-7.05 (m, 5H), 4.34 (t, *J* = 7.6 Hz, 2H), 3.92 (dd, J_1 = 15.6 Hz, J_2 = 14.5 Hz, 2H), 3.61 (m, 2H), 2.98 (m, 2H), 2.65 (m, 3H), 2.31 (s, 3H), 1.81 (quin *J* = 7.6 Hz, 2H), 1.29 (sext *J* = 7.5 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H)

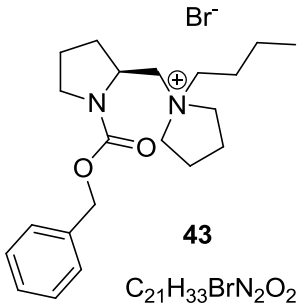
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 144.98 (d), 143.61 (d), 142.63 (s), 142.48 (d), 139.45 (s), 129.18 (d, 2C), 128.53 (d, 2C), 127.86 (d), 126.28 (d), 122.92 (d), 116.53 (s), 66.27 (d), 62.15 (t), 61.59 (t), 55.34 (t), 35.88 (q), 33.36 (t), 33.29 (t), 19.23 (t), 13.19 (q)

Anal. Calcd. for $C_{22}H_{29}F_6N_3O_5S$: C; 44.51; H, 4.92; N, 7.08 Found: C, 44.85; H, 4.96; N, 7.20.

6.4 Synthesis of organocatalytic ionic liquids

6.4.1 (*S*)-1-((1-((Benzyloxy)carbonyl)pyrrolidin-2-yl)methyl)-1-butylpyrrolidin-1-ium bromide

Cbz protected (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine **42** (1.08 g, 3.77 mmol) was heated with a 1.5 fold excess of butyl bromide (0.77 g, 5.65 mmol) for three days until TLC (CH_2Cl_2:MeOH 6 : 1) showed complete conversion. Remaining halide was removed under reduced pressure in high vacuum. Ionic liquid was obtained as orange oil (1.58 g, 3.73 mmol, 99%).



43

$C_{21}H_{33}BrN_2O_2$
425.40 g/mol

$[\alpha]_{589}^{20}$ = 40.881 (CH_2Cl_2, c = 1.22)

IR: ν = 3396 cm^{-1}, 2959 cm^{-1}, 2876 cm^{-1}, 1690 cm^{-1}, 1454 cm^{-1}, 1409 cm^{-1}, 1355 cm^{-1}, 1355 cm^{-1}, 1101 cm^{-1}

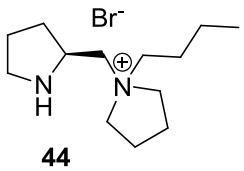
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.28 (s, 5H), 5.05 (s, 2H), 4.33-3.58 (m, 6H), 3.49 (t, 3H), 3.36, (t, 1H), 3.19 (m, 1H), 2.38-1.49 (m, 10H), 1.36 (sext, 1H, *J* = 7.07 Hz), 0.94 (t, 3H, *J* = 6.55 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 156.9 (s), 137.1 (s), 129.5 (d, 2C), 129.2 (d), 128.8 (d, 2C), 68.4 (t), 63.9 (t, 2C), 63.1 (t), 59.3 (t), 54.6 (d), 47.4 (t), 31,9 (t), 26.1 (t), 24.9 (t), 23.0 (t), 22.4 (t), 20.7 (t), 14.6 (q)

Anal. Calcd. for $C_{21}H_{33}BrN_2O_2$: C, 59.29; H, 7.82; N, 6.59. Found: C, 59.40; H, 7.69; N, 6.87

6.4.2 (*S*)-1-Butyl-1-(pyrrolidin-2-ylmethyl)pyrrolidin-1-ium bromide

To cleave the protecting group, IL **43** (0.9 g, 1.8 mmol) was dissolved in abs MeOH. Pd on charcoal (0.39 g, 0.18 mmol) was added, the mixture was degassed and subsequently hydrogenated in a Parr Apparatus at a pressure of 5.5 bar for 35 min. The reaction mixture was filtered over celite to remove the catalyst and solvent was removed under reduced pressure to give the desired ionic liquid as yellow orange oil in quantitative yield (0.534 g, 1.8 mmol).



44

$C_{13}H_{27}BrN_2$
445.52 g/mol

[α]$_{589}^{20}$ = 16.366 (CH_2Cl_2, c = 0.68)

IR: ν = 3406 cm^{-1}, 2960 cm^{-1}, 2874 cm^{-1}, 1648 cm^{-1}, 1554 cm^{-1}, 1459 cm^{-1}, 1381 cm^{-1}, 1029 cm^{-1}, 910 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.13 (m, 1H), 3.84-3.61 (m, 6H), 3.57 (t, 2H, *J* = 8.31 Hz), 3.47-3.36 (m, 2H), 3.06-2.73 (m, 2H), 2.36-1.95 (m, 5H), 1.83-1.50 (m, 4H), 1.39 (sext 2H, *J* = 7.24 Hz), 0.94 (t, 3H, *J* = 7.14 Hz)

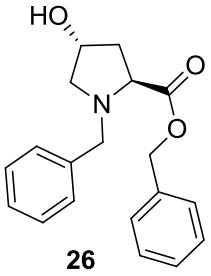
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 63.4 (t), 63.3 (t), 63.2 (t), 59.9 (t), 53.9 (d), 50.1 (t), 47.2 (t), 31.4 (t), 25.5 (t), 21.8 (t), 21.5, (t), 19.7 (t), 13.7 (q)

Analytical data were in accordance to literature.[196]

6.4.3 (2*S*,4*R*)-Benzyl-1-benzyl-4-hydroxypyrrolidine-2-carboxylate

Trans-4-hydroxyproline (6.2 g, 47 mmol) and $NaHCO_3$ (9.9 g, 118 mmol) were suspended in DMF. Benzylchlorid (14.9 g, 118 mmol) was added drop wise and the mixture was stirred at 110 °C for 6 hours. After TLC showed full conversion, the reaction mixture was poured in 500 mL water und 200 mL EA. Layers were separated and the aqueous layer was extracted twice with EA. Combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtrated. Solvent

was removed under reduced pressure. The obtained yellowish oil (14.6 g, 47 mmol, > 99 %) was directly used for the next step without further purification.



26

$C_{19}H_{21}NO_3$
311.37 g/mol

$\mathbf{r_f}$ = 0.17 (CH_2Cl_2:MeOH 20 : 1)

$\mathbf{[\alpha]_{589}^{20}}$ = -50.093 (CH_2Cl_2, c = 1.125)

IR: ν = 3380 cm^{-1}, 3030 cm^{-1}, 2947 cm^{-1}, 1730 cm^{-1}, 1605 cm^{-1}, 1495 cm^{-1}, 1454 cm^{-1}, 1351 cm^{-1}, 1170 cm^{-1}, 1083 cm^{-1}, 1027 cm^{-1}, 974 cm^{-1}, 910 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.35 (s, 5H), 7.28 (s, 5H), 5.13 (s, 2H), 4.46 (m, 1H), 3.81 (dd, 2H), 3.69 (s, 1H, OH), 3.34 (dd, 1H, J_1 = 10.66 Hz, J_2 = 5.47 Hz), 2.53 (dd, 1H, J_1 = 10.17 Hz, J_2 = 3.72 Hz), 2.28, (m, 1H), 2.14 (dd, 1H, J_1 = 8.02 Hz, J_2 = 3.32 Hz), 2.04 (m, 1H)

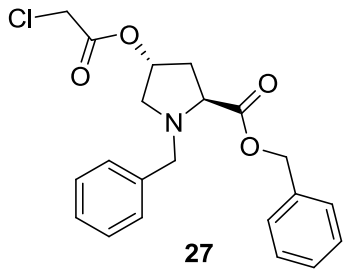
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 173.4 (s), 138.1 (s), 136.0 (s), 129.0 (d, 2C), 128.7 (d, 2C), 128.3 (d, 4C), 127.1 (d, 2C), 70.3 (d), 66.5 (t), 63.4 (d), 61.2 (t), 58.1 (t), 41.6 (t)

HR/MS for $C_{19}H_{21}NO_3$: $[M]^+$ calcd. 312.1594, found: 312.1598

6.4.4 (2*S*,4*R*)-Benzyl-1-benzyl-4-(2-chloracetoxy)pyrrolidine-2-carboxylat

Protected *trans*-4-hydroxyprolin **26** obtained according procedure 6.4.3 (3.7 g, 12 mmol) was dissolved in dry CH_2Cl_2 under N_2 and cooled to 0 °C. Subsequently 2-chloro acetylchlorid (3.34 g, 30 mmol) and NEt_3 (3.0 g, 30 mmol) were added drop wise. The reaction mixture was stirred over night at room temperature, till TLC showed complete conversion (LP:EA 4:1). Workup started with twice extraction with 2N HCl, followed by extraction with saturated $NaHCO_3$-solution and brine. Combined organic layers were dried over Na_2SO_4, filtrated and solvent was removed

under reduced pressure. Flash chromatography (LP:EA 4:1) of the brown material yielded 4.3 g (11.2 mmol, 94 %) yellow, viscose oil.



27

$C_{21}H_{22}ClNO_4$
387.12 g/mol

$\mathbf{r_f}$ = 0.40 (LP:EA 4 : 1)

$\mathbf{[\alpha]_{589}^{20}}$ = - 35.106 (CH_2Cl_2, c = 1.055)

IR: ν = 2953 cm^{-1}, 1744 cm^{-1}, 1707 cm^{-1}, 1498 cm^{-1}, 1420 cm^{-1}, 1356 cm^{-1}, 1169 cm^{-1},1127 cm^{-1}

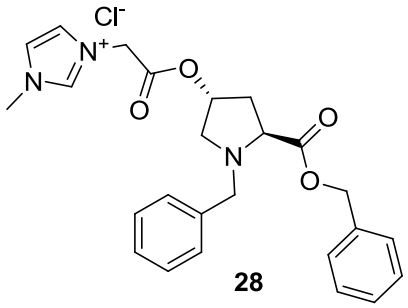
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 7.28 (m, 5H), 5.32 (sept., 1H, *J* = 2.9 Hz), 5.14 (s, 2H), 4.01 (s, 2H), 3.74 (q, 2H), 3.45 (dd, 1H, J_1 = 11.15 Hz, J_2 = 6.21 Hz), 2.63 (dd, 1H, J_1 = 11.34 Hz, J_2 = 3.13 Hz), 2.43 (m, 1H), 2.26 (dd, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.6 (s), 166.8 (s), 137.4 (s), 135.4 (s), 128.9 (d, 2C), 128.6 (d, 2C), 128.5 (d), 128.4 (d, 2C), 128.3 (d, 2C), 127.3 (d), 75.2 (d), 66.8 (t), 63.8 (d), 57.9 (t), 57.6 (t), 40.8 (t), 36.2 (t)

HR/MS for $C_{21}H_{22}ClNO_4$: $[M]^+$ calcd. 388.1310, found: 388.1309

6.4.5 3-(2-((3*R*,5*S*)-1-Benzyl-5-(benzyloxycarbonyl)pyrrolidin-3-yloxy)-2-oxoethyl)-1-methyl-1H-imidazol-3-ium chloride

Equimolar amounts of compound **27** (3.4 g, 8.8 mmol) and freshly distilled methylimidazole (0.7 g, 8.8 mmol) were heated in a round bottom flask at 80 bis 90 °C temperature of oil bath for a few hours until TLC showed no spot of starting material (CH_2Cl_2: MeOH 30 : 1). The hygroscopic product was dried in high vacuum to yield 4.1 g (8.7 mmol, >99 %) brown, glassy solid.



28

$C_{25}H_{28}ClN_3O_4$
469.96 g/mol

$[\alpha]_{589}^{20}$ = -20.841 (CH_2Cl_2, c = 0.7)

IR: ν = 3358 cm^{-1}, 3154 cm^{-1}, 3028 cm^{-1}, 1736 cm^{-1}, 1645 cm^{-1}, 1574 cm^{-1}, 1369 cm^{-1}, 1208 cm^{-1}, 1174 cm^{-1}, 877 cm^{-1}

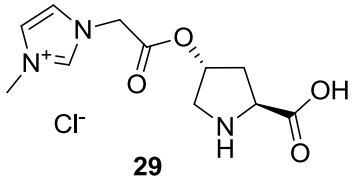
^{1}H-NMR (200 MHz, D_2O): δ = 10.28 (s, 1H), 7.52 (s, 1H), 7.27 (m, 5H), 7.21 (m, 5H), 5.42 (s, 2H), 5.22 (m, 1H), 5.05 (s, 1H), 3.94 (s, 3H), 3.88 (d, 1H, *J* = 5.086 Hz), 3.68 (m, 2H), 3.37 8m, 1H), 2.70 (dd, 1H, J_1 = 3.326 Hz, J_2 = 11.151 Hz), 2.44-2.14 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.0 (s), 166.1 (s), 138.7 (d), 137.5 (s), 135.7 (s), 129.0 (d, 2C), 128.6 (d, 3C), 128.4 (d), 128.3 (d, 3C), 127.4 (d), 123.8 (d), 122.8 (d), 75.4 (d), 66.7 (t), 63.3 (d), 57.5 (t), 57.4 (t), 49.9 (t), 36.7 (q), 35.9 (t)

Anal. Calcd. for. $C_{25}H_{28}ClN_3O_4$: C, 63.89 H, 6.01 N, 8.94. Found: C, 62.82, H, 5.81, N, 8.53

6.4.6 1-(2-((3*R*,5*S*)-5-Carboxypyrrolidin-3-yloxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride

Ionic liquid **28** (1.26 g, 2.7 mmol) was dried in high vacuum for 24 hours, stored under Ar and dissolved in 7 mL dry MeOH. The brown solution was transferred into a Parr apparatus and degassed with Ar. Subsequently 0,45 g Pd on charcoal were added. Hydrogenation to cleave the protecting groups was performed at rt and a pressure of 5,5 bar H_2 for 40 minutes. The mixture was filtrated over celite and after removal of the solvent and drying in high vacuum 0.81 g (2.7 mmol) yellowish, solid were obtained in quantitative yield.



29

$C_{11}H_{16}ClN_3O_4$
289.72 g/mol

$[\alpha]_{589}^{20}$ = 8.928 (EtOH, c = 0,0056)

IR: ν = 3096 cm^{-1}, 2496 cm^{-1}, 1727 cm^{-1}, 1630 cm^{-1}, 1645 cm^{-1}, 1580 cm^{-1}, 1440 cm^{-1}, 1378 cm^{-1}, 1212 cm^{-1}, 1165 cm^{-1}, 1081 cm^{-1}, 979 cm^{-1}

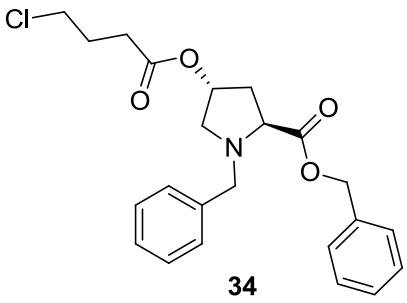
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.04 (s, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 5.56 (quin, 1H, *J* = 4.2 Hz), 5.27 (s, 2H), 4.31 (dd, 1H, J_1 = 8.28 Hz, J_2 = 9.8Hz), 4.00 (s, 3H), 3.64, (m, 2H), 2.64 (dd, 1H, J_1 = 8.99, J_2 = 14.67), 2.36 (m, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 169.6 (s), 166.3 (s), 137.8 (d), 123.6 (d), 123.3 (d), 75.4 (d), 58.8 (d), 49.6 (t), 48.5 (t), 35.9 (q), 34.7 (t)

Anal. Calcd. for. C, 45.60; H, 5.57; N, 14.50. Found: C, 43.85; H, 5.42; N, 14.04

6.4.7 (2*S*,4*R*)-Benzyl-1-benzyl-4-(4-chlorbutanoyloxy)pyrrolidine-2-carboxylat

According to procedure 6.4.4, 4-chlorobutanoyl chloride (1.85 g, 13 mmol) and NEt_3 (1.31 g, 13 mmol) were added to benzyl protected *trans*-4-hydroxyprolin **26** (1.63 g, 5.2 mmol). The mixture was stirred at rt until TLC (LP:EA 1:1) showed complete conversion. After chromatographical purification light yellow oil was obtained (1.7 g, 4.2 mmol) in 79 % yield.



34

$C_{23}H_{26}ClNO_4$
415.91 g/mol

$\mathbf{r_f}$ = 0.40 (LP:EA 4 : 1)

$\mathbf{[\alpha]_{589}^{20}}$ = -27.591 (CH_2Cl_2, c = 0.295)

IR: ν = 3031 cm^{-1}, 2956 cm^{-1}, 2809 cm^{-1}, 1728 cm^{-1}, 1454 cm^{-1}, 1166 cm^{-1}, 1144 cm^{-1},1010 cm^{-1}, 908 cm^{-1}, 737 cm^{-1}, 679 cm^{-1}

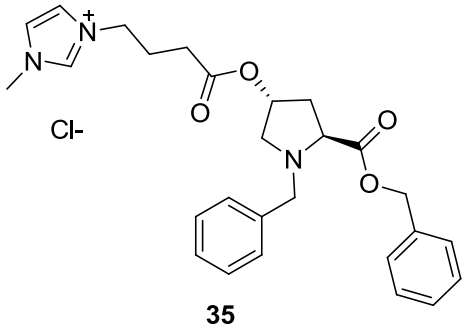
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.288 (m, 5H), 7.19 (m, 5H), 5.15 (quin., 1H, *J* = 2.25 Hz), 5.06 (s, 2H), 3.85 (d, 1H, *J* = 13.10 Hz), 3.52 (m, 4H), 3.36 (dd, 1H, J_1 = 10.75 Hz, J_2 = 6.26 Hz), 2.51-2.18 (m, 4H), 2.13 (dd, 1H, J_1 = 3.32 Hz, J_2 = 7.62 Hz), 1.99 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.15 (s), 168.3 (s), 141.6 (s), 135.6 (s), 129.2 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 128.4 (d, 4C), 72,9 (d), 66.9 (t), 63.7 (d), 58.2 (t), 57.6 (t), 44.0 (t), 36.4 (t), 31.2 (t), 27.5 (t)

HR/MS for $C_{23}H_{26}ClNO_4$: $[M]^+$ calcd. 416.1623, found: 416.1629

6.4.8 3-(4-((3*R*,5*S*)-1-Benzyl-5-(benzyloxycarbonyl)pyrrolidin-3-yloxy)-4-oxobutyl)-1-methyl-1H-imidazol-3-ium chloride

According to procedure 6.4.5, chloride **34** (1.66 g, 3.98 mmol) and freshly distilled methyl imidazole (0.49 g, 5.97 mmol) were heated in a round bottom flask at 80 °C. oil bath temperature and stirred for 5 d, until no spot of starting material was detected via TLC (LP: EA 4 : 1). The excess of methyl imidazole was removed under reduced pressure and stirring at 55 °C. 1.97 g (3.96 mmol, >99 %) brown, glassy solid could be obtained.



35

$C_{27}H_{32}ClN_3O_4$
498.01 g7mol

$[\alpha]_{589}^{20}$ = -12.100 (EtOH, c = 0.495)

IR: ν = 3379 cm^{-1}, 2925 cm^{-1}, 1726 v 1630 cm^{-1}, 1573 cm^{-1}, 1496 cm^{-1}, 1377 cm^{-1}, 1163 cm^{-1}, 1103 cm^{-1}, 1026 cm^{-1}, 864 cm^{-1}, 700 cm^{-1}

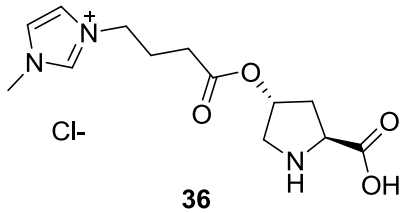
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 10.70 (s, 1H), 7.36 (s, 1H), 7.33 (s, 1H), 7.28 (s, 5H), 7.21 (s, 5H), 5.13 (m, 1H), 5.01 (s, 2H), 4.38 (t, 2H, J = 7.28 Hz), 3.99 (s, 3H), 3.84 (m, 1H), 3.55 (m, 2H), 3.34 (dd, 1H, J_1 = 6.26, J_2 = 10.95), 2.46 (dd, 1H, J_1 = 3.9, J_2 = 10.56), 2.41-2.04 (m, 6H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.6 (s), 171.9 (s), 137.7 (d), 137.6 (s), 135.6 (s), 128.9 (d, 2C), 128.6 (d, 2C), 128.4 (d), 128.3 (2d, 4C), 127.2 (d), 122.9 (d), 121.8 (d), 73.4 (d), 66.5 (t), 63.7 (d), 58.1 (t), 57.6 (t), 48.8 (t), 36.6 (q), 33.6 (t), 30.3 (t), 25.7 (t)

Anal. Calcd. for: C, 65.12; H, 6.48; N, 8.44. Found: C, 65.38; H, 6.11; N, 8.36.

6.4.9 3-(4-(((3*R*,5*S*)-5-Carboxypyrrolidin-3-yl)oxy)-4-oxobutyl)-1-methyl-1H-imidazol-3-ium chloride

According to procedure 6.4.6, ionic liquid **35** (1.9 g, 3.8 mmol) was dried in high vacuum for 24 hours, stored under Ar and dissolved in 15 mL abs. MeOH. The brown solution was transferred into a Parr apparatus and degassed with Ar. Subsequently 0.82 g Pd on charcoal were added. Hydrogenation to cleave the protecting groups was performed at rt and a pressure of 5.0 bar H_2 for 40 minutes. The mixture was filtered over celite and after removal of the solvent and drying in high vacuum 1.19 g (3.8 mmol) brownish solid were obtained in quantitative yield.



36

$C_{13}H_{20}ClN_3O_4$
317.77 g/mol

[α]$_{589}^{20}$ = 16.665 (EtOH, c = 0.0096)

IR: ν = 3357 cm^{-1}, 2925 cm^{-1}, 1723 cm^{-1}, 1624 cm^{-1}, 1573 cm^{-1}, 1379 cm^{-1}, 1163 cm^{-1}, 1082 cm^{-1}, 845 cm^{-1}

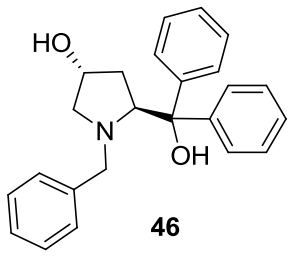
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.53 (d, 2H, *J* = 16.04 Hz), 5.32 (m, 1H); 4.19 (t, 2H, *J* = 7.23 Hz), 4.11 (m, 1H), 3.85 (s, 3H), 3.54 (dd, 1H, J_1 = 4.3 Hz, J_2 = 13.1 Hz), 3.35 (m, 1H), 2.51-2.0 (m, 6H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 175.8 (s), 172.9 (s), 125.1 (d), 123.7 (d), 123.5 (d), 75.1 (d), 71.3 (d), 54.5 (t), 51.8 (t), 36.5 (q), 31.2 (t), 26.5 (t), 26.2 (t)

Anal. Calcd. for.$C_{13}H_{20}ClN_3O_4$: C, 49.14; H, 6.34; N, 13.22 Found: C, 48.89; H, 6.91; N, 13.32

6.4.10 (3*R*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-ol

2.1 g (6.7 mmol) of **26** in 40 mL dry THF were placed in a three necked round bottom flask fitted with an argon inlet and a septum. The mixture was cooled to – 78 °C and a solution of phenyllithium (1.8 mol/L in dibutyl ether, 11.2 mL, 20.2 mmol) was slowly added using a syringe. After 20 min full conversion was confirmed via TLC (PE:EA 1:1). The mixture was allowed to warm to – 30 °C and quenched by adding 16 mL of saturated NH_4Cl solution. After warming to room temperature the layers were separated. The aqueous layer was extracted twice with THF and the organic layer was washed with water and brine, dried over Na_2SO_4 and filtrated. The solvent was removed under reduced pressure. Recrystalization from EA / n-Hexane yielded pure product as a pale yellow solid (1.8 g, 5.1 mmol, 76%). The remaining crude oil was purified via column chromatography (LP:EA 2:1), yielding additional 0.3 g pure product giving an overall yield of the reaction of 90 %.



46

$C_{24}H_{25}NO_2$
359.46 g/mol

$\mathbf{r_f}$ = 0.29 (LP:EA 2:1)

$\mathbf{[\alpha]_{589}^{20}}$ = 36.951 (CH_2Cl_2, c = 0.985)

mp = 155-157 °C

IR: ν = 3438 cm^{-1}, 3030 cm^{-1}, 2818 cm^{-1}, 1597 cm^{-1}, 1495 cm^{-1}, 1448 cm^{-1}, 1381 cm^{-1}, 1265 cm^{-1}, 1210 cm^{-1}, 1044 cm^{-1}, 917 cm^{-1}, 860 cm^{-1}

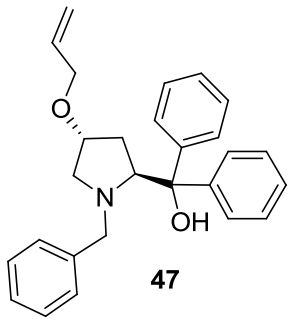
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.69 (d, 2H, *J* = 7.43 Hz), 7.53 (d, 2H, *J* = 7.23 Hz), 7.33-6.85 (m, 11H), 4.87 (bs, 1H, OH), 4.34 (t, 1H, *J* = 7.82 Hz), 4.21 (quin, 1H, *J* = 2.64 Hz), 3.24 (s, 2H), 3.02 (dd, 1H, J_1 = 4.69 Hz, J_2 = 11.15 Hz), 2.46 (dd, 1H, J_1 = 3.91 Hz, J_2 = 11.15 Hz), 1.82 (m, 2H), 1.35 (bs, 1H, OH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 147.6 (s), 146.0 (s), 139.4 (s), 128.6 (d, 2C), 128.3 (d, 2C), 128.2 (d, 2C), 128.1 (d, 2C), 127.0 (d), 126.6 (d), 126.4 (d), 125,6 (d, 2C), 125.4 (d, 2C), 76.8 (s), 70.9 (d), 70.5 (d), 62.1 (t), 61.2 (t)

HR/MS for $C_{24}H_{25}NO_2$: $[M]^+$ calcd.: 360.1958, found: 360.1954

6.4.11 ((2*S*,4*R*)-4-(Allyloxy)-1-benzylpyrrolidin-2-yl)diphenylmethanol

Diol **46** (1.6 g, 4.4 mmol) was placed in a 50 mL Schlenk flask under argon and dissolved in 25 mL of dry DMF. NaH (0.4 g, 10.5 mmol, moistened with ~40% mineral oil) was added under argon counter current flow. The mixture was stirred at room temperature until gas evolution ceased (~1 h). Allyl bromide (420 µl, 4.9 mmol) was added using a Hamilton syringe and the reaction mixture was stirred overnight. TLC (LP:EA = 4 : 1) still showed some starting material, so another portion NaH (0.4 g, 10.5 mmol) was added and the stirring was continued for two days. Afterwards TLC showed full conversion. The reaction was quenched with 1 g (12 mmol) $NaHCO_3$ and 20 mL of diethyl ether. The solution was transferred to a separating funnel and washed three times with 20 mL of water. After drying over Na_2SO_4 the solvent was removed under reduced pressure, yielding a white, crystalline solid (1.8 g, 4.4 mmol, 100.7%). Solvent residues were removed under high vacuum and the crude product was applied in the next step without further purification.



47

$C_{27}H_{29}NO_2$
399.52 g/mol

$\mathbf{r_f}$ = 0.16 (LP:EA 20:1)

$[\alpha]_{589}^{20}$ = 32.737 (CH_2Cl_2, c = 1.00)

mp = 116-119 °C

IR: ν = 3453 cm^{-1}, 3030 cm^{-1}, 2908 cm^{-1}, 2800 cm^{-1}, 1597 cm^{-1}, 1494 cm^{-1}, 1447 cm^{-1}, 1274 cm^{-1}, 1095 cm^{-1}, 1006 cm^{-1}, 858 cm^{-1}, 762 cm^{-1}, 699 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.76 (d, 2H, *J* = 7.16 Hz), 7.60 (d, 2H, *J* = 7.50 Hz), 7.36-6.97 (m, 11H), 5.98-5.76 (m, 1H), 5.32-5.09 (m, 2H), 4.94 (bs, 1H, OH), 4.33 (t, 1H), 3.88 (m, 2H), 3.26 (d, 2H, *J* = 10.24 Hz), 3.04 (dd, 1H, J_1 = 4.32 Hz, J_2 = 11.04 Hz), 2.60 (dd, 1H), 2.07-1.77 (m, 2H)

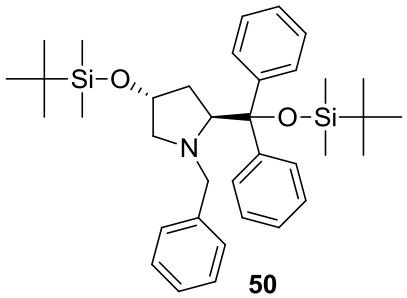
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 147.8 (s), 146.1 (s), 139.6 (s), 134.8 (d), 128.6 (d, 2C), 128.31 (d, 2C), 128.29 (d, 2C), 128.2 (d, 2C), 127.0 (d), 126.6 (d), 126.4 (d), 125.7 (d, 2C), 125.5 (d, 2C), 116.8 (t), 77.5 (d), 77.1 (s), 70.5 (d), 69.9 (t), 61.2 (t), 59.2 (t), 36.0 (t)

HR/MS for $C_{26}H_{28}NO_2$: $[M]^+$ calcd.: 400.2271, found: 400.2275

6.4.12 (2*S*,4*R*)-1-Benzyl-4-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy) diphenylmethyl) pyrrolidine

0.5 g (1.4 mmol) of **46** in 20 mL dry CH_2Cl_2 were placed in a Schlenk flask under argon and cooled to -15 °C. Freshly distilled dry 2,6-lutidine (0.65 ml, 5.6 mmol) and 1.2 mL (4.9 mmol) TBDMS triflate were added using Hamilton syringes. The reaction mixture was allowed to slowly warm up to room temperature and stirred for five days until TLC (LP:EA 5:1) confirmed full conversion. The reaction was quenched by adding 5 mL of saturated $NaHCO_3$ solution. Organic layer was washed with

$NaHCO_3$ solution and water. Combined aqueous layers were extracted with CH_2Cl_2 once. Combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, yielding the desired product as crude yellow oil. MPLC purification yielded 0.7 g (1.2 mmol, 86%) of clear, pale yellow oil.



50

$C_{36}H_{53}NO_2Si_2$
587.98 g/mol

$\mathbf{r_f}$ = 0.51 (PE:EA 20:1)

$[\alpha]_{589}^{20}$ = - 65.731 (CH_2Cl_2, c = 0.495)

IR: ν = 3027 cm^{-1}, 2954 cm^{-1}, 2928 cm^{-1}, 2855 cm^{-1}, 1494 cm^{-1}, 1449 cm^{-1}, 1360 cm^{-1}, 1251 cm^{-1}, 1060 cm^{-1}, 1027 cm^{-1}, 833 cm^{-1}, 771 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.64 (m, 2H), 7.53 (m, 2H), , 7.37-7.02 (m, 11H), 4.41-4.22 (m, 2H), 3.72 (m, 1H), 3.18 (quin, 1H, J = 5.61 Hz), 2.32 (dd, 1H, J_1 = 10.15, J_2 = 5.16), 2.15 (dd, 1H, J_1 = 10.14, J_2 = 5.43), 1.98 (t, 2H, J = 6.52), , 0.88 (s, 9H), 0.77 (s, 9H), -0.11 (s, 3H), -0.16 (s, 3H), -0.37 (s, 3H), -0.44 (s, 3H)

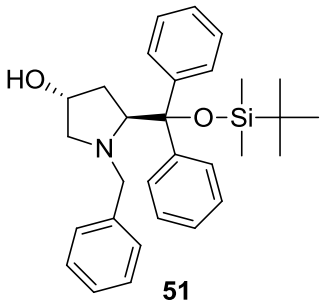
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 143.8 (s), 143.0 (s), 141.1 (s), 130.2 (d, 2C), 129.9 (d, 2C), 128.4 (d, 2C), 128.0 (d, 2C), 127.4 (d), 127.2 (d, 2C), 126.9 (d), 126.6 (d, 2C), 126.3 (d), 84.1 (s), 71.2 (d), 70.5 (d), 62.4 (t), 61.4 (t), 38.5 (t), 26.3 (q, 3C), 25.8 (q, 3C), 19.0 (s), 18.0 (s), -2.8 (q, 2C), -3.2 (q, 2C)

HR/MS for $C_{36}H_{53}NO_2Si_2$: $[M]^+$ calcd.: 588.3688, found: 588.3712

6.4.13 (3*R*,5*S*)-1-Benzyl-5-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin-3-ol

Silyl ether **50** (0.55 g, 0.9 mmol) was placed in a round bottomed flask and dissolved in 10 mL methanol. Camphorsulfonic acid (0.35 g, 1.4 mmol) was added slowly under vigorous stirring causing the solution to turn reddish. After three days stirring at room temperature TLC (LP:EA = 8 : 1) showed full conversion. Reaction was quenched with about 2 g of solid $NaHCO_3$. Methanol was carefully evaporated under reduced pressure and the residue was dissolved in ethyl acetate and water. The layers were separated; the aqueous layer was extracted with additional EA. The combined organic layers were washed with saturated $NaHCO_3$ solution, water and brine, respectively. After drying over Na_2SO_4 the solvent was removed under reduced pressure, yielding brownish oil as crude product.

MPLC purification yielded 0.34 g (0.68 mmol, 76%) of clear, pale yellow oil.



51

$C_{30}H_{39}NO_2Si$
473.72 g/mol

r_f = 0.23 (PE:EA 8 : 1)

$[\alpha]_{589}^{20}$ = - 77.048 (CH_2Cl_2, c = 1.005)

IR: ν = 3320 cm^{-1}, 2957 cm^{-1}, 2855 cm^{-1}, 1493 cm^{-1}, 1445 cm^{-1}, 1336 cm^{-1}, 1250 cm^{-1}, 1057 cm^{-1}, 833 cm^{-1}, 773 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.65 (m, 2H), 7.57 (m, 2H), 7.36-7.07 (m, 11H), 4.45-4.30 (m, 2H), 3.76 (m, 1H), 3.49 (quin, 1H, J = 5.09), 2.41 (dd, 1H, J_1 = 10.96, J_2 = 4.89), 2.22 (dd, 1H, J_1 = 10.96, J_2 = 4.49), 2.08 (m, 2H, J = 7.73), 1.37 (bs, 1H OH), 0.92 (s, 9H), -0.38 (s, 3H), -0.42 (s, 3H)

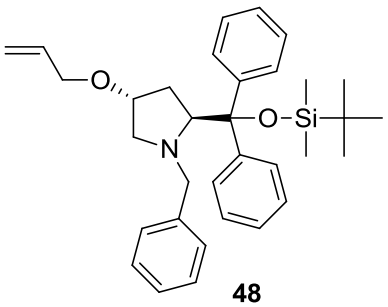
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 143.7 (s), 142.9 (s), 140.8 (s), 130.1 (d, 2C), 130.0 (d, 2C), 128.4 (d, 2C), 128.1 (d, 2C), 127.5 (d), 127.3 (d, 2C), 127.0 (d), 126.7 (d, 2C) 126.4 (d), 84.2 (s), 71.2 (d), 70.7 (d), 62.4 (t), 61.3 (t), 38.4 (t), 26.4 (q, 3C), 19.0 (s), -2.8 (q), -3.1 (q)

HR/MS for $C_{30}H_{39}NO_2Si$: $[M]^+$ calcd.: 474.2823, found: 474.2832

6.4.14 (2*S*,4*R*)-4-(Allyloxy)-1-benzyl-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine

Secondary alcohol **51** (0.72 g, 1.5 mmol) was placed in a Schlenk flask under argon and dissolved in 20 mL of dry DMF. NaH (~60% suspension, moistened with mineral oil; 0.3 g, 7.8 mmol) was added under argon counter current flow. The mixture was stirred at room temperature and turned dark reddish brown. After one hour allyl bromide (0.2 mL, 2.3 mmol) was added using a syringe, causing the reaction mixture to turn yellow. After two days stirring at room temperature TLC (LP:EA = 4 : 1) showed still some starting material, so another 0.05 mL (0.6 mmol) allyl bromide were added. After further stirring for 24 h TLC showed full conversion. The reaction was quenched with 5 mL of saturated NH_4Cl solution and the mixture was transferred into a separating funnel. 20 mL of ethyl acetate were added and the layers were separated. The organic layer was washed three times with water and once with brine. The combined aquaeous layers were extracted with ethyl acetate again, which was then washed with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, yielding 0.83 g (107%) of crude, yellow product.

Solvent residues were removed under high vacuum and the crude product was applied in the next step without further purification.



48

$C_{33}H_{43}NO_2Si$
513.79 g/mol

$\mathbf{r_f}$ = 0.39 (LP:EA 20 : 1)

$\mathbf{[\alpha]_{589}^{20}}$ = - 43.996 (CH_2Cl_2, c = 0.985)

IR: ν = 2954 cm^{-1}, 2855 cm^{-1}, 1662 cm^{-1}, 1494 cm^{-1}, 1446 cm^{-1}, 1250 cm^{-1}, 1085 cm^{-1}, 1057 cm^{-1},919 cm^{-1}, 833 cm^{-1}, 773 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.64 (m, 2H), 7.34-7.06 (m, 11H), 5.93-7.70 (m, 1H), 5.25-5.05 (m, 2H), 4.31 (m, 1H), 3.72 (m, 3H), 3.12 (quin. 1H, *J* = 4.99 Hz), 2.28 (t, 2H, *J* = 4.60), 2.17-1.99 (m, 2H), 0.91 (s, 9H), -0.39 (s, 3H), -0.43 (s, 3H)

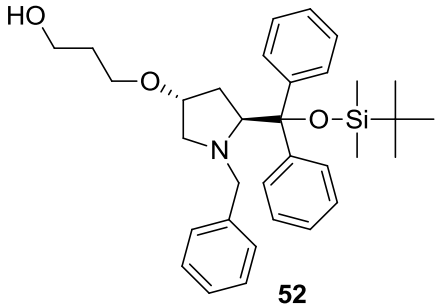
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 143.9 (s), 143.1 (s), 141.0 (s), 135.0 (d), 130.1 (d, 2C), 130.0 (d, 2C), 128.4 (d, 2C), 128.0 (d, 2C), 127.5 (d), 127.3 (d, 2C), 126.9 (d), 126.7 (d, 2C), 126.4 (d), 116.5 (t) 84.2 (s), 78.3 (d), 70.7 (d), 69.9 (t), 62.3 (t), 57.8 (t), 35.7 (t), 26.4 (q, 3C), 19.0 (s), -2.8 (q), -3.1 (q)

HR/MS for $C_{33}H_{43}NO_2Si$: $[M]^+$ calcd.: 514.3136, found: 514.3150

6.4.15 3-(((3*R*,5*S*)-1-Benzyl-5-(((tert-butyldimethylsilyl)oxy)-diphenylmethyl)pyrrolidin-3-yl)oxy)propan-1-ol

Allylether **48** (1.43 g, 2.78 mmol) was placed in a Schlenk flask under argon and dissolved in 30 mL dry THF. The mixture was cooled to -15 °C and a solution of BH_3 in THF (8.36 mL, 3 eq. 8.36 mmol) was added via a syringe. The reaction was allowed to warm up to rt and stirred for 18 h until TLC (LP:EA %:1) showed complete conversion. Solid K_2CO_3 (2.6 g, 14 mmol) was added to the mixture, followed by careful addition of a hydro peroxide solution (1.5 mL 30%, 11.12 mmol). Reaction was stirred at rt for 4 h. Full oxidation of the borane intermediate was checked via

TLC. Remaining hydro peroxide was destroyed with a saturated solution of sodium thio sulphate. After 10 min stirring a saturated solution of NH_4Cl was added to the reaction. Layers were separated and the aqueous layer was extracted twice with Et_2O. Combined organic layers were washed with water and brine respectively, dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure to give a mixture of the Markovnikov and anti-Markovnikov alcohols (1.428 g). Chromatographic purification (100x KG, LP:EA 6:1) yielded the desired alcohol as colourless liquid (0.724g, 1.36 mmol, 49%).



52

$C_{33}H_{45}NO_3Si$
531.80 g/mol

r_f = 0.14 (LP:EA 6:1)

$[\alpha]_{589}^{20}$ = -60.743 (CH_2Cl_2, c = 0.948)

IR: ν = 3388 cm^{-1}, 3026 cm^{-1}, 2928 cm^{-1}, 2855 cm^{-1}, 1494 cm^{-1}, 1444 cm^{-1}, 1359 cm^{-1}, 1251 cm^{-1},1058 cm^{-1}, 833 cm^{-1}, 747 cm^{-1}

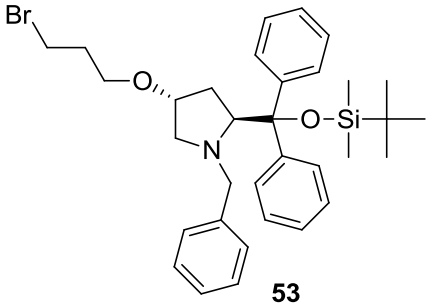
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.68-7.59 (m, 2H), 7.59-7.50 (m, 2H), 7.35-7.05 (m, 11H), 4.40-4.21 (m, 2H), 3.77-3.61 (m, 3H), 3.34 (td, 2H, J_1 = 2.79 Hz, J_2 = 1.37 Hz), 3.07 (quin, 1H, J = 4.99 Hz), 2.29 (d, 2H, J = 4.50 Hz), 2.15-2.02 (m, 2H), 1.73 (quin, 2H, J = 5.62 Hz), 0.91 (s, 9H), -0.40 (s, 3H), -0.44 (s, 3H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 143.8 (s), 143.0 (s), 140.8 (s), 130.03 (d, 2C), 129.96 (d, 2C), 128.3 (d, 2C), 128.1 (d, 2C), 127.5 (d), 127.3 (d, 2C), 127.0 (d), 126.7 (d, 2C), 126.5 (d), 84.1 (s), 79.1 (d), 70.6 (d), 68.5 (t), 62.3 (t, 2C), 57.9 (t), 35.6 (t), 32.0 (t), 26.3 (q, 3C), 19.0 (s), -2.9 (q), -3.1 (q)

HR/MS for $C_{33}H_{45}NO_3Si$: $[M]^+$ calcd.: 532.3241, found: 532.3258

6.4.16 2*S*,4*R*)-1-Benzyl-4-(3-bromopropoxy)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine

Primary alcohol **52** (0.080 g, 0.15 mmol) was dissolved in 4 mL dry DCM. The mixture was cooled to 0 °C and triphenylphosphine (0.079 g, 0.3 mmol, 1.5 eq) and tetrabromo methane (0.0995g, 0.3 mmol, 1.5 eq) were added. The mixture was allowed to warm to rt and stirred for 60 min until TLC (LP:EA 8:1) showed full conversion. The reaction was quenched with a saturated solution of $NaHCO_3$ and layers were separated. Aqueous layer was again extracted with DCM and combined organic layers were washed with water and brine respectively. Careful evaporation of solvent at rt gave the desired bromide as raw product. Bromide was purified via column chromatography (LP:EA 16:1) to yield 0.088 g (0.147 mmol, 98%) light yellow liquid, which was very unstable and had to be used immediately or stored at -20 °C.



53

$C_{33}H_{44}BrNO_2Si$
594.70 g/mol

r_f = 0.36 (LP:EA 16:1)

$[\alpha]_{589}^{20}$ = -44.205 (CH_2Cl_2, c = 1.150)

IR: ν = 2953 cm^{-1}, 2926 cm^{-1}, 2854 cm^{-1}, 1494 cm^{-1}, 1445 cm^{-1}, 1255 cm^{-1}, 1088 cm^{-1}, 1059 cm^{-1},1027 cm^{-1}, 833 cm^{-1}, 701 cm^{-1}

^{1}H-NMR (200 MHz, CD_2Cl_2): δ = 7.59-7.38 (m, 4H), 7.31-6.91 (m, 11H), 4.19 (m, 2H), 3.38 (t, 2H, *J* = 6.55 Hz), 3.18 (t, 2H, *J* = 5.38 Hz), 3.01 (quin, 1H, *J* = 4.84 Hz), 2.14 (t, 2H, *J* = 4.40 Hz), 2.04-1.83 (m, 4H), 1.60 (m, 1H), 0.83 (s, 9H), -0.48 (d, 3H)

^{13}C-NMR (50 MHz, CD_2Cl_3): δ = 144.4 (s), 143.5 (s), 141.6 (s), 130.5 (d, 2C), 130.3 (d, 2C), 128.7 (d, 2C), 128.3 (d, 2C), 127.7 (d), 127.6 (d, 2C), 127.2 (d), 127.1 (d, 2C), 126.7

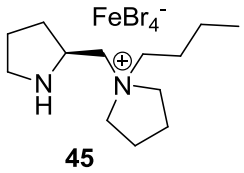
(d), 84.6 (s), 79.4 (d), 71.2 (d), 66.4 (t), 62.8 (t), 58.2 (t), 35.9 (t), 33.5 (t), 31.3 (t), 26.4 (q, 2C), 19.1 (s), -3.0 (q, 2C)

HR/MS for $C_{33}H_{44}BrNO_2Si$: $[M]^+$ calcd.: 594.2397, found: 594.2422

6.5 Synthesis of iron containing chiral ionic liquids

6.5.1 (*S*)-1-Butyl-1-(pyrrolidin-2-ylmethyl)pyrrolidin-1-ium-tetrabromoferrate(III)

Equimolar amounts of IL **44** (0.534 g, 1.84 mmol) and $FeBr_3$ (0.542 g, 1.84 mmol) were weighted into a round bottom flask and covered with a layer of dry MeOH. After the exothermic reaction was finished, solvent was evaporated and obtained iron containing IL was dried in high vacuum and isolated as dark reddish solid (1.05 g, 1.8 mmol, >99%).



45

$C_{13}H_{27}Br_4FeN_2$
586,83 g/mol

$[\alpha]_{389}^{20}$ = 21.427 (EtOH, c = 0.0056)

mp = 57-60 °C

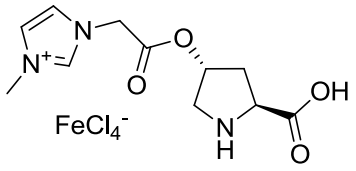
IR: ν = 2959 cm^{-1}, 2873 cm^{-1}, 2719 cm^{-1}, 1570 cm^{-1}, 1455 cm^{-1},1399 cm^{-1}, 1302 cm^{-1}, 1026 cm^{-1}, 1004 cm^{-1}

Thermal analysis: TGA showed no thermal decomposition below 150 °C.

Anal. Calcd. for $C_{13}H_{27}Br_4FeN_2$: C, 26.61; H, 4.64; N, 4.77. Found: C, 26.76; H, 4.26; N, 4.45

6.5.2 1-(2-(((3*R*,5*S*)-5-Carboxypyrrolidin-3-yl)oxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium iron(III) chloride

According to procedure 6.5.1, to IL Cl **29** (0.604 g, 2.07 mmol) equimolar amount of $FeCl_3$ (0.3357 g, 2.07 mmol) and dry methanol were added. Iron containing IL was dried in high vacuum and isolated as brown-black solid (0.939 g, 2.07 mmol, >99%).



30a

$C_{11}H_{16}Cl_4FeN_3O_4$
451.92 g/mol

$[\alpha]_{589}^{20}$ = 60.700 (EtOH, c = 0.0056)

mp = = 89-93 °C

IR: ν = 3101 cm^{-1}, 2955 cm^{-1}, 1749 cm^{-1}, 1631 cm^{-1}, 1564 cm^{-1}, 1439 cm^{-1}, 1371 cm^{-1}, 1217 cm^{-1}, 1173 cm^{-1}, 1019 cm^{-1}, 833 cm^{-1}

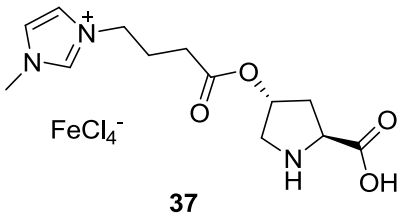
Thermal analysis: TGA showed no thermal decomposition below 150 °C.

DSC showed a glass transition at 13.9 °C.

Anal. Calcd. for: C, 29.23; H, 3.57; N, 9.3. Found: C, 27.69; H, 3.33; N, 8.85

6.5.3 3-(4-(((3*R*,5*S*)-5-Carboxypyrrolidin-3-yl)oxy)-4-oxobutyl)-1-methyl-1H-imidazol-3-ium iron(III) chloride

According to procedure 6.5.1, to IL Cl **36** (1.061 g, 3.34 mmol) an equimolar amount of $FeCl_3$ (0.5417 g, 3.34 mmol) and dry methanol were added. The mixture was stirred at rt for 2 min, MeOH was removed and iron containing IL was dried in high vacuum and isolated as orange-black solid (1.605 g, 3.34 mmol, quant.).



37

$C_{13}H_{20}Cl_4FeN_3O_4$
479.97 g/mol

[α]$_{589}^{20}$ = 38.232 (EtOH, c = 0.0136)

mp = 62-68 °C

IR: ν = 3101 cm^{-1}, 2956 cm^{-1}, 1731 cm^{-1}, 1631 cm^{-1}, 1572 cm^{-1}, 1379 cm^{-1}, 1159 cm^{-1}, 1020 cm^{-1}, 832 cm^{-1}, 743 cm^{-1}

Thermal analysis: TGA showed no thermal decomposition below 150 °C.

Anal. Calcd. for $C_{13}H_{20}Cl_4FeN_3O_4$: C, 32.53; H, 4.20; N, 8.75. Found: C, 31.92; H, 3.95; N, 8.15

6.6 Henry reaction

6.6.1 General procedure for asymmetric Henry reaction:

Sock solutions containing ligand, $Cu(OAc)_2$ and nitro methane in *i*-PrOH were prepared. To a certain amount of stock solution (10 mol% ligand, 20 mol% $Cu(OAc)_2$ and 18 equiv. nitromethane with respective to the amount of aldehyde) 0.1 mmol freshly distilled aldehyde was added. The mixture was cooled to 0 °C and stirred for 72 h. Reaction mixture was diluted with 20 mL diethylether and extracted with saturated NH_4Cl solution und brine. Organic layer was dried over Na_2SO_4, filtered and solvent was removed under reduced pressure. Raw yield was determined and the residue was directly taken for NMR and HPLC-analysis. Chromatographical purification was done with a 50 fold amount SG and LP:EA and yielded the desired alcohol.

NMR Quantification:

5-10 mg of sample were weighted on a analytical scale (0.01 mg accuracy) directly into an NMR tube. A similar, but exactly known, amount of toluene as an analytical standard (5-10 mg) was added and spectra in deuterated MeOH were measured. The

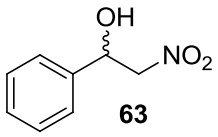
integrals of a proton signal of the product can be directly correlated to the integral of the CH_3 signal of toluene by comparison of the weight.

The racemic product of each aldehyde was taken to establish a HPLC-method for enantiomeric separation. Determination between the signals of the (*R*)- and (*S*)-enantiomers was done by a literature experiment using a Cu(II) spartein complex according to a procedure published by Maheswaran.[63] As reported by Maheswaran, this experiment gave an excess of the (*R*)-enantiomer of 2-nitro-1-phenylethanol. This knowledge allowed assigning the signals in HPLC chromatograms to the appropriate enantiomer.

For other nitroaldol products sample with high *ee* values were taken for measurement of optical rotation and obtained values were compared with literature values and HPLC signals were assigned.

6.6.1.1 2-Nitro-1-phenylethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.



63

$C_8H_9NO_3$
167.16 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.34 (s, 5H), 5.38 (dd, 1H), 4.49 (m, 2H), 2.77 (d, 1H, OH)

Chiral HPLC: Chiralpak AS-H; *n*-heptane/*i*-propanol = 98:2; 0.5 ml/min; 212 nm

t_{R1} = 118.8 min (*S*)

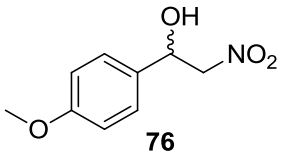
t_{R2} = 117.6 min (*R*)

Analytical data are in accordance with literature values.[225]

6.6.1.2 1-(4-Methoxyphenyl)-2-nitroethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.

[225] Yang, Wen; Du, Da-Ming. *Eur. J. Org. Chem.* **2011**, *8*, 1552



76

$C_9H_{11}NO_4$
197.19 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 7.24 (d, 2H), 6.82 (d, 2H), 5.21 (dd, 1H), 4.51 (m, 2H)

Chiral HPLC: Chiralpak AS-H; *n*-heptane/*i*-propanol = 95:5; 1.0 ml/min; 212 nm

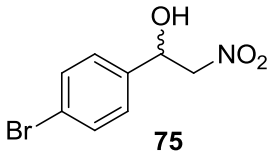
t_{R1} = 22.6 min (*S*)

t_{R2} = 23.6 min (*R*)

Analytical data are in accordance with literature values.[226]

6.6.1.3 1-(4-Bromophenyl)-2-nitroethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.



75

$C_8H_8BrNO_3$
246.06 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 7.54 (d, 2H), 7.36 (d, 2H), 5.38 (dd, 1H), 4.61 (m, 2H)

Chiral HPLC: Chiralcel IA; *n*-heptane/*i*-propanol = 85:15; 0.8 ml/min; 230 nm

t_{R1} = 12.5 min (*R*)

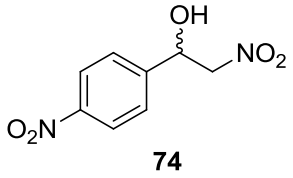
t_{R2} = 16.1 min (*S*)

Analytical data are in accordance with literature values.[227]

6.6.1.4 3-Nitro-1-(4-nitrophenyl)ethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.

[226] Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. J.*Org.Chem*. **2010**, *75*, 1313
[227] Reddy, B.V.; Reddy, S.M.; Manisha S.; Madan, C. *Tetrahedron:Asymmetry*. **2011**, *22*, 530



74

$C_8H_8N_2O_5$
212.16 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 8.25 (d, 2H), 7.69 (d, 2H), 5.52 (dd, 1H), 4.68 (m, 2H)

HPLC: Chiralpak AS-H; *n*-heptane/*i*-propanol = 85:15; 1.0 ml/min; 212 nm

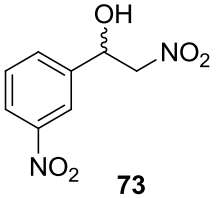
t_{R1} = 33.5 min (*S*)

t_{R2} = 35.5 min (*R*)

Analytical data are in accordance with literature values.[228]

6.6.1.5 2-Nitro-1-(3-nitrophenyl)ethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.



73

$C_8H_8n_2O_5$
212.16 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 8.37 (s, 1H), 8.19 (d, 1H), 7.87 (d, 1H), 7.64 (t, 1H), 5.54 (dd, 1H), 4.69 (m, 2H), 3.93 (m, 1H, OH)

Chiral HPLC: Chiralcel IA; *n*-heptane/*i*-propanol = 85:15; 0.8 ml/min; 254 nm

t_{R1} = 13.6 min (*S*)

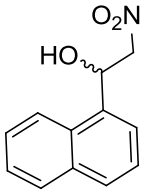
t_{R2} = 15.0 min (*R*)

Analytical data are in accordance with literature values.[229]

[228] Blay, G.; Hernandez-Olmos, V.; Pedro, J.R. *Tetrahedron:Asymmetry*. **2010**, *21*, 578
[229] Zhang, G.; Woggon, W.D.; Yashima, E. *Adv. Synth. Catal.* **2009**, *351*, 1255

6.6.1.6 1-(Naphthalen-1-yl)-2-nitroethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.



72

$C_{12}H_{11}NO_3$
217.22 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 8.23-7.44 (m, 7H), 6.21 (dd, 1H), 4.72 (m, 2H)

Chiral HPLC: Chiralpak AS-H; *n*-heptane/*i*-propanol = 90:10; 0.5 ml/min; 220 nm

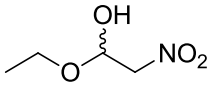
t_{R1} = 29.4 min (*S*)

t_{R2} = 33.7 min (*R*)

Analytical data are in accordance with literature values.[230]

6.6.1.7 1-Ethoxy-2-nitroethanol

Preparation according to general procedure 6.6.1 gave the desired alcohol.



77

$C_4H_9NO_4$
135.12 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.68 (d, 2H), 4.54 (t, 1H), 4.27 (q, 2H), 1.26 (t, 3H)

Chiral HPLC: Chiralpak AS-H; *n*-heptane/*i*-propanol = 85:15; 1.0 ml/min; 230 nm

t_{R1} = 14.6 min (*S*)

t_{R2} = 17.9 min (*R*)

Analytical data are in accordance with literature values.[231]

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[230] Yang, Wen; Du, Da-Ming. *Eur. J. Org. Chem.* **2011**, *8*, 1552
[231] Suribabu, J.; Prasenjit, S.; Sridhar, S.; Sekarpandi, S.; Tharmalingam, P. *Tetrahedron*, **2008**, *64*, 11724

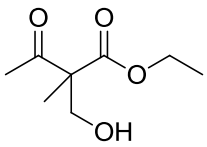
6.7 Hydroxymethylation

6.7.1 General procedure for the iron catalyzed hydroxymethylation.

β-ketoester (1 mmol) and iron containing IL (0.01 mmol) were mixed and a 37% aqueous formaldehyde solution (100 µL, 6 mmol) was added to the violet solution. The reaction was stirred at room temperature until TLC indicated complete conversion. Water was evaporated under reduced pressure and the remaining yellow oil was directly subjected to flash column chromatography (LP:Et_2O 1:1) to yield the hydroxymethylated β-oxo ester as colourless liquid.

6.7.1.1 Ethyl-2-(hydroxymethyl)-2-methyl-3-oxobutanoate

Preparation according to general procedure 6.7.1 gave the hydroxymethylated product **94** as colourless liquid in 99% yield.



94
$C_8H_{14}O_4$
174.19 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.10 Hz, 2H), 3.88/3.71 (2d, *J* = 11.34 Hz, 2H), 3.09 (br s, 1H, OH), 2.12 (s, 3H), 1.29 (s, 3H), 1.19 (t, *J* = 7.14 Hz, 3H)

Chiral GC: column BGB 175, 30 m x 0.25 mm x 0.25 µm

80 °C, 5.0 r -100 °C, 0.5 r -120 °C, 5.5 min hold, 10 r -200 °C, 1 min hold;

inlet 230 °C, flow 2 mL/min, split flow 40, split ratio 20; detector 250 °C

t_{R1} = 45.6 min

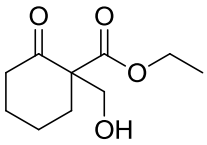
t_{R2} = 46.7 min

Analytical data were in accordance with literature values.[232]

[232] Akeboshi, T.; Ohtsuka, Y.; Sugai, T.; Ohta, H. *Tetrahedron* **1998**, 54, 7387.

6.7.1.2 Ethyl 1-(hydroxymethyl)-2-oxocyclohexane carboxylate

Preparation according to general procedure 6.7.1 gave **92** as colourless liquid in 30% yield.



92

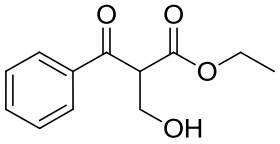
$C_{10}H_{16}O_4$
200.23 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.18 (q, *J* = 7.17 Hz, 2H), 3.76/3.63 (2d, *J* = 11.35 Hz, 2H), 3.00 (br s, 1H, OH), 2.60-2.24 (m, 3H), 1.96 (m, 1H), 1.61-1.48 (m, 4H), 1.21 (t, *J* = 7.14 Hz, 3H)

Analytical data were in accordance with literature values.[233]

6.7.1.3 Ethyl 2-(hydroxymethyl)-3-oxo-3-phenylpropanoate

Preparation according to general procedure 6.7.1 gave **90** as colourless liquid in 80% yield.



90

$C_{12}H_{14}O_4$
222.24 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ =7.93 (m, 2H), 7.45 (m, 3H), 4.55 (t, *J* = 5.67 Hz, 1H), 4.18 (m, 4H), 2.92 (br s, 1H, OH), 1.15 (t, *J* = 7.14 Hz, 3 H).

Analytical data were in accordance with literature values.[234]

[233] Chan, T. H.; Schwerdtfeger, A. E. *J. Org. Chem.* **1991**, *56*, 3294.
[234] Lecomte, V.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 1666

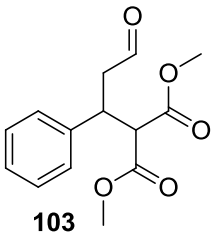
6.8 Michael addition

6.8.1 General procedure for organocatalysed Michael additions.

Cinnamon aldehyde (189 µL, 1.5 mmol), secondary amine containing IL as organocatalyst (0.1 mmol), benzoic acid (0.0122 g, 0.1 mmol) and 45 µL water were placed into a round bottom flask and dissolved in 4 ml EtOH. Malonic diethyl ester (151 µL, 1 mmol) was added via a syringe and the reaction mixture was stirred for 24 h until TLC (LP:EA 5:1) showed complete conversion. The mixture was filtered over silica. The obtained crude product was taken to establish a GC method for analytical separation of enantiomers to determine the enantioselectivity of the reaction.

6.8.1.1 Dimethyl 2-(3-oxo-1-phenylpropyl)malonate

Preparation according to general procedure 6.8.1 gave the desired product.



103

$C_{14}H_{16}O_5$
264.27 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 7.18 (m, 5H), 3.96 (m, 1H), 3.68 (m, 4H), 3.44 (s, 3H), 2.85 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 199.2 (s), 168.6 (s), 168.0 (s), 139.7 (s), 128.8 (d, 2C), 128.0 (d, 2C), 127.6 (d), 57.2 (d), 52.7 (q), 52.5 (q), 47.2 (t), 39.5 (d)

Chiral HPLC: Chiralcel IA, *n*-heptane/*i*-propanol = 85:15; 0.8 ml/min; 212 nm

t_{R1} = 14.4 min

t_{R2} = 16.1 min

Analytical data are in accordance to literature values.[235]

[235] Fleischer, I.; Pfaltz, A. *Chem. Eur. J.* **2010**, *16*, 95

6.9 Cyclopropanation

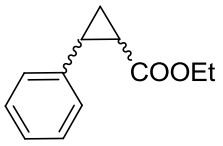
6.9.1 General procedure for cyclopropanation reaction.

Under argon counter current 1 mL freshly distilled styrene was added to either 1 mL stock solutions of copper complexes (c = 0.1 mmol/mL) or a solution of 0.1 mmol of the appropriate chiral catalyst and 0.1 mmol Cu(II) salt in dry DCM. The mixture was stirred under reflux and a solution of 1 mmol ethyl diazoacetate in 4 mL dry DCM was added via a syringe pump over a period of 6 h. After cooling to rt the reaction mixture was stirred for another 16 h and subsequently filtered through a short pad of silica and washed with DCM to remove the catalyst complex. Solvent and remaining styrene was removed under reduced pressure and crude product was taken for chiral GC, NMR and GC/MS analysis. A mixture of pure diastereomers was obtained after chromatographical purification with LP:EA 50:1.

6.9.1.1 Ethyl 2-phenylcyclopropanecarboxylate

Preparation according to general procedure 6.9.1 gave the desired cyclopropanes.

The isolated racemic products were purified via flash chromatography.



$C_{12}H_{14}O_2$
190.24 g/mol

cis isomer **80**

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.38-6.95 (m, 5H), 3.79 (q, 2H, *J* = 7.04 Hz), 2.55 (m, 1H), 2.00 (m, 1H), 1.645 (m, 2H), 0.89 (t, 3H, *J* = 7.14 Hz)

Chiral GC: column BGB 175, 30 m x 0.25 mm x 0.25 µm

80 °C, 0.5 r -100 °C, 0.1 r -110 °C, 5 min hold, 20 r -200 °C, 1 min hold;

inlet 230 °C, flow 2 mL/min, split flow 40, split ratio 20; detector 250 °C

t_{R1} = 60.77 min

t_{R2} = 62.07 min

trans isomer **81**

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.39-6.98 (m, 5H), 4.04 (q, 2H, *J* = 7.17 Hz), 2.44 (m, 1H), 1.82 (m, 1H), 1.52 (m, 2H), 1.21 (t, 3H, *J* = 7.04 Hz)

Chiral GC: column BGB 175, 30 m x 0.25 mm x 0.25 µm

80 °C, 0.5 r -100 °C, 0.1 r -110 °C, 5 min hold, 20 r -200 °C, 1 min hold;

inlet 230 °C, flow 2 mL/min, split flow 40, split ratio 20; detector 250 °C

t_{R1} = 72.55 min

t_{R2} = 73 13 min

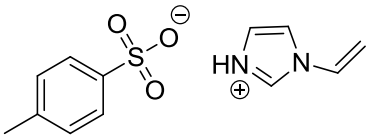
Analytical data of both isomers are in accordance to literature values.[236]

6.10 Olefin metathesis

6.10.1 1-Vinyl-1H-imidazol-3-ium 4-methylbenzenesulfonate

Vinylimidazole **60** (0.1053 g, 1 eq., 1.12 mmol) and p-tolyl solfonic acid monohydrate (0.2288 g, 1.20 mmol) were weighted into a flask and dissolved in dry DCM. After 30 min refluxing the salt was directly used in solution.

To obtain the crude salt **61** vinylimidazole (0.1053 g, 1 eq., 1.12 mmol) and p-tolyl solfonic acid monohydrate (0.2288 g, 1.20 mmol) were dissolved in toluene and evaporation of solvent at 60 °C and 140 mbar gave the salt in pure form and quantitative yield.



59

$C_{12}H_{14}N_2O_3S$

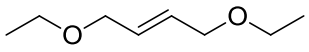
266.31 g/mol

[236] Khanbabaee, K.; Basceken, S.; Flörke, U. *Tetrahedron Asym*. **2006**, *17*, 2804

^{1}H-NMR (200 MHz, MeOD): δ = 9.18 (s, 1H), 8.01 (s, 1H), 7.68 (m, 3H), 7.24 (m, 3H), 5.94 (dd, 1H, J_1 = 2.53 Hz, J_2 = 15.65 Hz), 5.44 (dd, 1H, J_1 = 2.54 Hz, J_2 = 8.60 Hz), 2.37 (s, 3H)

6.10.2 (*E*)-1,4-Diethoxybut-2-ene

Starting material A (either salt **59** or allyl ether **48**) was weighted into a Schlenk flask. Dry DCM was added and air was removed from the mixture *via* freeze and pump. Under argon counter current 4 eq. of allyl ethylether and Grubbs catalyst (1st or 2nd generation) were added. The reaction mixture was stirred at reflux for 4 hours. TLC (LP:EA 20:1) showed starting material A but also an additional spot. Crude mixture was separated *via* column chromatography, yielding pure starting material and homo metathesis product **60**.



60

$C_8H_{16}O_2$
144 g/mol

^{1}H-NMR (200 MHz, MeOD): δ = 8.37 (s, 1H), 8.19 (d, 1H), 7.87 (d, 1H), 7.64 (t, 1H), 5.54 (dd, 1H), 4.69 (m, 2H), 3.93 (m, 1H, OH)

Analytical data are in accordance with literature values.[237]

[237] Zhang, G.; Woggon, W.D.; Yashima, E. *Adv. Synth. Catal.* **2009**, *351,* 1255

7 Appendix

7.1 Abbreviations

$[C_2mim]$	1-ethyl-3-methylimidazolium chloride
$[C_4mim]$	1-butyl-3-methylimidazolium chloride
$[C_7mim]$	1-heptyl-3-methylimidazolium
$[EtPy][CF_3COO]$	ethyl pyridinyl triflate
$10_{rel}\%$	relative%
9-BBN	9-borabicyclo[3.3.1]nonane
Å	Ångström
A^-	anion
AcCN	aceto nitril
AcO /OAc	acetate
Ag	argentum, silver
aq.	aqueous
Ar	argon
BA	benzoic acid
BF_4	tetra fluoro borate
BH_3	borane
BINOL	1,1′-Bi-2-naphthol
box	bisoxazoline
Br	bromide
cat	catalyst
CBr_4	tetrabromo methane
Cbz	carboxybenzyl

Cd	cadmium
$CDCl_3$	deuterochloroform
CH_2	methylene
CH_2Cl_2	dichloro methane
CIL	chiral ionic liquid
Cl	chloride
cm^{-1}	wavenumber
Co	cobalt
CSA	camphorsulphonic acid
Cu	copper
$Cu(OAc)_2$	copper acetate
$CuCl_2$	copper chloride
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloro methane
DHP	3,4-dihydro-*2H*-pyran
DIBAL	diisobutyl aluminium hydrid
DIPEA	diisopropyl amine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EA	ethyl acetate
EDA	ethyl diazoacetate
ee	enantiomeric excess
El	electrophile
eq.	equivalent(s)

Et_2O	diethylether
EtOH	ethanol
Fe	iron
GC	gas chromatography
GC-MS	gas chromatography – mass spectrometry
h	hour
H_2O	water
HA	Brønsted acid
hal	halide
HCHO	formaldehyde
HCOOH	formic acid
HIV	Human Immunodefficiency Virus
HPLC	high performance liquid chromatography
HR/MS	high resolution mass spectrometry
Hz	hertz
IL	ionic liquid
i-PrOH	iso propanol
IR	Infrared spectroscopy
ISTD	internal standard
k_1, k_2	rate constants
K_2CO_3	potassium carbonate
$LiAlH_4$	lithium aluminium hydrid
lig	ligand
$LiNTf_2$	lithium bis trifloursulfonic imide
LiOH	lithium hydroxide
LP	light petrol

m	multiplet
M	metal
Me	methyl
MeOH	methanol
mg	milli gram
MHz	mega hertz
$Mg(OH)_2$	magnesia hydroxide
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
N	nitrogen
N_2	molecular nitrogen
NaH	sodium hydrid
Na_2SO_4	Sodium sulphate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NEt3	triethy amine
NH_4Cl	ammonium chloride
Ni	nickel
NMR	nuclear magnetic resonance
NO_2	nitro
NTf_2	bistriflimide
nuc	nucleophile
O	oxygen
OH	hydroxy
OTf	trifluoromethanesulfonate (triflate)
Pd	palladium

$Pd(PPh_3)_4$	palladium tetrakis triphenyl phosphine
PF_6	hexafluoro phosphate
PG	protecting group
pKa	acid dissociation constant
PPh_3	triphenyl phosphine
ppm	parts per million
PpTOS	pyridinium *p*-toluenesulfonate
pTOS	*p*-toluenesulfonic acid, *p*-toluenesulfonate
q	quartet
quant	quantitative
quin	quintet
rac	racemic
rt	room temperature
s	singlet
SDBS	sodium dodecyl benzene sulfonate
sept	septet
sext	sextet
Sn	tin
SQUID	superconducting quantum interference device
t	triplet
TBAF	tetra-N-butylammonium fluoride
TBDMSOTf	tert-butyldimethylsilyl trifluoromethanesulfonate
TBS/TBDMS	tert-butyldimethylsilyl group
TFA	trifluoroacetic acid
TFAE	2,2,2-trifluoro-1-(9-anthryl)ethanol
THF	tetrahydrofurane

THP	tetrahydropyranyl-(ether)
Ti	titanium
TLC	thin layer chromatography
TLC-MS	thin layer chromatography – mass spectroscopy
vs	versus
X	if not stated otherwise, any halogen
Zn	zinc

7.2 Figures

7.3 Schemes

7.4 Tables

Curriculum Vitae

PERSONAL DETAILS:

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EDUCATION:

- Sept 2008-2012 Ph.D. research, fFORTE WIT college, Vienna University of Technology
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- Oct. 2005 Diploma Examination with distinction (MSc equivalent)
  Diploma thesis: „Bestimmung von Holz- und Rindenpechen in archäologischen Proben mittels der Pyrolyse-Gaschromatographie“ under supervision of Prof.Leopold Puchinger
- Oct. 1991-2005 Studies of Technical Chemistry at Vienna University of technology; Specialisation: Organic Chemistry and Technology
- 1983-1991 Grammar School with A-level with distinction
- 1979-1983 Elementary School

WORK EXPERIENCE and INTERNSHIP:

- Sept 2012-Dec. 2012 Project assistant in the research group Gärtner, Institute of Applied Synthetic Chemistry
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- Sept. 2008–Aug. 2012 University assistant at the Institute of Applied Synthetic Chemistry
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- May 2006-Aug. 2008 Scientific assistant in the competence centre „Holz GmbH Wood Kplus" c/o University of Natural Resources and Live Sciences
- March-April 2006 Project assistant in the research group Gärtner, "synthesis of synthons and reagents", Institute of Applied Synthetic Chemistry; Vienna University of Technology
- 1993 and 1994 Internship in the Chemical-analytical laboratory of the a.ö. KH Klosterneuburg, analysis of medical samples
- Teaching activity lecture „Holz – und Naturfaserchemie", Prof. Barbara Hinterstoisser; supervision of students in basic courses, synthetic courses and bachelor thesis

ADDITIONAL QUALIFICATIONS:

- Sept 2008-Sept 2009 development and support of chemistry courses and workshops for 10-18 years aged pupils, especially girls, within the frame of WIT, FIT, and open day
- Dec. 2007 Project management
- Language skills: German, mother tongue
  English, excellent
- EDV MS Office 2007, Chem. Draw, Topspin, Spectrum, Chromatographic software…..
- since July 2007 voluntary working as LLL leader for breastfeeding, La Leche Liga Austria

PUBLICATIONS and CONFERENCE CONTRIBUTIONS:

Publications

- *Studies in organic archaeometry VII – differentiation of wood and bark pitches by pyrolysis capillary gas chromatography (Py-CGC)*
  Puchinger, L.; Sauter, F.; Leder, S.; Varmuza, K.; *Annali di chimica,* **2007**, *97*, 513.
- *From solvent to sustainable catalysis. Chloferrate ionic liquids in synthesis*
  Bica, K.; Leder, S.; Gärtner; P. *Current Org. Synth.* 2011, *8*, 824.
- *Chiral metal containing ionic liquids as catalysts in asymmetric synthesis*
  Abstract of Papers *239th ACS Meeting*, **2010**, San Francisco, United States
- *Design, synthesis and Applications of Novel Chiral ONN-Ligands for asymmetric alkylation*
  Bica, K.; Leder, S.; Mereiter, K.; Gärtner; P. *Chemical monthly.* 2012, accepted for publication.

Posters

- *Shigometry- Measurement of cold-water extracts from wood particles - a smart tool for early decay detection*
  Leder, S.; Weigl, M.; Grabner, M.; Wimmer, R.; *14th ISWFPC*, **2007**, Durban, South Africa
- *Bifunctional Chiral Ionic Liquids – At the Interface of Organo- and Transition Metal Catalysis*
  Leder, S.; Bica, K.; Gärtner, P. *EUCHEM conference on molten salts and ionic liquids*, **2010**, Bamberg, Germany
- *Design, Synthesis and Application of Novel Chiral Ionic Liquids from Amino Acids*
  Leder, S.; Bica, K.; Gärtner, P.; *Green solvents for Synthesis*, **2010**, Berchtesgaden, Germany
- *Chiral Pyridinium based Ionic Lquids as Novel Catalysts in Asymmetric Henry Reaction*
  Leder, S.; Enev, V.; Bica, K.; Gärtner, P.; *14th BDSHC Blue Danube Symposium on Heterocyclic Chemistry*, **2011**, Podbanske, Slovakia
- *Design, Synthesis and Application of Chiral Ionic Liquids as Novel catalysts in asymmetric Henry Reaction*
  Leder, S.; Enev, V.; Bica, K.; Gärtner, P.; *Materials and Technologies for Green Chemistry*, **2011**, Tallinn, Estonia

Vienna, 08. January 2013 DIin Sonja Leder