DISSERTATION

Chiral and Metal Functionalized Ionic Liquids in Organic Synthesis

Ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Doktors der technischen Wissenschaften unter der Leitung von

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Wien, im Oktober 2007

Short abstract

The design, synthesis and application of various chiral ionic liquids derived from chiral-pool components was investigated. Starting from camphor derivatives, chiral ionic liquids that could be used as alternative reaction media for the stereoselective Diels-Alder reaction were developed. New chiral ionic liquids with amido alcohol structure could be successfully applied as chiral shift reagents for the determination of enantiomeric excess of racemic salts. Furthermore, basic amino alcohol-derived ionic liquids were successfully applied as catalysts in the asymmetric alkylation of aldehyds and gave high enantioselectivities of up to 95% ee.

In the second part, the application of metal-containing ionic liquids as recyclable catalysts for C-C bond formation besides their application as mere reaction media was investigated.

The iron-containing ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) could be established as efficient and recyclable catalyst for biphasic Kumada-Corriu cross-coupling. Additionally, this ionic liquid was successfully applied in the iron-catalyzed Michael addition under microwave conditions as well as in hydroxymethylation in aqueous systems. In each case, the concept of metal-containing ionic liquid catalysts worked exceptionally well and showed several advantages compared to conventional catalysts.

Deutsche Kurzfassung

Im Rahmen dieser Dissertation wurden verschieden Synthesewege zur Herstellung von neuen chiralen ionischen Flüssigkeiten entwickelt und deren Anwendung untersucht. Ausgehend von Campher-Derivaten konnten chirale ionische Flüssigkeiten als neuartige Reaktionsmedien für die stereoselektive Diels-Alder Reaktionen synthetisiert werden. Neue chirale ionische Flüssigkeiten mit Amidoalkohol-Struktur konnten als chirale Shiftreagenzien zur Bestimmung des Enantiomerenüberschusses von racemischen Salzen entwickelt werden. Weiters wurden basische ionische Flüssigkeiten aus chiralen Aminoalkoholen synthetisiert, die erfolgreich in der asymmetrischen Alkylierung von Aldehyden eingesetzt wurden und Enantioselektivitäten von bis zu 95% ee ermöglichten.

Im zweiten Teil dieser Arbeit wurden metallhältige ionische Flüssigkeiten auf ihr Katalysevermögen untersucht. Dabei gelang es, die eisenhältige ionische Flüssigkeit 1-Butyl-3-methylimidazolium tetrachloroferrat (bmim-$FeCl_4$) als neuen und effizienten Katalysator für Kumada-Kreuzkupplungen zu etablieren. Auch der Einsatz dieser ionischen Flüssigkeit in der eisenkatalysierten Michael-Addition unter Mikrowellen-Bedingungen und in Hydroxymethylierungen in wässrigen Systemen konnte erfolgreich durchgeführt werden und zeigte deutliche Vorteile zu konventionellen Katalysatoren.

Ich möchte mich sehr herzlich bei Herrn Prof. Peter Gärtner für seine Unterstützung und Förderung in den letzten Jahren bedanken. Seine umsichtige Betreuung sowie seine konstruktiven Hilfestellungen gepaart mit der Freiheit eigene Ideen verwirklichen zu dürfen, haben die Zeit in seiner Forschungsgruppe zu einer sehr schönen und lehrreichen Zeit gemacht.

Mein Dank gilt auch Herrn Ass. Prof. Christian Hametner für die hilfsbereite Anfertigung zahlreicher NMR-Spektren sowie Thomas Fischer für die Messung der HPLC-Proben. Weiters danke ich Herrn Prof. Bernhard Lendl und seinem Dissertanten Guillermo Quintas Soriano für die gute Zusammenarbeit auf dem Gebiet der Raman- und IR-Spektroskopie.

Großer Dank gebührt auch allen derzeitigen und ehemaligen Mitgliedern meiner Arbeitsgruppe, die mir im Laufe der letzten Jahre mit Rat und Tat zur Seite gestanden sind und durch das familiäre Arbeitsklima geholfen haben den Laboralltag kurzweilig und amüsant zu gestalten. Es sind und waren dies Michaela Aigner, Stefan Böhmdorfer, Christian Einzinger, Karin Hofbauer, Thiti Junpirom, Amitava Kundu, Astrid Neumann, Martina Opietnik und Gligor Paceski.
Allen voran aber danke ich Christian Einzinger und Johanna Hämmerle für ihre Freundschaft, Geduld und stetige Hilfe in der schweren Zeit der Verfassung dieser Arbeit. Ich möchte mich bei ihnen auch sehr herzlich für die sorgfältige Durchsicht des Manuskripts bedanken.

Weiters möchte ich mich bei den Kollegen der FG „Stanetty/Mihovilovic“ für das angenehme Arbeitklima sowie für zahlreiche angeregte Diskussionen, Kuchenpausen und lange Abende im Aufenthaltsraum bedanken. Ein großes Dankeschön auch an Florian Untersteiner, der mir abgesehen von seiner Hilfe bei zahlreichen Computerproblemen auch sonst viele Weisheiten jeglicher Art mitgegeben hat.

Bei Michaela Aigner, Gerald Ebner, Jean-Baptiste Farcet, Philipp Gritsch, Anne Horan, Thiti Junpirom, Christian Maurer, Christoph Slouka, Katharina Schragl und Ivana Toth möchte ich mich für ihre Mitarbeit und ihr Interesse an meiner Dissertation im Rahmen ihrer Wahlpraktika bedanken.

Abschließend möchte ich mich noch aufrichtig bei meiner Familie bedanken, die durch ihren jahrelangen Rückhalt, ihre Unterstützung und ihr Verständnis in allen Belangen mein Studium und diese Dissertation ermöglicht haben.

1. Introduction

1.1 Ionic Liquids – Facts and application

Although Ionic Liquids (ILs) are often referred to as "new solvents", the phenomena of low melting organic salts is not a current invention but dates back to 1914 when the scientist Walden described ethylammonium nitrate, a salt that is liquid at room temperature.[1]
However, the growing awareness of the outstanding and sometimes peculiar properties that ILs possess has lead to a comet-like boost in IL research in the earlier days. Indeed, academic and industrial research is still growing exponentially and exiting developments and applications are constantly published.

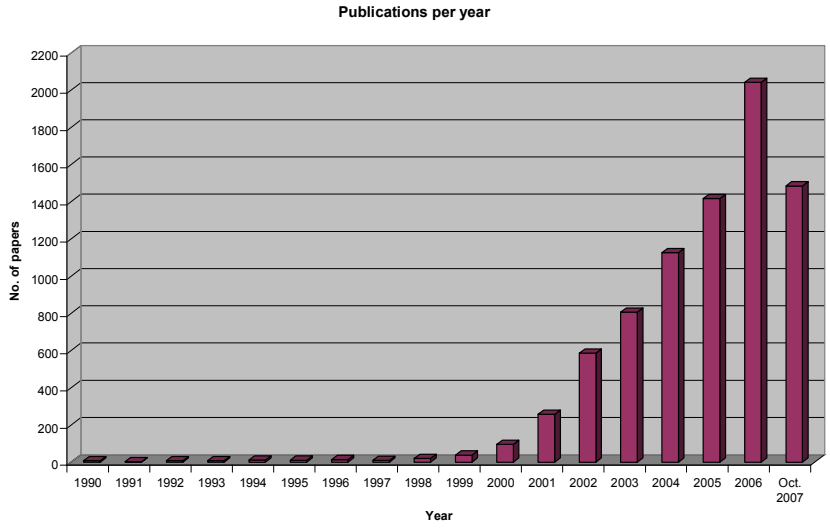

Figure 1: Yearly increase in number of publications (source Sci-Finder^{TM}) dealing with ionic liquids

The combination of a constantly growing number of possible cations and anions provides the possibility to create tailor-made ILs with different physical and chemical properties; still a generic definition includes the following issues only: [2]

(a) the substance is liquid (its glass temperature and/or melting point are below 100 °C) and
(b) it contains ions and therefore exhibits ionic conductivity.

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[1] Walden, P. *Bull. Acad. Imper. Sci. (St Petersburg)* **1914**, 1800.

[2] MacFarlane, D. R.; Seddon, K. R. *Aust. J. Chem.* **2007**, *60*, 3.

A variety of cations and anions that often fulfil these criteria is given in Figure 2:

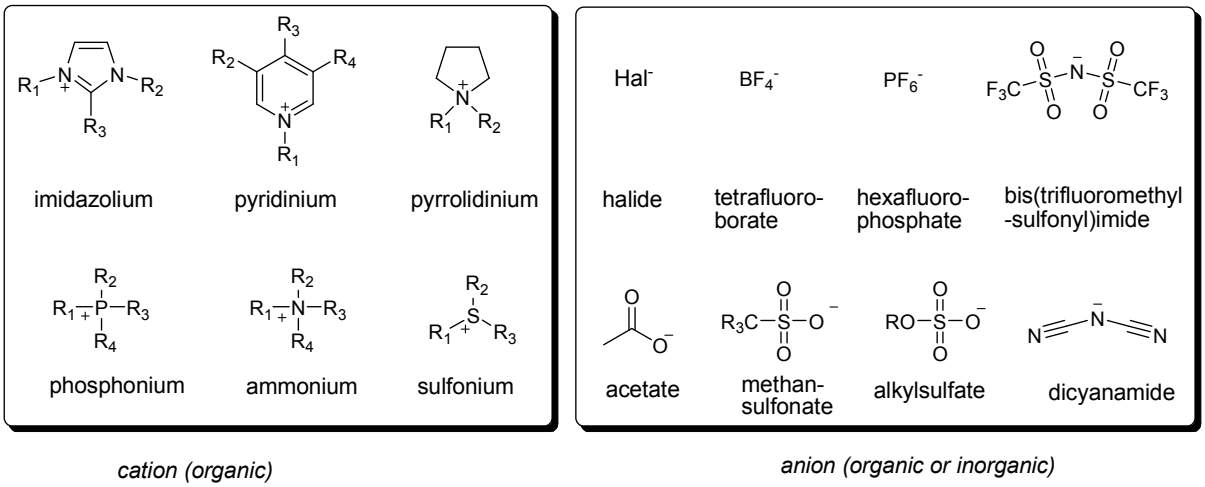

Figure 2: Typical cations and anions of ionic liquids

The application as process and performance chemicals has been subject of intensive research in both academia and industry and the field of potential and current applications is summarized in Figure 3.[3,4]

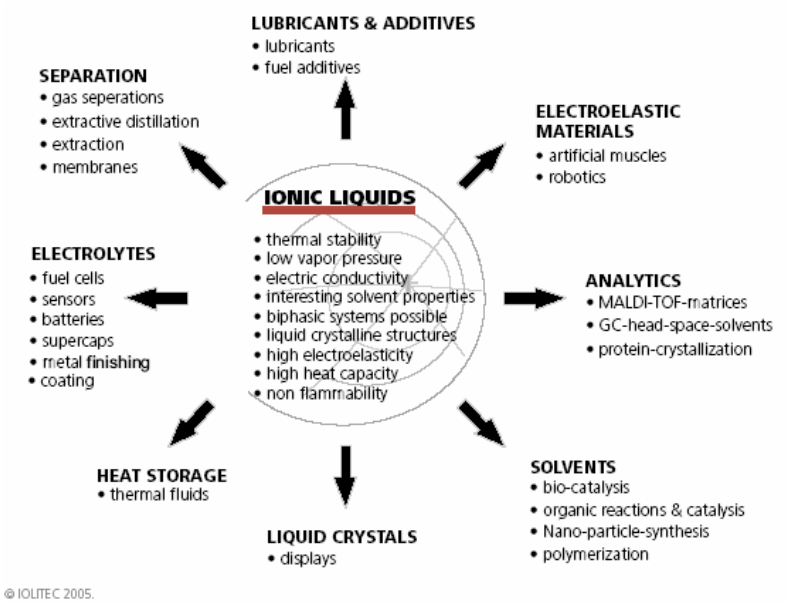

Figure 3: Properties of ionic liquids and their potential and current applications

The potential of ILs as alternative solvents for synthesis was recognized early and has attracted considerable interest in terms of environmentally benign chemistry according to the

[3] (a) Rodgers, R. D.; Seddon, K. R. *Science* **2003**, *302*, 792. (b) Rogers, R. D.; Seddon, K. R. *ACS Symposium Series* **2002**, *818* (Ionic liquids industrial applications for green chemistry), 1988.

[4] (a) Freemantle, M. *Chem. Eng. News* **2006**, *84*, 14. (b) ChemFiles, Vol. 5 No. 6. (c) ChemFiles, Vol. 6 No. 9.

Montreal protocol.[5] Volatile organic compounds are the common reaction media for industrial synthesis and about £ 4 billion are spent per year in oil refining, bulk and fine chemicals and pharmaceuticals on solvents only.[6] The desire for clean technologies has lead to a re-evaluation of many chemical processes and the application of ILs might be beneficial for sustainable chemistry. In the last decades, a wide range of organic reactions has been successfully performed in ILs as replacement for conventional solvents, and the first industrial process involving ILs was announced in March 2003.[7] Probably the best known example for the use of ILs as reaction media is the BASIL^{TM} process, which was introduced by BASF. This process went on stream at the end of 2004 in Ludwigshafen/Germany and is an excellent example of the sensible and highly beneficial use of ILs as alternative reaction media.

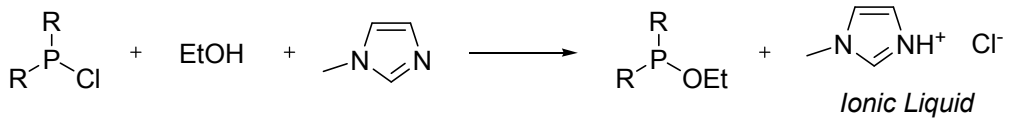

Figure 4: BASIL^{TM} technology for scavenging acids in the synthesis of ethoxyalkylphosphines

Instead of the previously used triethylamine, *N*-methylimidazole was used as acid scavenger in the production of diethoxyphenylphosphine. Thus, an IL and as a consequence two clear liquid layers were formed compared to the thick and non-stirrable slurry that was obtained with the common base triethylamine. Phase separation gave the pure product as upper layer without any need of additional solvents. Furthermore, despite the benefits of process improvement, *N*-methylimidazole functioned as nucleophilic catalyst. As a result dramatic increase in yield per unit volume and time was observed, which allowed the use of a continuously operated thumb-sized jet reactor instead of the 20 m^3 batch vessels that had to be used previously.

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[5] (a) Sheldon, R. A. *Chem. Commun.* **2001**, 2399. (b) Gordon, C. M. *Appl. Catal. A.* **2001**, *222*, 101. (c) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today*, **2002**, *2654*, 1.

[6] Sheldon, R. A. In *Precision process technology: Perspectives for pollution prevention*; Weijnen, M. P. C., Drinkenburg, A. A. H., Eds.; Kluwer: Dodrecht, 1993, 125.

[7] (a) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, 2003. (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (c) Wasserscheid, P.; Keim, W. *Angew. Chem.; Int. Ed.* **2000**, *39*, 3772. (d) Dupont, J.; deSouza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102,* 3667. (e) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A* **2002**, *182-183*, 419. (f) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267. (g) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351. (h) Zhao, H.; Malhotra, S. V. *Aldrichimica Acta* **2002**, *35*, 75. (i) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *60*, 1015. (j) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Proc.* **1999**, *1*, 223.

1.2 Ionic Liquids and chirality

Considering a 159 billion market in 2002 the large field of pharmaceuticals is doubtlessly of constant interest for research and development.[8] After some tragical incidents in the past, it is nowadays well known that chirality plays an important role in drug specificity. Indeed, nine of the top ten drug sales in 2003 were chiral compounds and six are sold on the market as single enantiomers (Figure 5).

CHIRAL BLOCKBUSTERS

In nine of top 10 drugs, the active ingredients are chiral

BRAND	GLOBAL 2003 SALES ($ BILLIONS)	ACTIVE INGREDIENT(S)	FORM OF ACTIVE INGREDIENT(S)	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 secretions
Nexium	3.8	Esomeprazole	Single enantiomer	Inhibitor of gastric acid secretions
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
TOTAL	$48.3			

NOTE: Sales figures from IMS Health.

Figure 5: Top ten drugs sold in 2003 [8]

It is therefore comprehensible that efficient strategies for the selective production of single enantiomers are permanently investigated. In general, there are three ways to synthesize a chiral compound (Figure 6):[9]

[8] Rouhi, A. M. *Chem. Eng. News,* **2004**, *82*, 47.

[9] (a) *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E21; Helmchen, G., Mulzer, J., Hoffmann, R. W., Schaumann, E., Eds.; Thieme: Stuttgart, 1995. (b) *Advanced Organic Chemistry*; March, J.; Mc-Graw-Hill: New York, 1977; 106.

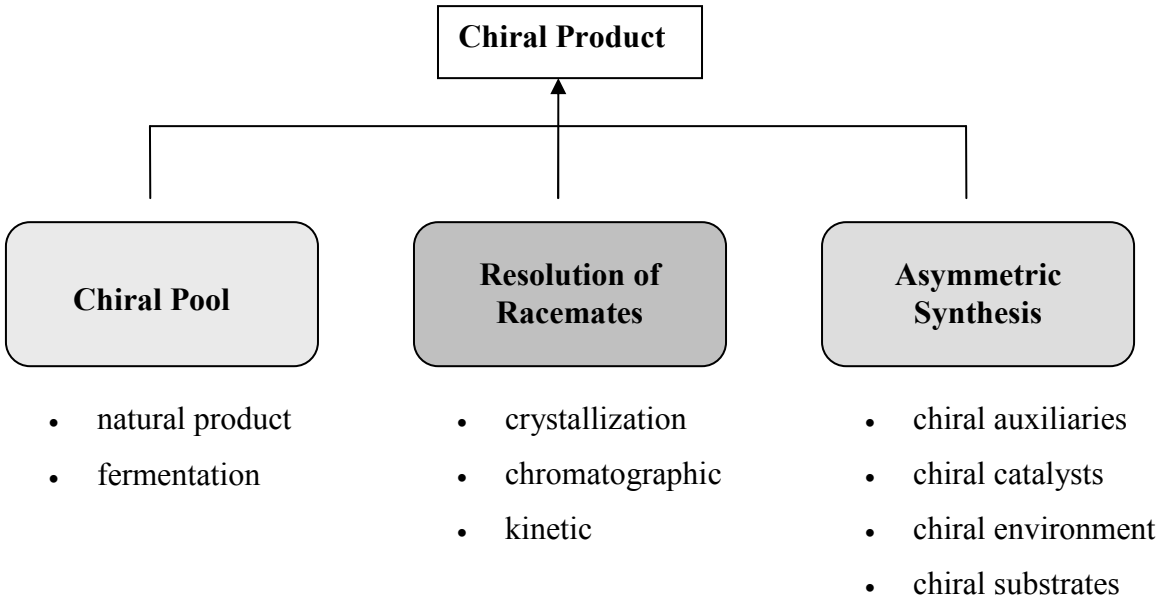

Figure 6 : Strategies for the synthesis of chiral molecules

A straight-forward and very efficient approach is to start from a chiral pool precursor that is present in nature in its enantiopure form and to transform it in several steps into the desired chiral drug without further manipulation of chirality. Unfortunately the chiral pool or chiral compounds that can be synthesized in fermentation are limited and other methods to induce chirality during the synthesis are necessary.

Alternatively but still common in industrial scale, products are synthesized in their racemic form and separated, which can be done either via crystallization, chromatography or kinetic resolution.

Asymmetric synthesis of chiral compounds can be performed by applying chiral auxiliaries, a catalyst or a chiral environment. Chiral auxiliaries, though very useful in laboratory scale are rarely used in bigger scale synthesis. Despite the fact that they usually provide high selectivity for a wide range of reactions, the need of stoichiometric amounts and additional steps for anchoring and cleavage prevents the extensive use in industry. Chiral catalysis is by far the most common and practical approach and nowadays the state-of-the-art method in industrial scale.

Finally, the application of a chiral environment is not common in laboratory nor in industrial scale, mainly because of high costs and low selectivity.

In general, a combination of asymmetric synthesis and resolution is applied during the production of a chiral drug.

The concept of ILs can be applied to several pathways by incorporating chirality in the IL to form a chiral ionic liquid (CIL).

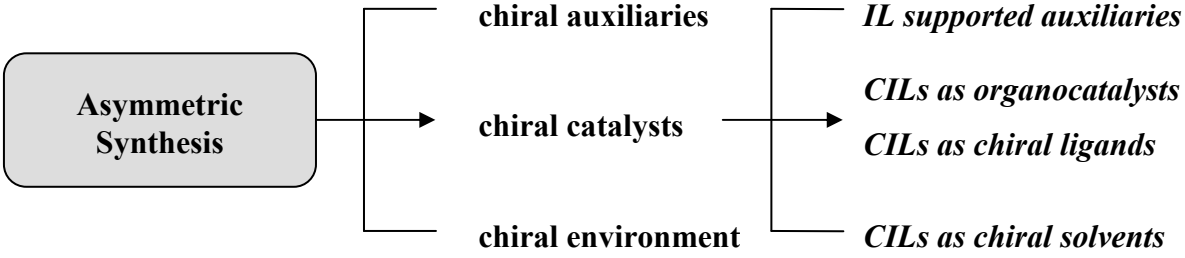

Figure 7: Application of chiral ionic liquids in asymmetric synthesis

The first example of a CIL was reported in 1997 by Howarth *et al.* who prepared the cation-chiral CIL *N,N*-di(2*S*-2-methylbutane)imidazolium bromide.[10] The number of publications dealing with CILs grew rapidly, and nowadays a large pool of CILs bearing either chiral cations, anions or seldom both and a wide variety of functionalities is available.[11]

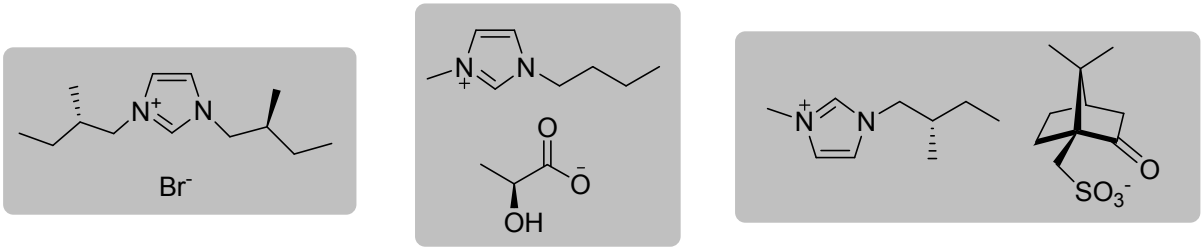

Figure 8: First examples of chiral ionic liquids with (a) chiral cation (left), (b) chiral anion (middle) and (c) chiral cation and anion (right). [10,12,13]

In most cases, CILs are referred to as new chiral solvents which could create an enantioselective environment for chirality transfer. However, the use of CILs is not only limited to application as solvent but possible for catalyst design or as chiral ligand itself.
Even the application of CILs in the context of IL supported chiral auxiliaries has been performed, which could possibly overcome some disadvantages of auxiliary chemistry and enhance the attractivity of this pathway.[14]

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[10] Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.

[11] For reviews: (a) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A.-C.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081. (b) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921. (c) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281.

[12] Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23.

[13] Machado, M.Y.; Dorta, R. *Synthesis* **2005**, *15*, 2473.

[14] Aigner, M. *Diplomarbeit* , Vienna University of Technology, Vienna, Austria, 2006.

2. Applications of Chiral Ionic Liquids

Despite the rapid design of new CILs, successful applications remained hidden for some time. In fact, it took nine years after the first CIL was published that a truly enantioselective synthesis was reported. Nevertheless, even this field is growing rapidly, and applications can be divided into four different groups:

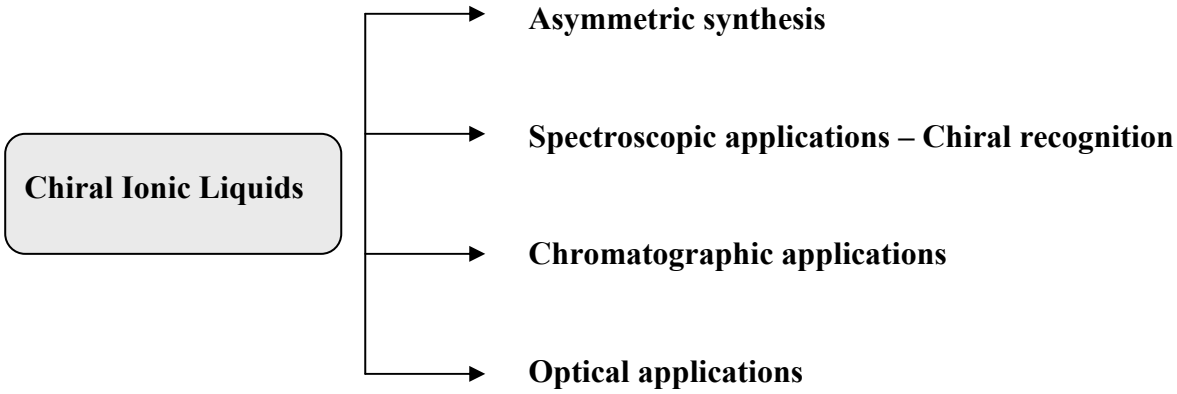


Figure 9: Applications of chiral ionic liquids in literature

2.1 Chiral ionic liquids in asymmetric synthesis

Chiral solvents have already been used as sole inducer of chirality in asymmetric synthesis. In 1975, Seebach *et al.* performed an electrochemical stereoselective reduction of ketones in the presence of chiral amino ethers as solvents and obtained a modest enantioselectivity of 23% ee.[15] However, enantioselectivity remained modest in most cases, not to mention the ridiculously high costs and complicate preparation. It was early recognized that CILs bear the potential to act as chiral environment and could overcome some of these complications. It has been reported that ILs possess a polymer-like behaviour and show a high degree of organization, therefore a significant transfer of chirality can be expected.[16] These specific properties combined with the comparable simple synthesis and the possibility for recyclation suggest that CILs could outperform classical chiral solvents in asymmetric synthesis.

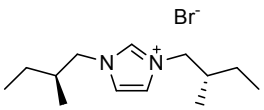
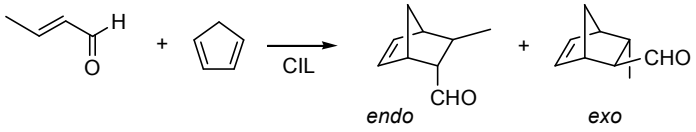
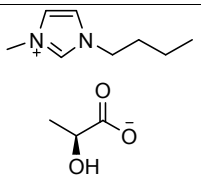
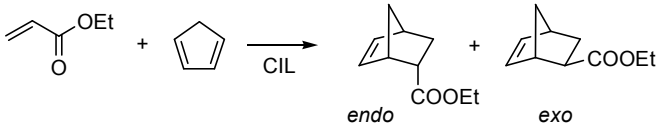
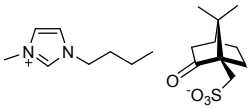
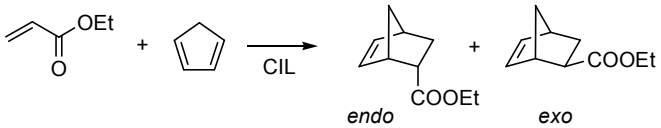
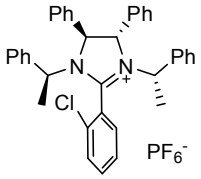
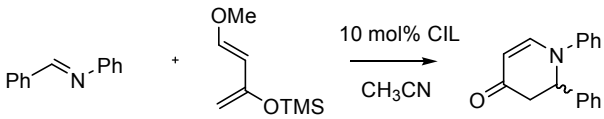
[15] (a) Seebach, D.; Oei, H. A. *Angew. Chem.* **1975**, *87*, 629. (b) Seebach, D.; Oei, H. A. *Angew. Chem.; Int. Ed.* **1975**, *14*, 634.

[16] Antonietty, M.; Kuang, D.; Smarsly, B.; Zhou, Y. *Angew. Chem.; Int. Ed.* **2004**, *43*, 4988. (b) Dupont, J. *J. Braz. Chem. Soc.* **2004**, *15*, 341.

2.1.1 Diels-Alder reactions in chiral ionic liquids

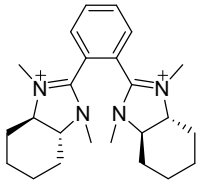
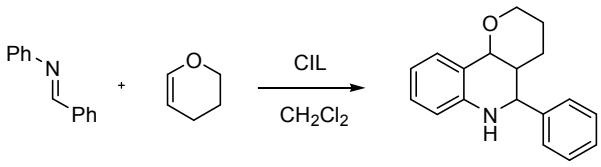
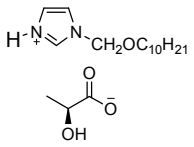
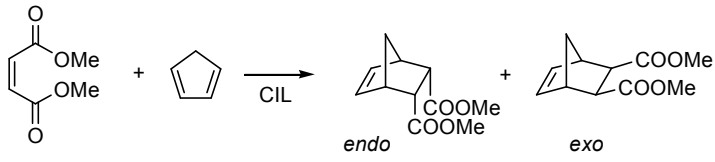
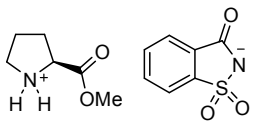
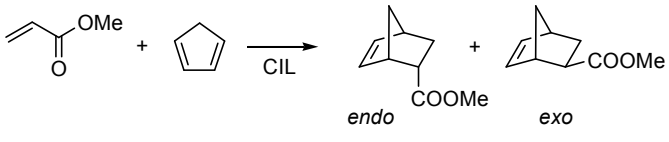
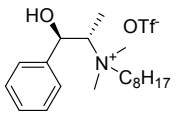
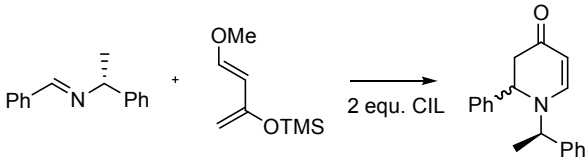
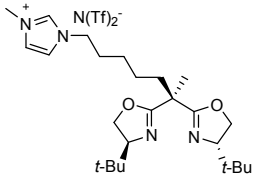
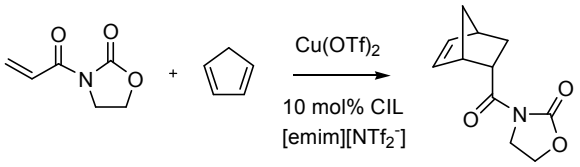
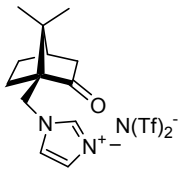
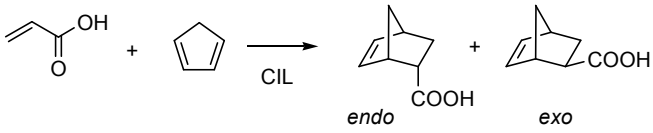
ILs have been successfully used as solvent and as Lewis acid catalyst for Diels-Alder reactions to enhance the reaction rate and selectivity. It could be shown that an explicit hydrogen bond between the cation and the carbonyl group of the dienophile is responsible for the improvement. It is therefore not surprising that the impact of a chiral environment or chiral catalyst on the stereoselective Diels-Alder reaction is subject of many papers dealing with CILs.

Table 1: Stereoselective Diels-Alder reactions in chiral ionic liquids

Entry	CIL	Reaction	Lit.
1		 yield = 36% *endo*:*exo* = 13:1 ee<5%	10
2		 yield = 87% *endo*:*exo* = 4.4:1	12
3		 yield = 29% *endo*:*exo* = 6.1:1	17
4		 yield = 76% ee < 1%	18

[17] Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* **2005**, *70*, 10106.

[18] Jurčíik, V.; Wilhem, R. *Tetrahedron: Asymmetry* **2006**, *17*, 801.

5	 2 $B[C_6H_3(CF_3)_2]_4^-$	 yield = 67% *endo*:*exo* = 1.5:1	18
6		 yield = 95% *endo*:*exo* = 3.3:1	19
7		 yield = 87% *endo*:*exo* = 3.9:1	20
8		 yield = 66% de < 60%	21
9		 yield = 100% *endo*:*exo* = 7.3:1 ee = 95%	22
10		 yield = 67% *endo*:*exo* = 7.3:1	23

In contrast to many papers published later, the first example of a CIL present in literature was already applied in asymmetric synthesis: The Diels-Alder reaction of crotonaldehyde or

[19] Janus, E.; Goc-Maciejewska, I.; Łożyński M.; Pernak, J. *Tetrahedron Lett.* **2006**, *47*, 4079.

[20] Tao, G.; He, L.; Liu, W.; Xu, L.; Xiong, W.; Wang T.; Kou Y. *Green Chem.* **2006**, *8*, 639.

[21] Pegot, B.; Van Buu, O.; Gori, D.; Vo-Than, G. *Beilstein J. Org. Chem.* **2006**, *2*, 18.

[22] Doherty, S.; Goodrich, P.; Hardacre, C.; Knight, J. G.; Nguyen, M. T.; Pârvulescu, V. I.; Paun, C. *Adv. Synth. Catal.* **2007**, *349*, 951.

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

methacrolein with cyclopentadiene in the presence of chiral and achiral dialkylimidazolium salts and dichloromethane as co-solvent was investigated (Table 1, entry 1). The results clearly showed that these ILs act as Lewis acid and catalyze Diels-Alder reactions at low temperature and high *endo:exo* selectivities were observed compared to non-catalyzed reactions. However, diastereoselectivity obtained with the CIL *N,N*-di(2*S*-2-methylbutane)imidazolium bromide did not significantly differ from the one obtained with the IL diethylimidazolium bromide and only very low enantiomeric excess, <5%, was achieved with this CIL.

One year later, Earle *et al.* published the use of ionic solvents as a safe alternative to lithium perchlorate-diethyl ether mixtures for various Diels-Alder reactions (entry 2). The neutral non-chiral ILs 1-butyl-3-methylimidazolium trifluoromethansulfonate, bmim-PF_6 and bmim-BF_4 but also the anion-chiral IL bmim-(*S*)-lactat were applied. The reaction rate of the Diels-Alder reaction between ethyl acrylate and cyclopentadiene in the CIL bmim-(*S*)-lactat was considerable higher than in the non-chiral ILs, and 87% yield could be isolated after only 2 hours. A moderate diastereoselectivity of 4.4:1 was found, but again, no enantioselectivity was observed using bmim-(*S*)-lactate as reaction media.

The effect of the anion on the diastereoselectivity on the same Diels-Alder reaction was investigated by Nobuoka *et al.* who used the anion-chiral CIL 1-butyl-3-methylimidazolium (1*R*)-camphor-10-sulfonate [bmim-(1*R*)-CSA] in bmim-BF_4 (entry 3). The use of a bulky camphorsulfonate caused an increase of free imidazolium cations, which resulted in an high *endo:exo* ratio of 10.3:1. Interestingly, the CIL 3-butyl-2,3-dimethyl camphorsulfonate bm_2im-CSA that lacks the acidic C_2-H proton gave a dramatically reduced diastereoselectivity of 3.0:1.

A range of new chiral mono- and bisimidazolinium salts was prepared by Jurčík and Wilhelm and applied as catalysts in normal and inverse electron demand aza-Diels-Alder reactions (entry 4). In general, 10 mol% of the imidazolinium salts showed good catalytic activity in the reaction of Danishefsky's diene with imines in acetonitrile, but no asymmetric induction was obtained. The inverse electron demand aza Diels-Alder reaction of *N*-benzylideneaniline and dihydropyrane could not be catalyzed by mono-imidazolinium salts (entry 5). However, when the bis-imidazolinium salt with the very lipophile and bulky anion $B[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_4^-$ was applied, the reactivity increased dramatically and 67% yield of both diastereomers in a *syn:anti* ratio of 1.5:1 as racemates was obtained.

Protic imidazolium ILs have been tested as reaction media in the Diels-Alder reaction of dimethylmaleate and methyl acrylate (Table 1, entry 6). High conversion of 95% and

endo:exo selectivities of 3.7:1 with protic 1-alkylimidazolium and 1-alkoxyimidazolium lactates were obtained. However, the differences in yield and diastereoselectivity between the racemic (*rac*)-lactates and the enantiopure *(L*)-lactates were neglible.

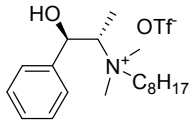
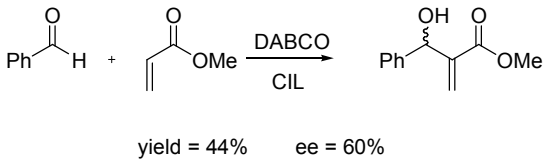
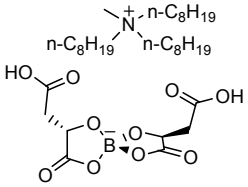
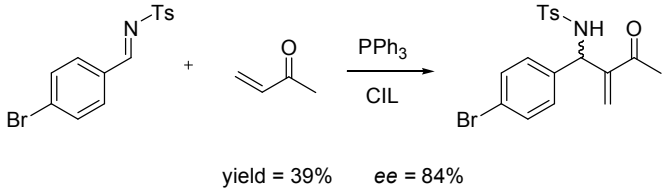
Easily prepared amino acid based CILs with chiral ammonium cation and the environmentally benign anions nitrate and saccharinate were applied as catalysts in the cycloaddition of methyl acrylate and cyclopentadiene (Table 1, entry 7). Excellent yields in the range of 89-99% were obtained with all amino acid CILs, whereas saccharinates showed better diastereoselectivities than the corresponding nitrates. Similar results were observed (*endo:exo* around 3-4:1) compared to the use of bmim-BF_4 as solvent. Again, no enantioselectivity >3% could be found, and the low steric requirement of methyl acrylate was considered to be the primary reason for the low selectivity.

The asymmetric aza Diels-Alder reaction of chiral imines with Danishefsky's diene in chiral ephedrinium-derived ILs was investigated by Pégot *et al.* (entry 8). The corresponding cycloadduct was obtained with diastereoselectivities up to 60% de in good yield without any use of co-solvent or Lewis-acidic catalyst. The use of this CIL resulted in a "matched" case of double stereoinduction and in an enhancement of diastereoselectivity compared to 32% de that was obtained when no CIL but a catalytic amount of $ZnCl_2$ was added.

The only example of a highly stereoselective Diels-Alder reaction was reported by Doherty *et al.* who used imidazolium-tagged bis(oxazolines) as chiral ligands in the copper(II)-catalysed cycloaddition of *N*-acryloyloxazolidinone and cyclopentadiene (entry 9). When 10 mol% of the IL-supported chiral ligand were used with the IL 1-ethyl-3-methylimidazolium bis(trifluoromethansulfonyl)imide [emim-$N(Tf)_2$] as cosolvent, a significant enhancement in rate and enantioselectivity was observed compared to dichloromethane, and complete conversion and enantioselectivities of up to 95% ee were achieved. The catalyst could be successfully recycled ten times without loss of activity or enantioselectivity. No leaching of the imidazolium-tagged chiral ligand was observed whereas significant leaching was found in the case of an uncharged bis(oxazoline) ligand in emim-$N(Tf)_2$.

2.1.2 Asymmetric Baylis-Hillman Addition

Table 2: Stereoselective Baylis-Hillman reaction in chiral ionic liquids

Entry	CIL	Reaction	Lit.
1		 yield = 44% ee = 60%	24
2		 yield = 39% *ee* = 84%	25

The first example of distinct asymmetric induction using CILs as reaction media was reported in 2004 by the group of Vo-Thanh who studied the asymmetric Baylis-Hillman reaction of benzaldehyde and methylacrylate (Table 2, entry 1). The reaction was performed under solvent-free conditions using DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane) as Lewis base in the presence of 0.5-3 equivalents of chiral ephedrinium IL. The excess of CIL lead to a noticeable enhancement in selectivity, and the product was isolated in 60% yield with an enantiomeric excess of 44%. Interestingly, enantioselectivity dropped significantly when the hydroxyl functionality of the CIL was protected with an acetyl group. A control experiment run with *N*-methylephedrine gave a considerably lower enantioselectivity of 9% only but resulted in a higher yield of 75%.

The work of Gausepohl *et al.* on the enantioselective aza-Baylis-Hillman reaction is an impressive example that careful design of a tailor-made CIL for a specific reaction is the best way to induce high selectivity via a chiral reaction media (Table 2, entry 2). Considering the zwitterionic intermediate that is formed during the reaction, it was recognized that a bifunctional stabilization is necessary to prevent racemization and to obtain high enantioselectivity (Figure 10).

[24] Pégot, B.; Vo-Thanh, G.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425.

[25] Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem.; Int. Ed.* **2006**, *45*, 3689.

Thus anion-chiral methyltrioctylammonium ILs which contain a chiral dimalatoborate anion were synthesized in a simple 2-step procedure based on chiral pool (*L*)-malic acid.

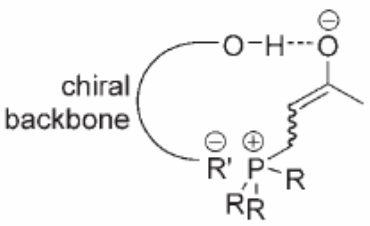
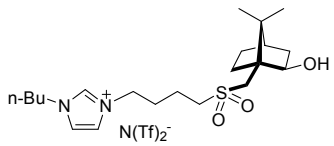
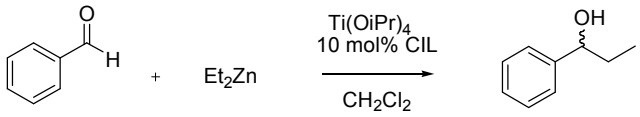
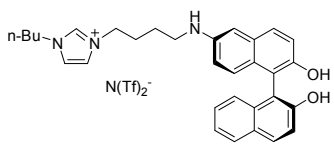
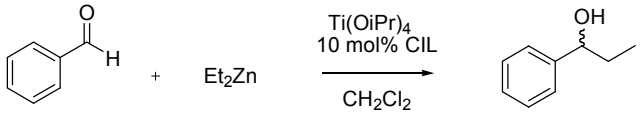
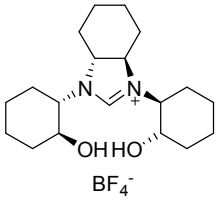
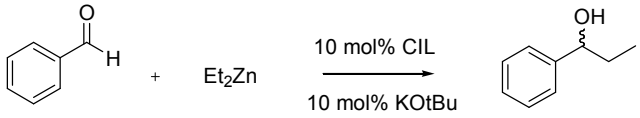


Figure 10: Interaction of anion-chiral CIL with a zwitterionic intermediate

When tested in the aza-Baylis-Hillman reaction between methyl vinyl ketone and *N*-(4-bromobenzylidene)-4-toluenesulfonamide using PPh_3 as nucleophilic catalyst, enantiomeric excess up to 84% could be obtained with conversion varying between 34 and 39%. This strategy of efficient chirality transfer via strong intermolecular interactions between solvent molecules and intermediates lead to the highest asymmetric induction ever obtained with a chiral solvent as the sole source of chirality.

2.1.3 Asymmetric Alkylation

Table 3: Asymmetric alkylation of aldehyds in chiral ionic liquids

Entry	CIL	Reaction	Lit.
1		 conversion > 99% ee = 65%	26
2		 conversion > 99% ee = 82%	27
3		 yield = 67% ee = 66%	28

An early example for the successful use of CILs in asymmetric alkylation was published in 2004 by Gadenne, Hesemann and Moreau, who prepared IL supported chiral ligands for

[26] Gadenne, B.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron Lett.* **2004**, *45*, 8157.

[27] Gadenne, B.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron Lett.* **2005**, *16*, 2001.

[28] Jurčíik, V.; Gilani, M.; Wilhem, R. *Eur. J. Org. Chem.* **2006**, 5103.

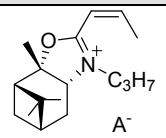
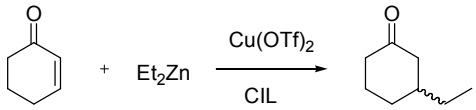
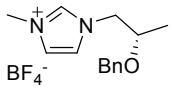
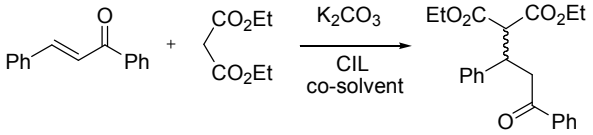
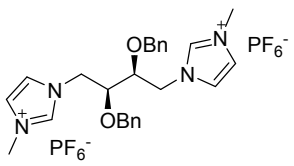
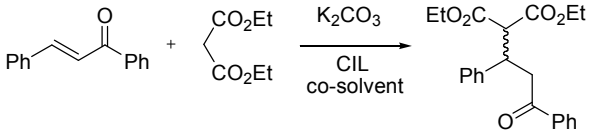
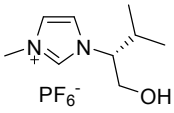
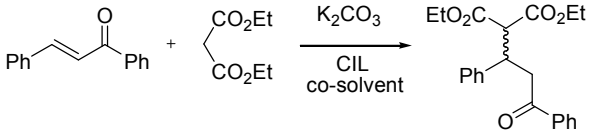
transition metal promoted addition of organozinc reagents (Table 3, entry 1). Various hydrophobic ILs containing chiral camphorsulfonamide units were used in the titanium catalyzed asymmetric addition of diethylzinc to benzaldehyde. However, to carry out the reaction in homogenous solution, toxic dichloromethane had to be used as solvent. An *exo*-borneol derivative proved to be superior and enantioselectivities of 65% as well as complete conversion could be obtained. These ionic catalyst systems showed catalytic properties similar to related non-ionic compounds, but it is noteworthy that the IL supported chiral ligands could be reused four times without loss in activity or selectivity.

Chiral binaphthyls have proved to be extremely efficient auxiliaries and ligands in asymmetric catalysis; hence easily recoverable BINOL ligands with an ionic imidazolium tag were developed by Gadenne *et al.* one year later (entry 2). Again, the ionic structure allowed a tuning of solubility of the supported BINOL ligands and combined the advantages of homogeneous catalysis and easy separation and recycling of the chiral ligand. Higher enantioselectivities up to 82% ee compared to the camphorsulfonamid CILs could be obtained in the titanium(IV) catalyzed asymmetric alkylation of benzaldehyde with diethylzinc in the presence of 10 mol% BINOL functionalized CIL.

The use of chiral imidazolinium salts bearing two hydroxyl-containing substituents as carbene precursors for diethylzinc addition to aldehyds was published by Jurčík *et al.* (entry 3). To generate the carbene, the CILs were deprotonated with *tert*-BuOK in toluene before diethylzinc solution and benzaldehyde were added. Moderate yield of 67% and an enantioselectivity of 67% ee could be obtained without further addition of titanium(IV) as Lewis acid.

2.1.4 Asymmetric Michael Addition

Table 4: Asymmetric Michael addition in chiral ionic liquids

Entry	CIL	Reaction	Lit.
1	 A = BF_4^-, PF_6^-	 yield = 90% ee = 76%	29
2		 yield = 95% ee = 24%	30
3		 yield = 95% ee = 10%	30
4		 yield =85% ee = 15%	31

Another successful application of terpene-based CILs in the enantioselective addition of diethylzinc was reported by Malhotra and Wang (Table 4, entry 1). Copper-catalyzed enantioselective Michael addition of diethylzinc to various enones has been achieved in the presence of α-pinene derived CILs. A significant improvement of selectivity from 17 to 74% ee was observed when the amount of CIL was increased from 3 to 25 mol%, however, only a small change in enantiomeric excess was observed when further increasing the CIL loading from 25 to 35 mol%. Best results were obtained in the copper-catalyzed addition of diethylzinc to cyclohexenone with an excellent yield of 90% and good enantioselectivity of 76% in the presence of 35 mol% CIL at -20 °C.

[29] Malhotra, S. V.; Wang, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1032.

[30] Wang, Z.; Wang, Q.; Zhanga Y.; Bao W. *Tetrahedron Lett.* **2005**, *46*, 4657.

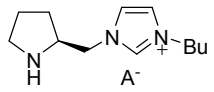
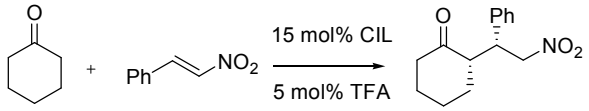
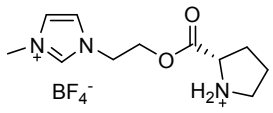
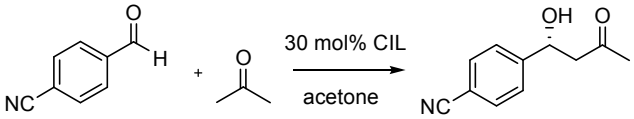
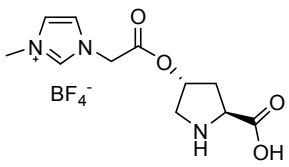
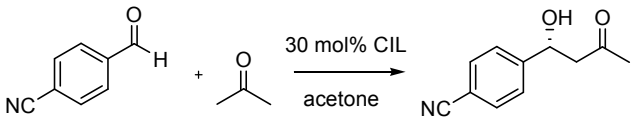
[31] Ou, W.-H.; Huang, Z.-Z. *Green Chem.* **2006**, *8,* 731.

The group of Bao investigated the influence of (*S*)-(-)-ethyl lactate and (*S*)-(+)-diethyltartrate derived CILs on asymmetric Michael addition of diethyl malonate to chalcone. Excellent yields in the range of 90-96% were obtained in the presence of a 10-fold excess of CIL using potassium carbonate as base and toluene as co-solvent. The lactate-derived CIL proved to be superior, however, only modest enantiomeric excess of 25% ee was observed, whereas the tartrate derivate only gave an enantiomeric excess of 10% ee (Table 4, entries 2 & 3).

The same reaction was performed in chiral hydroxyl-functionalized ILs prepared from (*L*)-alaninol, (*L*)-valinol and (*L*)-leucinol by Ou and Huang. Instead of toluene, the more polar acetonitrile was used as solvent; however, enantioselectivities are in the same range with up to 15% enantiomeric excess and moderate to good yields varying from 52 to 86% (entry 4) were obtained.

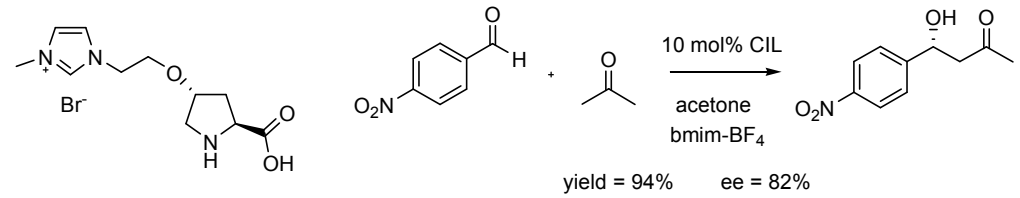
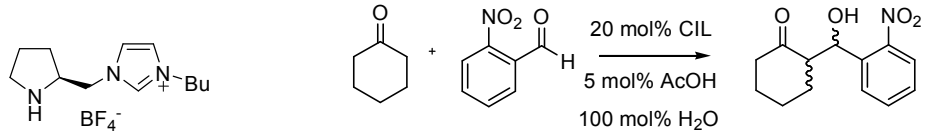
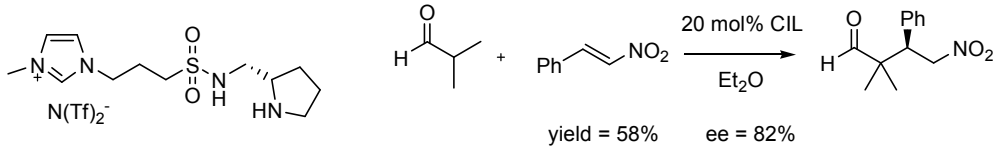
2.1.5 Organocatalysis

Table 5: Chiral ionic liquids in organocatalyis

Entry	CIL	Reaction	Lit.
1	 A = Br^-, BF_4^-, PF_6^-	 yield > 99% *syn:anti* > *99*:1 ee_{syn} = 99%	32
2	 CF_3COO^-	 yield = 10% ee = 11%	33
3		 yield = 59% ee = 72%	33

[32] Luo, S. Z.; Mi, X. L.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem.; Int. Ed*. **2006**, *45*, 3093.

[33] Miao W.; Chan, T.H. *Adv. Synth. Catal.* **2006**, *348*, 1711.

4			34
5			35
6			36

Organocatalysis of asymmetric reactions by simple metal-free organic molecules has received much attention and is a rewarding alternative to transition metal-catalyzed asymmetric synthesis.[37] Some successful examples of CILs in organocatalysis have been reported in the last two years.[32-36]

Starting from cheap chiral-pool (*S*)-proline, the group of Luo and Cheng developed a pyrrolidine-IL conjugate that turned out to be the first highly efficient CIL for asymmetric synthesis (Table 5, entry 1). This novel catalytic system could efficiently catalyze the Michael addition of a broad range of ketones and aldehyds and of nitroolefines as Michael acceptors with high yields (up to 100%), excellent enantioselectivity (up to 99%) and diastereoselectivity (*syn:anti* up to 99:1). The tuneable solubility of the CIL allowed a simple recyclation of the catalyst by precipitation via addition of diethyl ether for 4 times without loss of selectivity, although longer reaction times were needed to assure complete conversion. It was further suggested that the proximity of the IL unit to the active site may create a microenvironment that could exert synergistic effects for many reactions and that the bulky and planar imidazolium cation may shield part of the reaction intermediate.[32]

Another successful example for IL supported organocatalysis was published only one month later by Miao and Chan who used IL-anchored proline as efficient and recyclable catalysts for

[34] Zhou, L.; Wang, L. *Chem. Lett.* **2007**, *36*, 628.

[35] Luo, S. Z.; Mi, X. L.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Tetrahedron* **2007**, *63,* 1923.

[36] Ni, B.; Zhang Q.; Headley, A. D. *Green Chem.* **2007**, *9*, 737.

[37] (a) Dalko, P. I.; Moisan, L. *Angew. Chem.; Int. Ed.* **2001**, *40*, 3726; (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.

direct asymmetric Aldol reaction (entries 2 and 3). It seems that the presence of an acidic hydrogen is essential for proline derived catalysts: When (*S*)-proline was anchored on an IL moiety via an ester bond of the carboxyl group, only low selectivity and conversion was observed in the asymmetric Aldol reaction of acetone and 4-cyanobenzaldehyde. However, when IL-supported (2*S*, 4*R*)-4-hydroxyproline which retained the free carboxyl group was applied, much better yield of 72% and enantiomeric excess of 72% could be obtained. Superior catalytic activity of this IL-supported proline derivative compared to (*S*)-proline in neat ketone systems was observed, thus reducing the need for DMSO or DMF as solvent. Recyclation studies revealed that this catalyst can be easily recycled and reused with the same efficiency for four cycles. However, one major drawback is that toxic dichloromethane was used to precipitate the catalyst and regain the IL-supported proline.

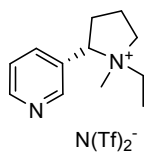
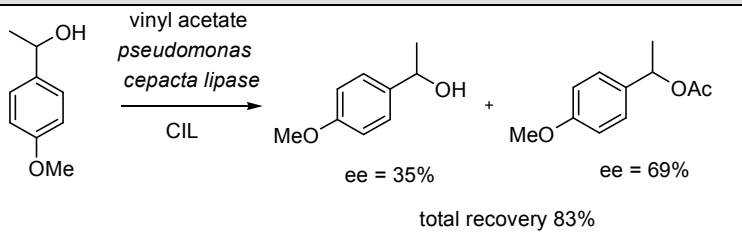
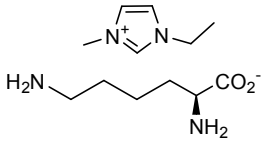
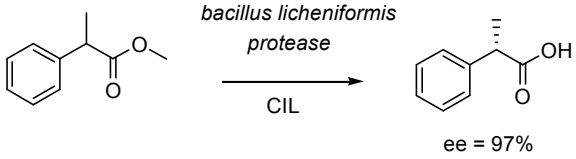
The same principle of a CIL containing an (*S*)-proline unit to obtain an efficient and recyclable asymmetric organocatalyst was applied by Zhou and Wang, who anchored (2*S*, 4*R*)-4-hydroxyproline on an imidazolium support via an ether bond (Table 5, entry 4). Direct asymmetric Aldol reactions of acetone with various aromatic aldehyds were carried out with 10 mol% of the (*S*)-proline unit in bmim-BF_4 and led to satisfactory yields and enantioselectivities. The products were isolated by extraction and the remaining CIL/bmim-BF_4 system could be recycled up to six times with constant selectivity and only minor decrease in product yield.

Pyrrolidine-containing CILs were less efficient in the direct asymmetric Aldol reaction than the proline systems (entry 5). Although these functionalized CILs could efficiently catalyze the Aldol reaction of 4-nitrobenzaldehyde and acetone in the presence of acidic additives such as acetic acid and water, only poor enantioselectivities of 10% were observed. However, enantioselectivities of up to 63% ee and complete conversion were observed in the Aldol reaction of cyclic ketones, although almost exact amounts of *syn* and *anti* product were formed.

A pyrrolidine-based CIL that includes a weakly acidic N-H proton was published by Headly *et al.*, who tethered a chiral pyrrolidine derivative via a sulfonamide functionality on an imidazolium support (Table 5, entry 6). This CIL was capable of catalyzing the Michael addition of aldehyds and nitrostyrene with moderate yields (up to 64%), good enantioselectivities (up to 82% ee) and high diastereoselectivities (*syn:anti* ratio up to 97:3) in the presence of a less-polar solvent like diethyl ether.

2.1.6 Chiral ionic liquids in biotransformation

Table 6: Chiral ionic liquids in biotransformation

Entry	CIL	Reaction	Lit.
1			38
2			39

An early example of the application of CILs in biotransformation was reported by Kitazume who performed the kinetic resolution of 1-(4-methoxyphenyl)ethanol by *Pseudomonas cepacia lipase* (Table 6, entry 1). A nicotine-derived CIL was used as reaction media without co-solvent, and medium enantioselectivities were obtained.

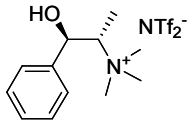
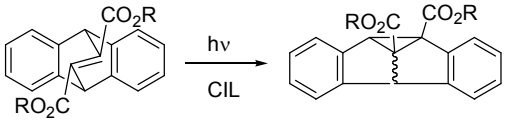
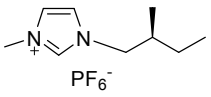
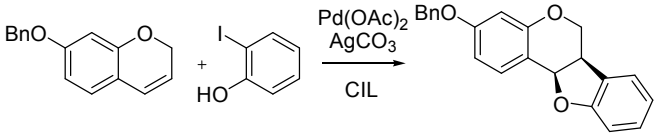
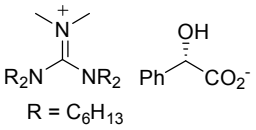
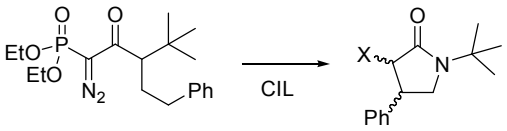
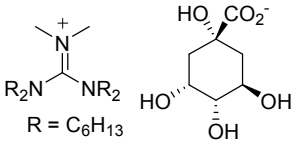
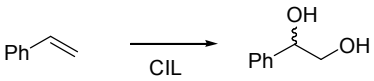
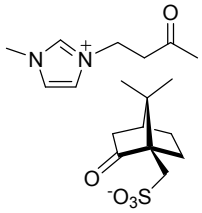
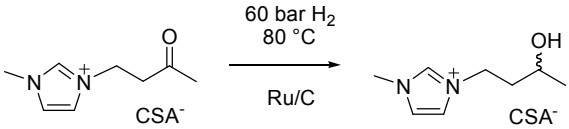
The group of Zhao *et al.* studied the enzymatic hydrolysis of phenylalanine methyl ester in aqueous solutions of CILs carrying anions of chiral α-amino acids (entry 2). The protease activity was stabilized and moderate to high enzyme enantioselectivities could be observed. Interestingly, higher enantioselectivities and yields of (*S*)-phenylalanine were observed in CILs based on (*R*)-amino acids compared to those derived from the (*S*)-isomers.

[38] Kitazume, T. U.S. Patent 0031875, 2001.

[39] Zhao, H.; Jackson, L.; Song, Z.; Olubajo, O. *Tetrahedron: Asymmetry* **2006**, *17*, 1549.

2.1.7 Others

Table 7: Other applications of chiral ionic liquids in asymmetric synthesis

Entry	CIL	Reaction	Lit.
1		 yield = 93% ee = 12%	40
2		 yield = 13% ee = 5%	41
3		 yield = 67% *trans*:*cis* = 67:33 ee = 85%	42
4		 yield = 95% ee = 85%	42
5		 yield > 99% ee = 80%	43

Enantioselective photodimerization

The group of Armstrong evaluated four different CILs derived from commercially available optically resolved materials as chiral inducing solvents for the enantioselective photoisomerization of dibenzobicyclo[2.2.2]octatriene (Table 7, entry 1). Enantiomeric excesses from 3 to 12% were obtained, indicating an ion pairing interaction of the CIL cations

[40] Ding, J.; Desikan, V.; Han, X.; Xiao, T. L.; Ding, R.; Jenks, W. S.; Armstrong, D. W. *Org. Lett.* **2005**, *7*, 335

[41] Kiss, L.; Kurtan, T.; Antus, S.; Brunner, H. *Arkivoc* **2003**, *5*, 69

[42] Branco, L.C.; Gois, P. M. P.; Lourenço, N. M. T.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Commun.* **2006**, 2371.

[43] Schulz, P. S.; Müller, N.; Bösmann, A.; Wasserscheid, P. *Angew. Chem.; Int. Ed.* **2007**, *46*, 1293.

with the deprotonated diacids. Although the observed enantiomeric excess only seems to be modest, it is one of the highest enantioselectivities obtained via a chiral environment for an irreversible, unimolecular photochemical reaction and the first report of chiral induction obtained by a CIL in this regard.

Heck reaction

The palladium-catalyzed Heck oxyarylation of 3-benzyloxypterocarpan using the CIL (*S*)-1-methyl-3-(2-methylbutyl)imidazolium hexafluorophosphate as solvent was investigated by Kurtan *et al* (Table 7, entry 2). However, asymmetric induction of the non-functionalized alkyl chain is low although the imidazolium salt was involved via carben-formation. The reaction resulted in an enantiomeric excess of 5% ee and 13% yield when $Pd(OAc)_2$ was used. Better yield of 28% but and a slightly lower ee of 4% was achieved with $PdCl_2$ as catalyst. When an achiral phosphin ligand was added, conversion was improved up to 45% but chirality was completely lost.

Guanidinium based CILs

Interesting examples of anion-chiral ILs were reported by Branco *et al.* who combined a guanidinium cation with anions of readily available natural chiral acids. Thus chiral mandelates, lactates, salts of quinic acid, camphorsulfonates and hydroxyprolinates were obtained and used as chiral inducing agent in two different reactions. The rhodium(II) catalyzed carbenoid asymmetric C-H insertion of α-phosphono-α-diazo-acetamids was performed using the guanidinium (*R*)-mandelate CIL as solvent in the presence of $Rh_2(OAc)_4$ as catalyst to obtain 67% yield of the product as two diastereomers in a *trans:cis* ratio of 67:33 and 27% enantiomeric excess (entry 3). The second reaction investigated was a Sharpless-type osmium-catalyzed asymmetric dihydroxylation of styrene and of 1-hexene to obtain chiral vicinal diols (entry 4). A remarkably high enantiomeric excess of 85 and 72% ee, resp. with excellent yields of 95 and 92% could be achieved when the chiral quinic acid guanidinium salt was used as solvent in combination with the catalytic system $K_2OsO_2(OH)_4$/NMO. It is noteworthy that a slow addition of the olefin that is generally necessary when NMO is used as co-oxidant was not required.

Asymmetric Hydrogenation

The maybe most intriguing example of chirality transfer was published by Wasserscheid *et al.* who could induce high selectivity by simple ion-pairing effects (entry 5).

N-Methylimidazolium-(*R*)-camphorsulfonate was reacted in a Michael-type reaction with methyl vinyl ketone. Hydrogenation of the obtained *N*-(3'-oxobutyl)-*N*-methylimidazolium-(*R*)-camphorsulfonate under heterogeneous conditions using ruthenium on charcoal in ethanol at 60 °C and 60 bar gave the corresponding hydroxybutyl-derivative in quantitative yield and enantioselectivities up to 80% ee. A strong correlation between enantioselectivity and increasing concentration of the imidazolium salt was observed, indicating the importance of ion-pair interaction. Given the simplicity and the large field of substrates that can be attached to the imidazolium salts, it is obvious that this methodology of chirality transfer bears an enormous potential for asymmetric transformations especially in industrial scale.

2.2 Spectroscopic applications

2.2.1 Chiral recognition in NMR

The first example of the spectroscopic application of CILs was reported in 2003 by Wasserscheid *et al*., who showed that CILs can be used for the determination of enantiomeric excess of samples by NMR integration (Table 8, entry 1).[44] In order to investigate interionic diastereomeric interactions between an enantiopure CIL and a racemic substrate, the authors performed ^{19}F-NMR spectroscopy of a mixture of racemic Mosher's acid sodium salt and an ephedrine-base CIL in a common NMR solvent. Depending on the ratio of CILs applied in the experiment, a splitting of the ^{19}F-signal of the CF_3-group was observed, thus giving evidence for the presence of chiral environment (Figure 11). The chemical shift difference made it possible to determine the amount of CIL indicating a minimum concentration of 0.3 mmol/ml in order to achieve sufficient resolution. Moreover, a significant enhancement of splitting in the presence of catalytic amounts of water was observed.

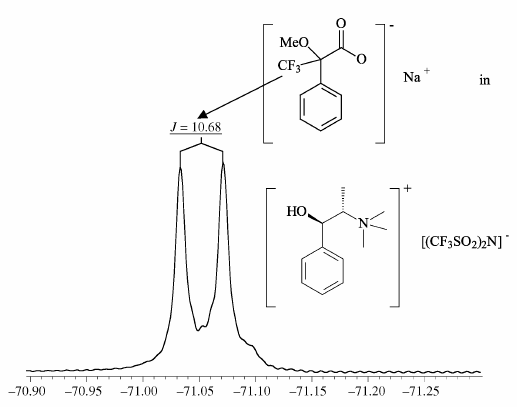


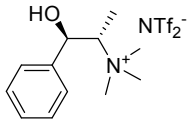
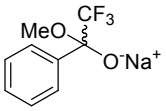
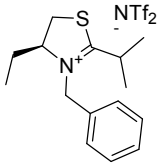
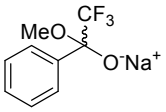
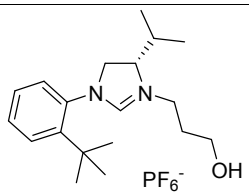
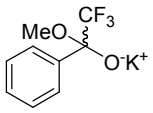
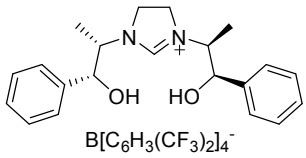
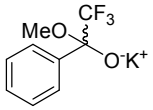
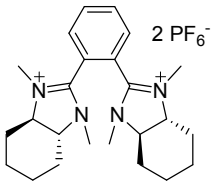
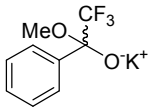
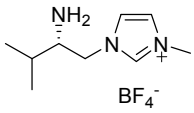
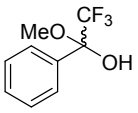
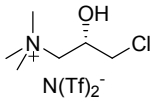
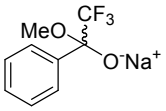
Figure 11: Diastereomeric interaction of racemic Moshers acid sodium salt with a chiral ionic liquid

The group of Gaumont repeated the experiment with chiral thiazolinium salts and obtained a splitting up to 30 Hz applying the *N*-benzylthiazolinium derivative (Table 8, entry 2).[45] This indicates the importance of an aromatic group for π–π stacking interactions between the racemic substrate and the CIL, since the corresponding *N*-ethyl salt only showed considerably weaker interactions.

[44] (a) Wasserscheid, P.; Bösmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200. (b) Bösmann, A.; Wasserscheid, P.; Bolm, C.; Keim, W. DE Patent 10003708, 2001.

[45] Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A.-C. *Chem. Commun.* **2003**, 2914.

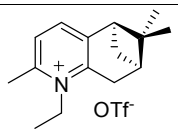
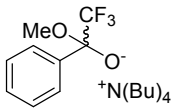
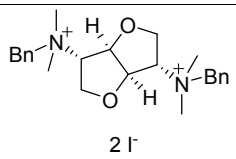
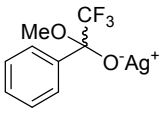
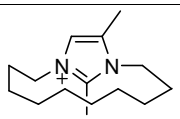
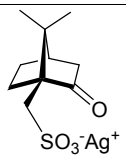
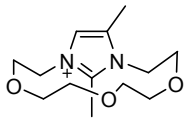
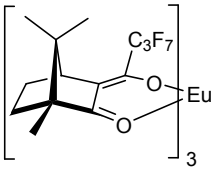
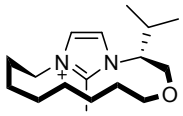
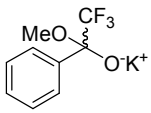
Table 8: Diastereomeric interaction of chiral ionic liquids in ^{19}F-NMR

Entry	CIL	Substrate	Conditions	ΔJ [Hz]	Lit.
1			8.2 eq. CIL CD_2Cl_2	11	44
2			1 eq. CIL C_6D_6	31	45
3			3.3 eq. CIL 1 equ. 18C6 CD_2Cl_2	63	46
4			1 eq. CIL acetone-d_6	151	28
5			1 eq. CIL acetone-d_6	53	18
6			3.7 eq. CIL aqu. CD_2Cl_2	35	47
7			24 eq. CIL CD_2Cl_2/D_2O	25	48

[46] Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* **2004**, 1224.

[47] Luo, S.-P.; Xu, D.-Q.; Yue, H.-D.; Wang, L.-P.; Yang W.-L.; Xu, Z.-Y. *Tetrahedron: Asymmetry* **2006**, *17*, 2028.

[48] Tran, C. D.; Oliveira, D.; Yu, S. *Anal. Chem.* **2006**, *78*, 1349.

8			10 eq. CIL CD_2Cl_2	4	[49]
9			1 eq. CIL CD_3CN	15	[50]
10			1 eq. CIL $CDCl_3$	7	[51]
11			10 eq. CIL 10 eq. Et_3NCl $CDCl_3$	19	[52]
12			3.0 eq. CIL 1 eq. 18C6 $CDCl_3$	7	[53]

Even higher splitting up to 63 Hz in ^{19}F and 60 Hz in ^{1}H-NMR spectroscopy was reported by Clavier *et al.* using (*S*)-valine derived CILs (Table 8, entry 3).[46] Once again, the presence of a phenyl group, in this case with an additional bulky *tert*-butyl substituent in ortho position was crucial for strong interactions. Additionally, a hydroxyethyl substituent was introduced for hydrogen bonding towards the cation. Instead of the sodium salt, Moshers acid potassium salt was used as racemic substrate in the presence of crown ether 18C6 in a polar aprotic solvent CD_2Cl_2.

The presence of a second hydroxyl group further improved diastereomeric interaction, as shown by the tridentate imidazolinium salts reported by Jurčík *et al.* (entry 4).[28] A strong influence of the anion was observed: Applying the BF_4^- salt, no interactions could be observed, whereas a high splitting of up to 152 Hz was observed when the borate salt was

[49] Drahoňovský, D.; Labat, G. C.; Ševčík, J.; Zelewsky, A. *Heterocycles* **2005**, *65*, 2169.

[50] Kumar, V.; Olsen, C. E.; Scha1ffer, S. J. C.; Parmar, V. S., Malhotra, S. V. *Org. Lett.* **2007**, *9*, 3905.

[51] Ishida, Y.; Miyauchi, H.; Saigo, K. *Chem. Commun.* **2002**, 2240.

[52] Ishida, Y.; Sasaki, D.; Miyauchi, H.; Saigo, K. *Tetrahedron Lett.* **2004**, *45*, 9455.

[53] Ishida,Y.; Sasaki, D.; Miyauchi, H.; Saigo, K. *Tetrahedron Lett.* **2006**, *47*, 7973.

used. In case of isomannide derived CILs, Mosher's acid silver salt was mixed with the bis(ammonium) iodide salt in CD_3CN to preform Mosher's acid chiral ammonium salt with a $\Delta\delta$ value of 15 Hz (entry 9).[50] When the solution was mixed with 4 additional equivalents of the chiral bis(ammonium) bis(trifluoromethansulfonyl)imide salt, the splitting was further enhanced to 23 Hz.

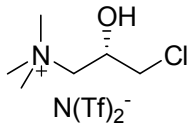
Chiral recognition ability between an imidazolium cation and camphorsulfonate were also published by Saigo *et al.* in 2002 (entry 10).[51] Two signals for the imidazolium proton at 7.2 ppm were observed in ^{1}H-NMR spectroscopy. However, in this case the planar-chiral cyclophane-type imidazolium salt was obtained as racemate and enantiopure camphorsulfonate was used to show diastereomeric interactions. Although the authors refer to this substance as CIL, previous separation of the racemic CIL has to be done before an application as chiral shift reagent is possible.

The introduction of a coordinating pseudo-crown ether chain in the planar chiral imidazolium salt improved the ability to interact with a chiral substrate (entry 11). A splitting of the imidazolium proton up to 19 Hz was observed when the chiral enantiopure shift reagent europium tris(β-diketonate) was added to the racemic imidazolium salt.[52] By introduction of a valinol-based cyclophane strucuture, it was possible to obtain these planar CILs in enantiopure form.[53] As result, chiral recognition with racemic substrates was possible, although a comparable low splitting of up to 7.3 Hz with Mosher's acid potassium salt was reported (Table 8, entry 12).

2.2.2 Chiral recognition in NIR-spectroscopy

The group of Tran and Oliveira developed a method in which a CIL was used for the determination of enantiomeric purity based on near-infrared techniques.[48]

The novel CILs (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium-bis(trifluoromethansulfonyl)imide were used to solubilize an analyte and to induce diastereomeric interaction for a variety of pharmaceutical products and amino acids.



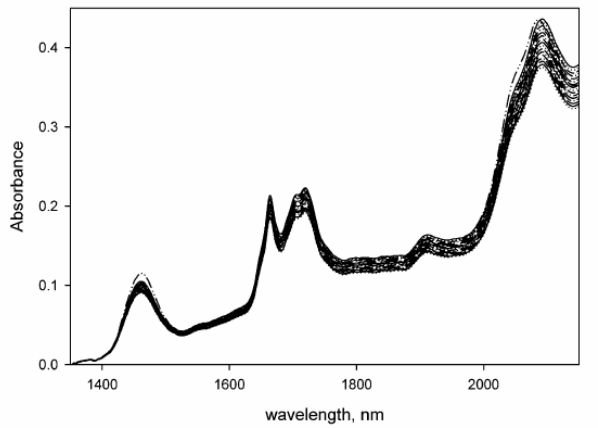


Figure 12: (a) Chiral ionic liquid used for enantiomere discrimination in NIR spectroscopy (left) and (b) NIR spectra of the pure chiral ionic liquid and 17 solutions of atenolol with different enantiomeric compositions

This CIL could be simply prepared in a one-step anion exchange reaction from commercially available (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium chloride and showed high solubility power.

2.2.3 Chiral recognition via fluorescence determination

The same CIL that was used for chiral recognition in NIR spectroscopy was also applied as both chiral selector and solvent for the determination of enantiomeric excess of the drugs propanolol, naproxen and warfarin via fluorescence spectroscopy.[54] The method was based on the use of fluorescence technique followed by partial least squares analysis of the data.

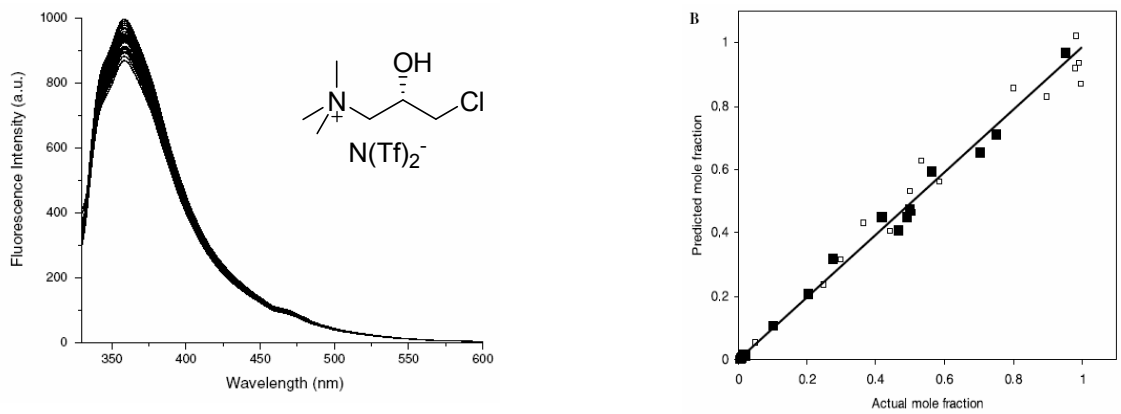


Figure 13: Fluorescence spectra of 34 solutions of warfarin with different enantiomeric compositions in the chiral ionic liquid (left) and predicted enantiomeric composition versus actual composition (right)

A sensitive and accurate determination of enantiomeric composition of these drugs could be achieved that proved to be superior to other techniques including HPLC, GC, NMR and FTIR in terms of accuracy, sensitivity and analysis times.

[54] Tran, C. D.; Oliveira, D. *Anal. Biochem.* **2006**, *356*, 51.

2.3 Application of chiral ionic liquids in chromatography

2.3.1 Chiral ionic liquids as stationary phases in gas chromatography

A great deal of interest has been laid in the application of ILs as selective transport membrane and for stationary phases in gas chromatography. Alkylimidazolium-based ILs have been successfully used as unusually stable stationary phases for gas chromatography and expressed dual nature properties, in that they separate both polar and non-polar compounds.[55] Extending the realm for chiral separation, there are two principle ways: A chiral selector can be dissolved in a non-chiral IL[56], or − more elegant − the IL can be chiral itself.[57]

The group of Armstrong published in 2004 the first direct enantiomeric separation of different compounds by using CIL stationary phases in gas chromatography. An *N,N*-dimethylephedrinium-based CIL that has been previously described by Wasserscheid *et al.* [44a] was coated on fused-silica capillary column with a brown polyimide layer to generate a new chiral stationary phase (CSP). A range of chiral alcohols and diols, chiral sulfoxides, some chiral epoxides and acetamides could be successfully separated.

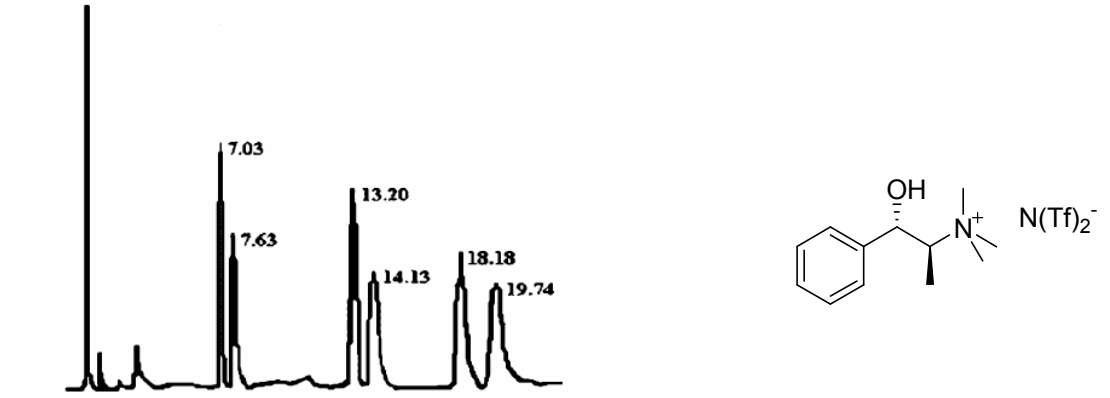


Figure 14: GC chromatogram (left) showing the enantiomeric separation of 2-phenethyl alcohol, 1-phenyl-1-butanol and trans-1,2-cyclohexenediol with a fused-silica capillary column coated with (1S,2R)-(+)-N,N-dimethylephedrinium bis(trifluoromethansulfonyl)imide (right)

Ephedrine is present in nature in both enantiomeric forms and as diastereomeric pseudoephedrine and thus it is possible to produce CSPs of opposite stereochemistry, which

[55] (a) Armstrong, D. W.; He, L.; Liu, Y. S. *Anal. Chem.* **1999**, *71*, 3873. (b) Anderson, J. L.; Armstrong, D. W. *Anal. Chem.* **2003**, *75*, 4851.

[56] Berthod, A.; He, L.; Armstrong, D. W. *Chromatographia* **2001**, *53*, 63.

[57] Ding, J.; Welton, T.; Armstrong, D. W. *Anal. Chem.* **2004**, *76*, 6819.

can reverse the enantiomeric elution order of the analytes. This cannot be done routinely with chiral selectors commonly used in GC or LC like the popular cyclodextrine CSPs. However, after several weeks of use, a loss of separation was observed for certain compounds like the alcohols. A dehydration induced incomplete racemization process that occurred at temperatures >140 °C was made responsible for the decreasing chiral recognition.

2.3.2 Enantiomeric separation in capillary electrophoresis

Capillary zone electrophoresis has become a very useful high performance separation technique for separation of small charged molecules or for the separation of peptides, proteins or fragments of nucleic acids. In the last years, great attention has been paid to the relevance of ILs as new media for capillary electrophoresis with IL-containing background electrolytes.[58]

The application of novel IL-type like surfactants and their polymers for chiral separation of acidic analytes in micellar electrokinetic chromatography was reported first by Rizvi and Shamsi in 2006.[59] Two amino-acid derived CILs and their polymers were synthesized and used as pseudo-stationary phase in capillary electrophoresis (Figure 15).

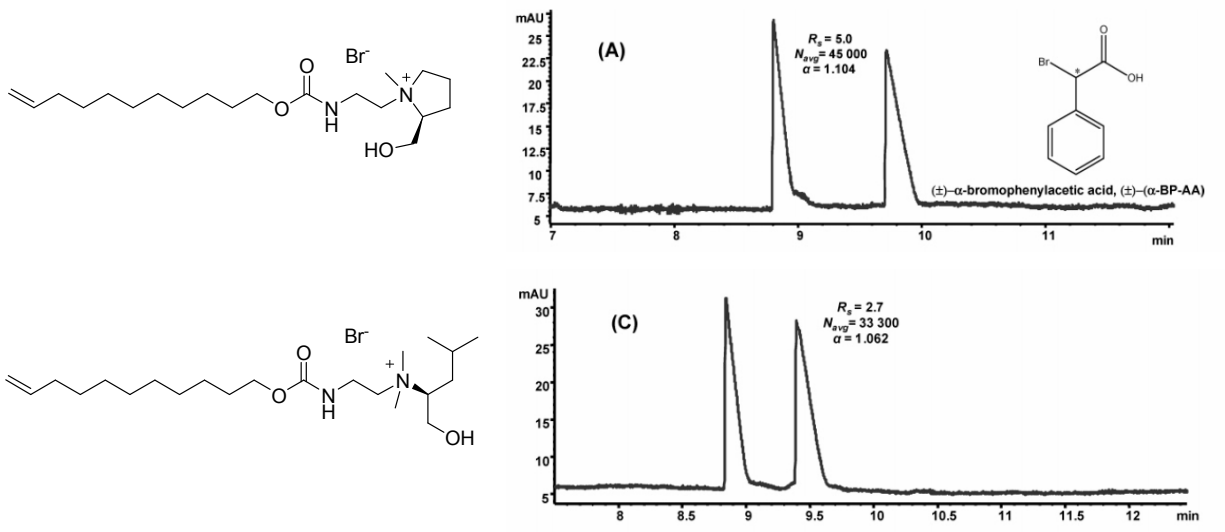


Figure 15: (a) Chiral ionic liquids used in capillary zone electrophoresis (left) and (b) comparision for enantioseparation of (rac)-α-bromophenylacetic acid (right)

It was found that chiral separation is strongly dependent on the presence of opposite charge as well as the structural compatibility between chiral selector and analyte. The two acidic

[58] (a) Huang, X.; Luckey, J. A.; Gordon, M. J.; Zare, R. N. *Anal. Chem.* **1989**, *61*, 766. (b) Yanes, E. G.; Gratz, S. R.; Baldwin, M. J.; Robinson, S. E.; Stalcup, A. M. *Anal. Chem.* **2001**, *73*, 3838.

[59] Rizvi, S. A. A.; Shamsi, S. A. *Anal. Chem.* **2006**, *78*, 7061.

analytes (*rac*)-α-bromophenylacetic acid and (*rac*)-2-(2-chlorophenoxy)propanoic acid could be separated with both CILs and their polymers at 25 mM surfactant concentration.

The evaluation of chiral ethyl- and phenylcholine (bistrifluoromethylsulfonyl)imide as additives for enantiomeric separation of anti-inflammatory 2-arylpropionic acids was investigated by François *et al.*[60] These CILs did not present direct enantioseparation with regard to this model analytes. However, a distinct increase in separation selectivity and resolution was observed when these CILs were applied in the presence of classical chiral cyclodextrin selectors.

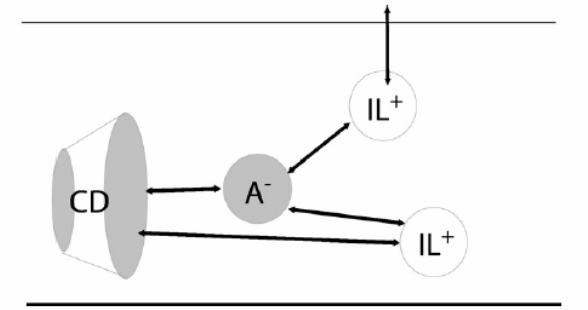


Figure 16: Schematic description of the interaction system between anionic profen A^-, chiral ionic liquid IL^+ cation, free in the background electrolyte or absorbed onto the capillary wall, and β-cyclodextrine derivatives.

Although the increase of resolution was often due to an increase of electroosmotic flow, in some cases a simultaneous increase of electrophoretic selectivity α_{eff} and of chiral resolution *R*s compared to a simple salt effect occurred that suggested a synergistic effect of the two selectors (Figure 16).

Maier *et al.* used the prolinol-derived CIL (*S*)-2-hydroxymethyl-1,1-dimethylpyrrolidinium tetrafluoroborate as additive for dynamic coating of silica capillaries.[61]

It was recognized that the addition of the CIL to acidic background electrolytes leads to a suppression of magnitude of electroosmotic flow and gradually changed its direction.

[60] François Y.; Varenne, A.; Juillerat, E.; Villemin, D.; Gareil, P. *J. Chromatogr., A* **2007**, *1155*, 134.

[61] Maier, V.; Horáková, J.; Petr, J.; Drahoňovský, D.; Ševčík, J. *J. Chromatogr., A* **2006**, *1103*, 137.

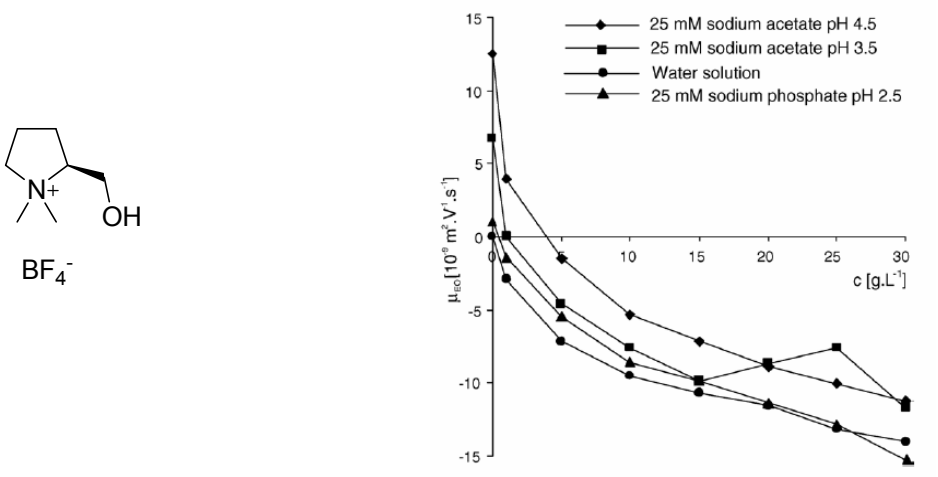


Figure 17: (a) (S)-Prolinol derived chiral ionic liquid (left) and (b) its influence on electroosmotic mobility in acidic background electrolytes and in water solution

Baseline separation was observed for five tricyclic antidepressants as model analytes. The application of this CIL as buffer additive offered smaller anodic electroosmotic flow compared to cationic surfactants that are usually used for generating electroosmotic flow in capillary electrophorese.

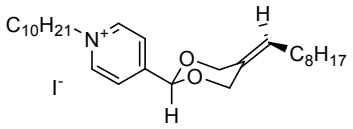
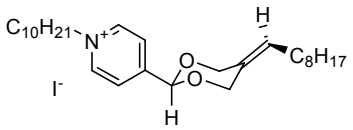
2.4 Optical application of chiral ionic liquids - Chiral liquid crystals

Besides their application for chiral recognition and for synthesis, the large field of material science has been only briefly explored. It has been recognized that room-temperature ILs are capable of forming thermotropic mesophases, and that CILs should be of substantial interest as chiral mesogenes.

The group of Plaquevant *et al.* designed novel ionic liquid/liquid crystals (IL^2Cs) having a 1,3-dioxane ring in their central rod-like core and a pyridinium IL unit.[62]

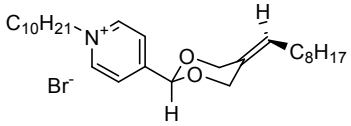
Differential scanning calorimetry and polarized microscopy revealed that most of this axial chiral compounds exhibited low melting or glass transition points and liquid crystalline states for some ILs. Generally, mesophases could be observed when the central core bears long chains on both sides to obtain calamitic molecules.[63] Liquid crystalline properties were more easily observed with halogene or tetrafluoroborate anions, although these salts expressed higher melting points than the corresponding hexafluorophosphates or triflimides. The transition temperatures were not significantly different for racemic and enantiopure compounds, however, the nature of mesophase was affected: Cholesteric (N*) phases were observed for pure (*R*) compounds whereas nematic or smectic phases were obtained for racemic compounds.

Table 9: Mesogenic properties of axially chiral ionic liquids

Entry [1]	CIL	T [°C][2]
1 (*R*)		N* 35/40 I
2 (*rac*)		Sm 44/55 I

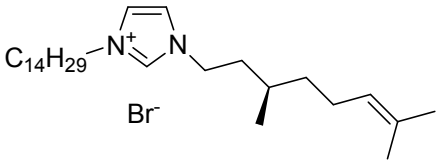
[62] Baudoux, J.; Judeinstein, P.; Cahard, D.; Plaquevent, J. C. *Tetrahedron Lett.* **2005**, *46*, 1137.

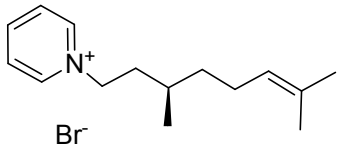
[63] Bradley, A. E.; Hardacre, C.; Holbrey, J. D.; Johnston, S.; McMath, S. E.; Nieuwenhuyzen, M. *Chem. Mater.* **2002**, *14*, 629.

3 (*rac*)		SmC 55 I

[1] (*rac*): *racemic*. [2] N*: cholesteric, Sm : scmetic, SmC : smectic C.

The mesogenic properties of citronellol-derived CILs were investigated by Tosoni *et al.*, who obtained new CILs by alkylation of pyridine or substituted imidazol with citronellyl bromide.[64] Smectic mesophases were observed for 1-citronellylpyridinium bromide and for 1-citronellyl-3-tetradecyl-1*H*-imidazolium bromide whereas the tetrafluoroborate salts revealed only isotropic melting.





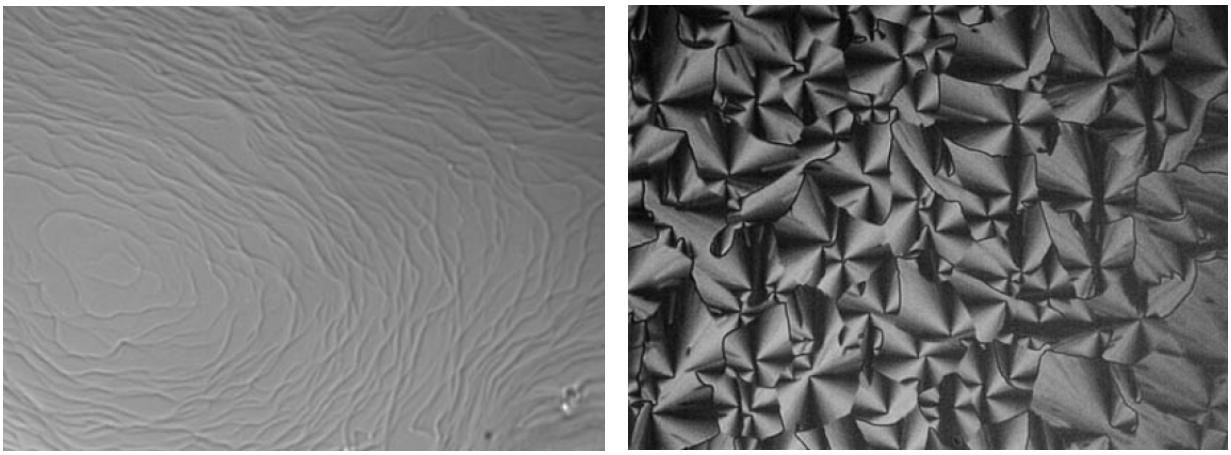


Figure 18: Texture of citronellyl-1H-imidazolium bromide as seen between polarizers at 24° upon cooling from the isotropic liquid (left) and of citronellylpyridinium bromide at -56° (right).

In binary mixture with a known nematic benzyliden mesogene the phase width of the nematic phase remained almost constant over an extended range from 0 to 0.7 but no chiral mesophase was observed. In contrast, when the known smectic mesogene 1-decyl-3-methylimidazolium bromide was doped with increasing amounts of 1-citronellyl-3-tetradecyl-1*H*-imidazolium bromide, a steady decrease of the smectic A phase resulted until only melting was observed.

[64] Tosoni, M.; Laschat, S.; Baro, A. *Helv. Chim. Acta* **2004**, *87*, 2742.

3. Task

In this work, the design and synthesis of knew chiral-pool derived ILs starting from camphor-derivatives and from chiral amino alcohols should be developed. The application of these knew CILs as sole inducer for chirality in asymmetric synthesis and for chiral recognition was further to be investigated.

In the second part of this thesis, the application of ILs as recyclable catalysts in organic synthesis beyond their use as mere reaction media should be explored. For this reason, metal-containing ionic liquids should be established as recyclable and environmentally benign catalysts for C-C-bond formation.

4. Results and Discussion

4.1 Camphor-derived chiral ionic liquids

4.1.1 Design of chiral ionic liquids as chiral solvents

Although the amounts of ILs used as solvents are usually considerably smaller compared to common organic solvents, the application of CILs as solvents for chiral transformations still demands a large volume of enantiopure compounds. Therefore, several terms and conditions should be accomplished for the sensible use of CILs as chiral reaction media:

- The synthetic pathway should start from a cheap enantiopure starting material, preferably derived from the "chiral pool" and present in nature in both enantiomeric forms.
- A simple, short and high yielding synthesis is necessary to avoid loss of chiral material.
- The synthesis should be easily performed on large scale. Chromatographic purification should therefore be circumvented.
- The obtained CIL should lack labile positions that can be subject to racemization.

Camphor derivatives have proved to be excellent chiral auxiliaries due to their special steric demands as well as reagents in various asymmetric reactions and transformations.[65]

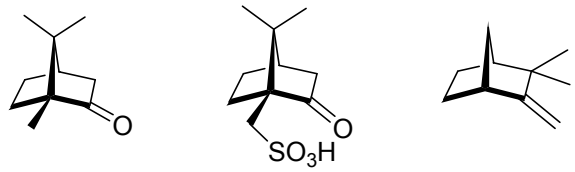


Figure 19: Camphor and its derivatives, camphorsulfonic acid and camphene.

Since camphor and its derivatives, camphorsulfonic acid and camphene, are cheap chiral pool natural products new CILs were designed containing a camphor moiety in the cationic part of the IL.

[65] Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

4.1.2 Camphor-derived chiral ionic liquids from camphor sulfonic acid

In a first approach to camphor-derived CILs, the IL moiety was attached via the easily functionalized position 10 in the camphor skeleton. This could be obtained by a synthetic pathway starting from camphor sulfonic acid **1**, a cheap chiral pool substrate that is well known in industrial scale for separation of racemic substrates.

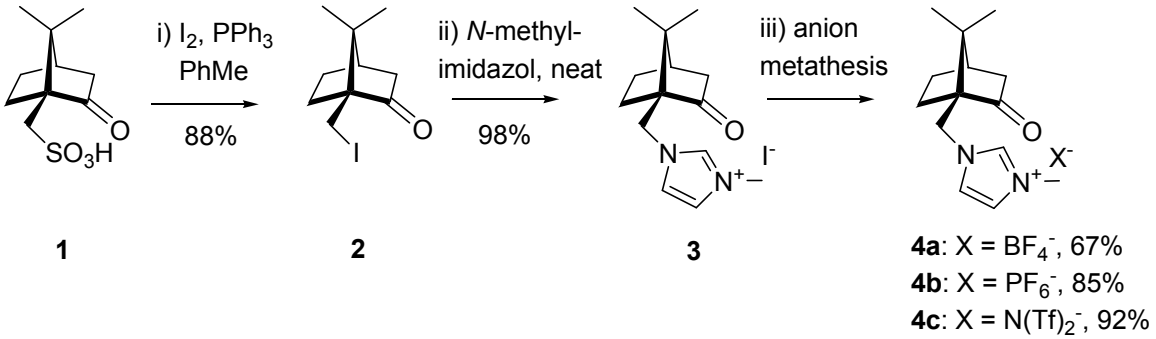


Figure 20: Synthesis of camphor-10-functionalized chiral ionic liquids

Treatment of (1*S*)-(+)-camphorsulfonic acid **1** with iodine/triphenylphosphine lead via nucleophilic substitution to intermediate 10-iodocamphor **2**[66] which was further reacted with *N*-methylimidazole to afford the imidazolium salt **3**. The reaction proceeded in excellent yield of 98%, even though long reaction times of 14 days and rough conditions (80 °C, neat, closed vessel) were necessary to ensure complete conversion, showing a typical inertness against nucleophilic substitution known from comparable neopentyl halides.

The synthesis of the water-soluble BF_4^- salt **4a** was best performed with $NaBF_4$ in acetone under anhydrous conditions. Insoluble NaI was separated via filtration over silica and remaining halide impurities could be removed by extraction of the dichloromethane solution of **4a** with small portions of cold water. In contrast, the hydrophobic hexafluorophosphate and triflimide salts **4b** and **4c** were synthesized directly in aqueous solution via anion metathesis using a 60% HPF_6 solution or $LiN(Tf)_2$ in H_2O. In both cases, the ionic liquid separated immediately as second, lower layer and could be obtained by simple phase separation. Alternatively, when performed on smaller scale, extraction of the CIL with dichloromethane was favourable to prevent losses during separation.

[66] Buston, J.; Coldham, I.; Mulholland, K. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2327.

All CILs **4a-c** obtained are soluble in moderately polar-aprotic solvents such as chloroform, dichloromethane and acetone as well as in polar-protic methanol, but insoluble in less-polar solvents, such as diethyl ether, ethyl acetate and hexane. This special solubility behaviour allowed the formation of stabile three-phase systems with the CIL as lowest layer.

Figure 21: Triple-phase system of n-hexane (upper layer), water (dyed with Ni^{2+}) and CIL 4c (lower layer)

Although good overall yields of 57% for **4a**, 73% for **4b** and 79% for **4c**, resp. could be obtained, the need of chromatographic separation of 10-iodocampher **2** from the by-products triphenylphosphine oxide and sulphide may be a limiting factor for up-scaling. Nevertheless, the new ionic liquids **4a-c** may be also interesting for chiral *N*-heterocyclic carbene (NHC) synthesis and transition metal catalysed reactions.

4.1.3 Camphor-derived chiral ionic liquids from camphene

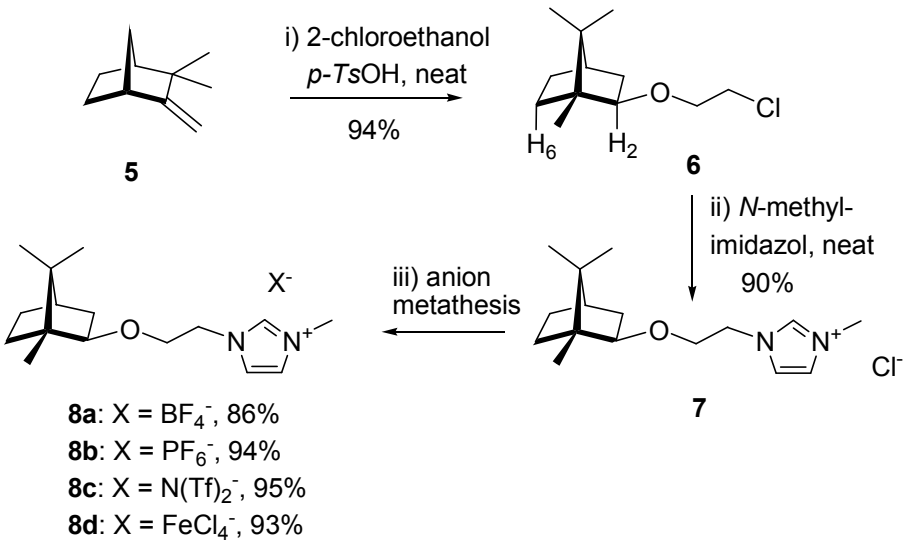


Figure 22: Synthesis of camphene-derived chiral ionic liquids

Treatment of technical (+)-camphene **5** being one of the cheapest chiral pool compounds with chloroethanol under acid catalysis led via a Wagner-Meerwein rearrangement to chloroethoxyborneol **6**.[67] In a first step, acid-induced protonation of the double bond of camphene gave the initial tertiary carbenium ion **I**. Consequently, a stereocontrolled Wagner-

[67] Yarovaya, O.L.; Korchagina, D. V.; Gatilov Y. V.; Barkash, V. A. *Russ. J. Org. Chem.* **2002**, *38*, 810.

Meerwein rearrangement gave the 2-norbornyl cation **II** which is further trapped by an electrophile, in this case by chloroethanol.

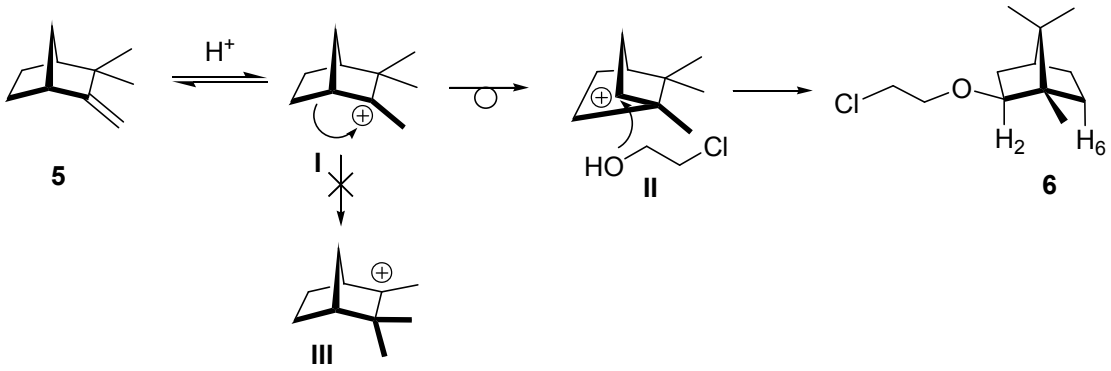


Figure 23: Wagner-Meerwein rearrangement from camphene to bornyl derivatives

This Wagner-Meerwein process is much more rapid than the competitive Nametkin rearrangement to the less stable carbocation **III** that could be also formed via methyl-group migration. The enantiospecifity of this process resulted in a selective formation of the *exo*-bornyl derivative **6**, which could be further proved by NOE-spectroscopy.

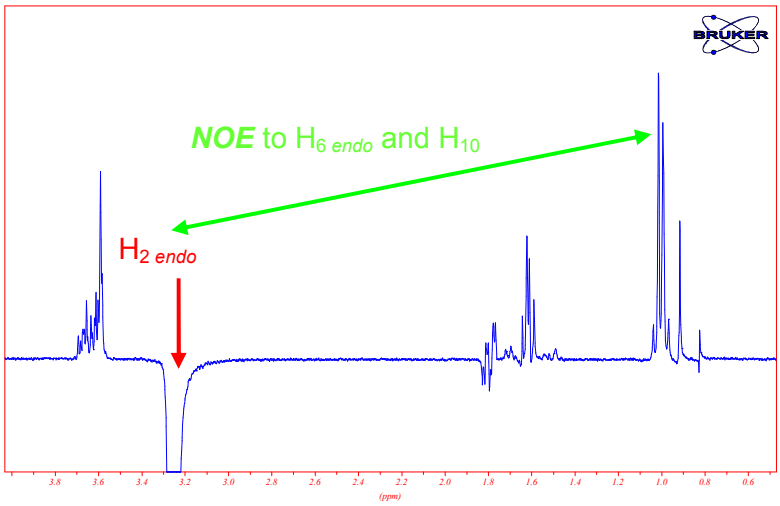


Figure 24: Evidence for the exo-product given by NOE-spectroscopy

In literature, hydrolysis and extraction of the crude product **6** with diethyl ether is necessary to avoid acid catalyzed decomposition that would occur during direct distillation from the crude reaction mixture.[68] However, the literature work-up could be improved to enable solvent-free conditions: By addition of a stoichiometric amount of triethylamine to the crude reaction mixture extraction could be circumvented and pure **6** could be distilled directly from the crude product.

[68] Zeijden A. A. H.; Mattheis, C. *Synthesis* **1996**, *7*, 847.

Quaternization with *N*-methylimidazole could be achieved best under sovent-free condition at 80 °C for 3 days to give the imidazolium chloride **7** as very hygroscopic crystals in 90% yield. Further anion metathesis as described above for **4b-d** proceeded in excellent yields of 86-95% and resulted in various ionic liquids **8a-c**.

The iron-containing room temperature CIL **8d** was easily prepared in an endothermic solid state reaction by mixing solid imidazolium chloride **7** and $FeCl_3 \cdot 6\ H_2O$, yielding the hydrophobic dark brown chiral ionic liquid as a lower phase and water, which could be easily separated.

Considering the difficult analytics of iron(III) containing species, characterization was done by both Raman spectroscopy as well as UV-VIS spectra. The characteristic feature at 333 cm^{-1} in the Raman spectra from the symmetric Fe-Cl stretch vibration indicates $FeCl_4^-$ as only counter-ion present and is in accordance with literature values for $FeCl_4^-$ and with the Raman spectra from the ionic liquid 1-butyl-3-methylimidazolium tetrachloroferrate (bmim-$FeCl_4$).[69,70] The same result was obtained from UV-VIS spectroscopy, giving the characteristic absorptions at 535 and 691 nm which have already been described for $FeCl_4^-$ anions.[71] The structure of the cation was examined via elemental analysis and proved the presence of the camphor-10-sceleton.

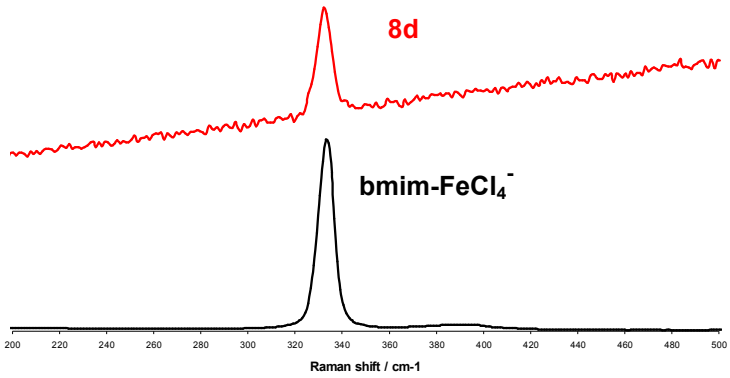


Figure 25: Raman spectra of chiral ionic liquid 8d and of bmim-$FeCl_4^-$

[69] Avery, J. S.; Burbridge C. D.; Goodgame, D. M. L. *Spectrochim. Acta* **1968**, *24A*, 1721.

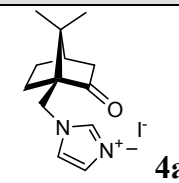
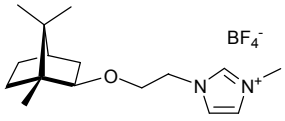
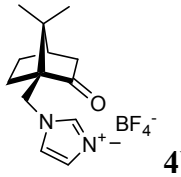
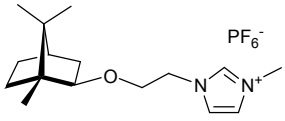
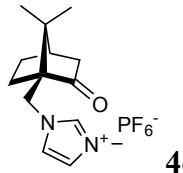
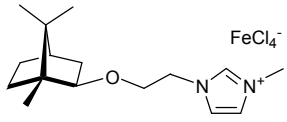
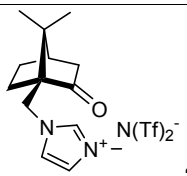
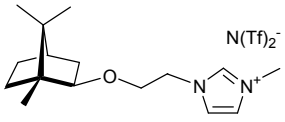
[70] (a) Sitze, M. S.; Schreiter, E. R.; Patterson, E. V.; Freeman R. G. *Inorg. Chem.* **2001**, *40*, 2298. (b) Hayashi, S.; Hamaguchi, H. *Chem Lett.* **2004**, *33*, 1590.

[71] Friedman, H. L. *J. Am. Chem. Soc.* **1952**, *74*, 5.

4.1.4 Melting behaviour

In general, melting points of camphene derived CILs were lower than the values observed for camphor-10-functionalized CILs, indicating stronger intermolecular interactions being present due to the carbonyl functionality of the camphor sulfonic acid derived CILs **4a-c**. Both tetrafluoroborate salts **4a** and **8a** are crystalline at room temperature but qualify as IL with a melting point <100 °C. Similarly, the triflimide salts showed the lowest melting point for both room-temperature CILs **4c** and **8c**. In case of hexafluorophosphate salt **8b** no melting point but a glass transition was observed, but the tetrachloroferrate CIL **8d** showed a very low melting point of -45 °C, thus allowing asymmetric synthesis at low temperature.

Table 10: Melting points of camphor-derived chiral ionic liquids

CIL	m.p.		CIL	m.p.
 **4a**	118-120 °C	decrease of melting point	 **8a**	46-48 °C
 **4b**	88-91 °C		 **8b**	T_g -28°C
 **4c**	58-60 °C		 **8c**	-45 °C
 **4d**	-39.7 °C		 **8d**	-54 °C

4.1.5 Microwave assisted synthesis of chiral ionic liquids

As already mentioned, the quaternization step in the synthesis of ILs can be time-consuming, especially in case of sterically hindered alkylation reagents and/or weak leaving groups like chloride. The use of microwave energy in organic synthesis as alternative to conventional heating is well established, leading in many cases to dramatically shortened reaction times and to increased yields.[72] Two fundamental pathways of energy transfer have been identified: *i*) dipole rotation, where a reagent with a high dielectric constant tries to align itself with the oscillating field and *ii*) ionic conduction, where ionic motion of free ions is generated by the electric field of microwaves, resulting in rapid heating.[73,74]

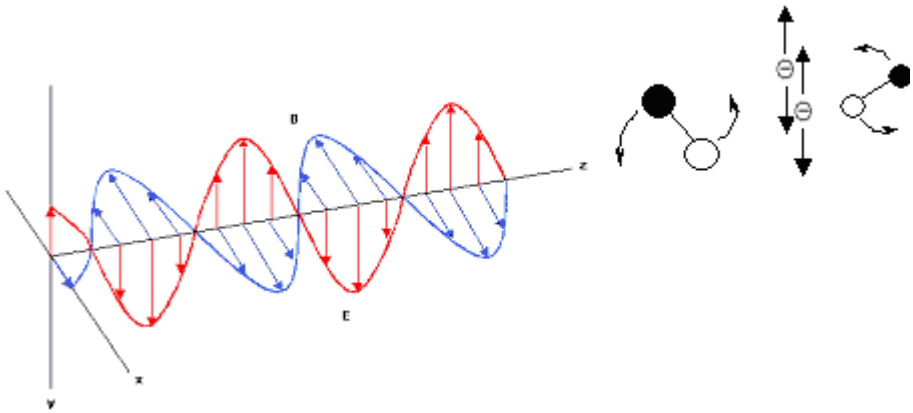


Figure 26: Energy transfer in oscillating field via dipole rotation and ionic conduction

Considering the ionic nature of ILs that makes them susceptible to interaction with electromagnetic fields, it is obvious that the application of microwave energy might be a highly useful tool not only for the synthesis of ILs[75], but also for the application of ILs as solvent, reagents and heating aids in microwave-promoted organic synthesis.[76] After some

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[72] (a) Lindström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (c) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851. (d) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83. (e) Varma, R. S. *Green Chem.* **2001**, *3*, 98. (e) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis*, **1998**, *9*, 1213.

[73] (a) Kappe, O.C. *Angew. Chem.; Int. Ed.* **2004**, *43*, 6250. (b) Whittaker, A. G. *New Scientist*, **1998**, *157*, 34.

[74] Hayes, B. L. *Microwave Synthesis – Chemistry at the Speed of Light*; CEM Publishing: Matthews, 2002.

[75] (a) Varma, R. S. *ACS Symposium Series* **2003**, *856* (Ionic Liquids as Green Solvents), 82. (b) Carmichael, A. J.; Deetlefs, M.; Earle, M. J.; Froehlich, U.; Seddon, K. R. *ACS Symposium Series* **2003**, *856* (Ionic Liquids as Green Solvents), 14.

[76] (a) Leveque, J.-M.; Cravotto, G. *Chimia* **2006**, *60*, 313. (b) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Comb. Chem. High Throughput Screening* **2004**, *7*, 511. (c) Habermann, J.; Ponzi, S.; Ley, S. V. *Mini-Rev. Org. Chem.* **2005**, *2*, 125.

exploring small-scale synthesis of ILs in household microwave ovens by Varma *et al.*, Deetlefs and Seddon reported a generic solvent-free process for ILs in large scale, giving a quick and low-waste access to a wide range of ILs based on nitrogen-containing heterocycles.[77,78]

In order to avoid the time-consuming quaternization step the synthesis of these alkylimidazolium salts was optimized applying microwave conditions. To investigate the optimal reaction temperature the reaction between camphor-derivative **6** and *N*-methylimidazole at 100, 125 and 150 °C was run under solvent-free conditions (Table 11, entry 1-3). A low power rate (50 W) was chosen to avoid initial overheating and the reaction was run for 15 minutes, showing only traces of imidazolium chloride **7** at 100 °C but a good conversion of 81% in case of 150 °C. A slightly lower temperature of 110 °C and 130 °C, resp. was chosen for the reaction between 10-iodocamphor **3** and *N*-methylimidazole, since irradiation at 150 °C lead to formation of by-products (entry 5-7). The crude imidazolium salts **3** and **7** appeared as brown solids, and recrystallization from a mixture of dry acetonitrile/ethyl acetate was necessary to obtain pure crystalline salts.

Table 11: Microwave assisted synthesis of imidazolium salts 7 and 3

Entry [a]	Product	Hold time	Temperature	Yield [c]
1	**7**	15	100	5
2	**7**	15	125	31
3	**7**	15	150	81
4 [b]	**7**	105	150	91 [d]
5	**3**	15	110	5
6	**3**	30	130	44
7	**3**	45	130	86

[a] Performed on a CEM Explorer microwave oven at 50 W using 5 mmol **6** and 5 mmol *N*-methylimidazole. [b] 1 ml of anhydrous ethyl acetate used as co-solvent. [c] Yield calculated from ^{1}H-NMR of crude product. [d] Isolated yield of crystalline product.

The extraordinary properties of ILs like ionic composition that make them useful as high absorbing additive and heating aid in microwave promoted organic synthesis, can complicate

[77] Varma, R. S.; Namboodiri, V. V. *Chem. Commun.* **2001**, 643.

[78] Deetlefs, M.; Seddon, K. R. *Green Chem*. **2003**, *5*, 181.

the microwave-assisted preparation of ILs. The more IL is formed, the better absorbing is the reaction mixture, which results in a better intake of microwave energy. Especially in the solvent-free synthesis of very viscous melts like crude imidazolium chloride **7**, it might be difficult to control temperature and avoid overheating, which would result in dark and impure products. As reflected in the temperature profile, a strong temperature fluctuation could not be circumvented, although a microwave oven with infrared-controlled temperature program was used. Therefore it was not possible to obtain complete conversion, since longer reaction times resulted in a complete collapse of the system with a sudden increase of reaction temperature and decomposition of the product. After 13 minutes of irradiation overheating led to decomposition which can be recognized in the sudden increase of pressure (Figure 27).

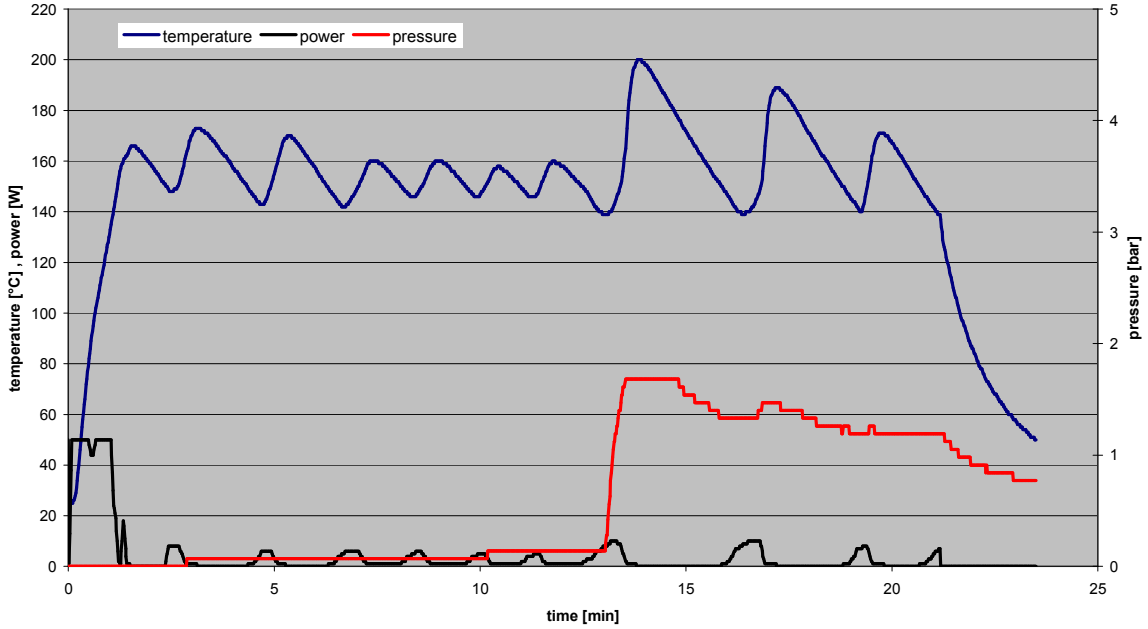

Figure 27: Temperature and pressure profile of the solvent-free microwave assisted synthesis of imidazolium chloride 7

However, this problem could be dealt with by addition of a small amount of a medium or low absorbing solvent. If 1 ml of anhydrous ethyl acetate was added to the starting materials, the problem of overheating could be controlled, although longer hold times were necessary to obtain complete conversion (Figure 28).

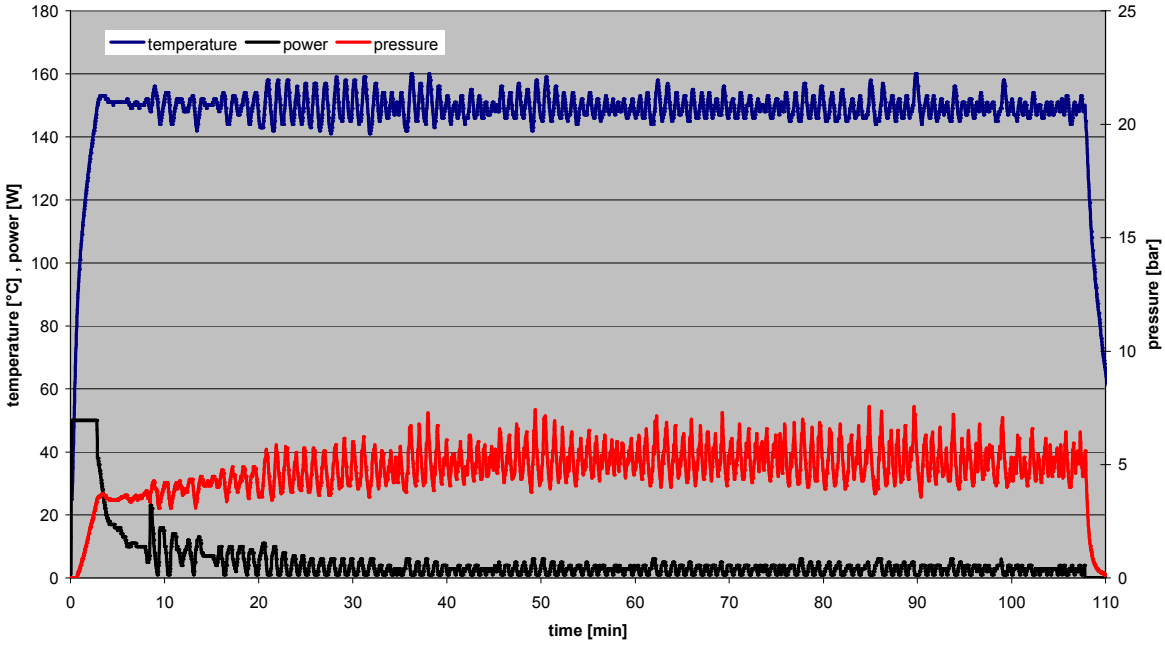

Figure 28: Temperature and pressure profile of the microwave assisted synthesis of imidazolium chloride 7 in the presence of 1 ml of anhydrous ethyl acetate

Furthermore, the resulting imidazolium salt was not soluble in the solvent anymore and precipitated during cooling. Simple decantation of remaining ethyl acetate gave the imidazolium chloride **7** as very pure crystals (Table 11, entry 4). Optimal reaction conditions were obtained at 150 °C and an irradiation hold time of 105 minutes yielding 91% of **7**, whereas longer irradiation did not give improved isolated yields (Figure 29).

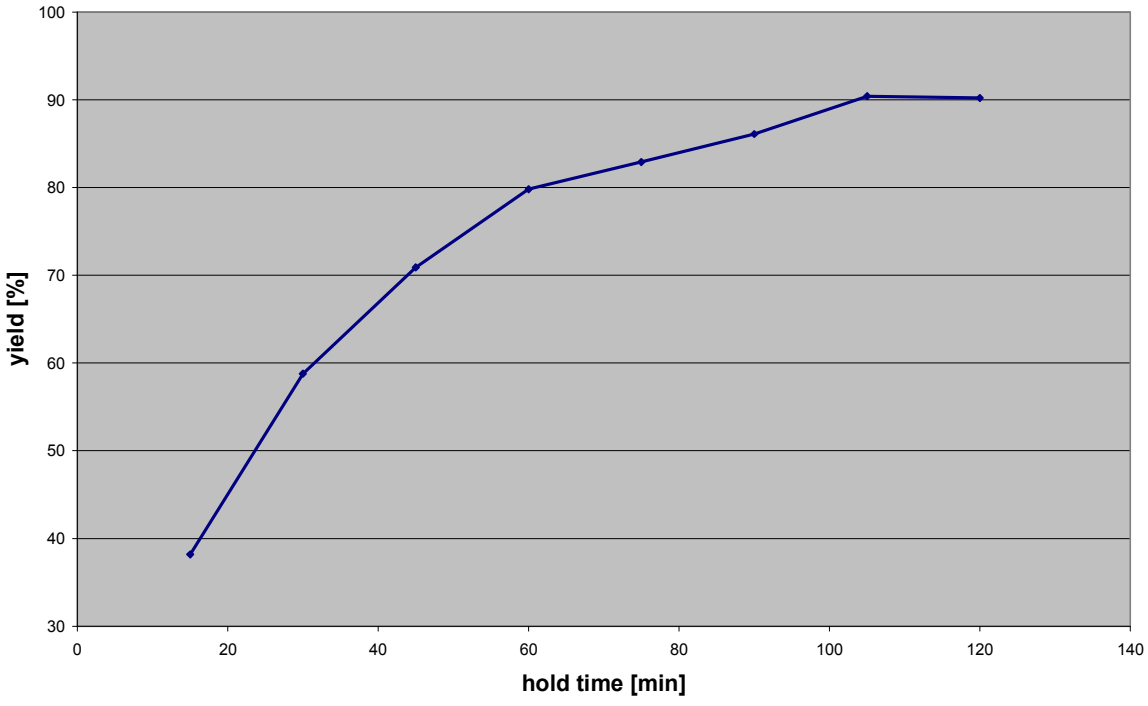

Figure 29: Isolated yield depending on irradiation time in the microwave assisted synthesis of 7

4.1.6 Application of camphor-derived chiral ionic liquids in stereoselective Diels-Alder reactions

In order to investigate the stereochemical induction of these CILs the Diels-Alder reaction between acrylic acid and cyclopentadiene was chosen as test reaction (Figure 30).

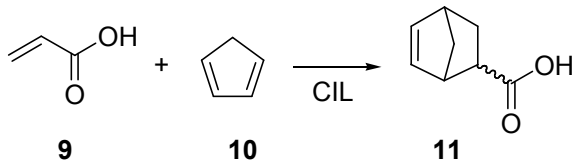

Figure 30: Stereoselective Diels-Alder reaction in chiral ionic liquids

Various Diels-Alder reactions have been studied in ILs utilizing them either as solvent or as additive, and, in general, a rate acceleration compared to conventional organic solvents was observed.[79] Also several examples of the stereoselective Diels-Alder and aza-Diels-Alder reaction in CILs have been reported so far, nevertheless, in most cases a co-solvent was used (Table 12).[10,12,17,18,19,20,21,22]

To further investigate the difference of chiral recognition for CILs with either cationic or anionic camphor moieties, the anion-chiral camphor-containing CIL 1-butyl-3-methylimidazolium camphorsulfonate [bmim-(1*S*)-CSA] was synthesized via anion-exchange from 1-butyl-3-methylimidazolium chloride **12** and the potassium salt of camphorsulfonic acid (Figure 31).

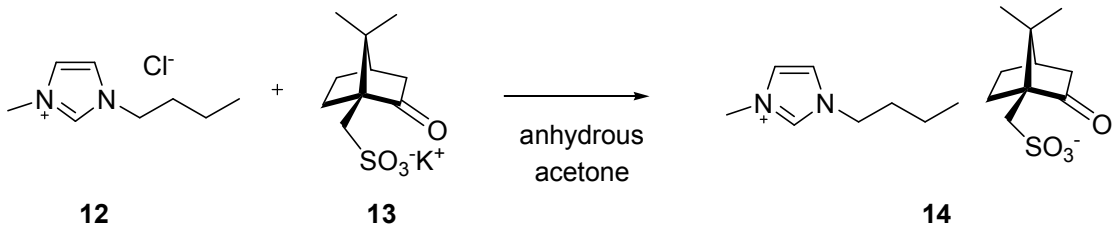

Figure 31: Synthesis of the anion-chiral ionic liquid 1-butyl-3-methylimidazolium camphorsulfonate 14

All reactions were run on 2 mmol scale using 1 g of the room temperature CILs **4c**, **8c**, **8e** and **14** as reaction media at room temperature and 0 °C, resp. No co-solvent was necessary, since both acrylic acid as well as cyclopentadiene turned out to be readily soluble in the CILs. The reaction proceeded smoothly without addition of further Lewis acid at both temperatures, and excellent yields of norbornene carbonic acid **11** could be obtained with the CILs **4c, 8c** and **8d** (Table 12). Isolation of the product could be easily achieved by extraction of **10** in the CIL

[79] Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465.

layer with diethyl ether. Standard basic extractive work-up and re-extraction after acidification gave the norbornene carbonic acid **11** in spectroscopic pure form.

Table 12: Results of the Diels-Alder reaction in various chiral ionic liquids

Entry [a]	CIL/solvent	T [°C]	Yield [b] [%]	*endo: exo* [c]
1	**4c**	25	94	4.8:1
2	**8c**	25	99	4.3:1
3	**8d**	25	97	6.0:1
4	**14**	25	68	4.0:1
5	**4c**	0	95	6.7:1
6	**8c**	0	89	6.5:1
7	**8d**	0	98	7.3:1
8	**14**	0	48	4.1:1
9	CH_2Cl_2	0	n.d.	3.5:1

[a] Performed with 2 mmol acrylic acid **9**, 3 mmol cyclopentadiene **10** for 90 min. [b] Isolated yield of **11** after extractive work-up. [c] Determined by GC-MS analysis.

In comparison, the reaction in CIL **14** resulted in considerably lower yields of **11** especially at 0 °C. In this particular case, stirring was difficult since CIL **14** showed the highest viscosity which could be a reason for the reduced yield. Best diastereoselectivities could be obtained in CIL **8d** at 0 °C, giving the *endo*-norbornene carbonic acid in a ratio of 7.3:1. In contrast, the diastereoselectivity achieved in CIL **14** containing camphor sulfonate as chiral anion was significantly lower with an *endo:exo* ratio of 4.1:1. Nevertheless, this is still an improvement to common organic solvents like CH_2Cl_2, which only gave an inferior diastereoselectivity of 3.5:1 under the same conditions.

Furthermore, CIL **8d** could be successfully recycled: After extraction of product **11** and removal of volatile material under reduced pressure, the remaining CIL could directly be subjected to the next run. Although a certain loss of ionic liquid material during phase separation was observed (about 10% losses for each run) the yield of norbornene carbonic acid **11** was still excellent. Diastereoselectivity remained constant for 2 recycling steps and was decreasing for the 4th and 5th run (Table 13, entries 4 & 5).

Table 13: Recyclation of chiral ionic liquid 8d in the stereoselective Diels-Alder reaction

Entry [a]	CIL	Yield [b]	*endo:exo* [c]
1	**8d**	98	7.3:1
2	**8d** [d]	99	7.4:1
3	**8d** [d]	98	7.3:1
4	**8d** [d]	95	6.3:1
5	**8d** [d]	94	4.7:1

[a] Performed with 2 mmol acrylic acid **9**, 3 mmol cyclopentadiene **10** for 90 min at 0 °C. [b] Isolated yield of **11** after extractive work-up. [c] Determined by GC-MS analysis. [d] 2nd, 3rd, 4th and 5th run, resp.

In order to examine enantioselectivity, norbornene carbonic acid **11** was transformed to its methyl ester derivative using *p*-TsOH and MeOH and relative amounts were determined via chiral GC analysis. Unfortunately, only very low enantiomeric excess of <3% ee could be detected in each case. This indicates that the chiral induction achieved by the use of these CILs as reaction media is to low to give a significant enantioselectivity.

4.2 Chiral ionic liquids with an amido alcohol structure

The lack of enantioselectivity in the Diels-Alder reaction is, though disappointing not surprising, given the context that common chiral solvents seldom give reasonable selectivity in chiral transformations, and are therefore not common in asymmetric synthesis. This can also be seen in various papers dealing with CILs as solvents that report no or neglible selectivity when used as solvent or additive in asymmetric transformations (2.1) and leads to the following conclusion:

The simple presence of any chiral group attached on an IL unit is not sufficient to induce chirality. In this context, a chiral environment which only consists of ions does not differ from a conventional chiral solvent.

To achieve selectivity, it is therefore necessary to force interaction between a CIL and the prochiral substrate, whether it is covalent bonding or non-covalent interactions.

This led to the development of CILs bearing coordination sites on the chiral part that is linked to the ionic liquid unit with a non-chiral spacer (Figure 32).

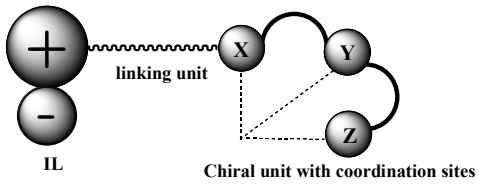

Figure 32: Design of chiral ionic liquids with coordination sites

4.2.1 Synthesis of amido alcohol chiral ionic liquids

In order to design CILs with more possibilities for interaction, amino alcohols were chosen as chiral starting material. (1*R*, 2*S*)-Ephedrine **15** is a reasonable prized amino alcohol bearing two chiral centres and is present in nature in both enantiomeric forms. Careful reaction with stoichiometric amounts of chloroacetyl chloride as linking unit in the presence of one equivalent of triethylamine at 0 °C resulted in a selective formation of the amide **16** without the formation of the undesired ester. Further reaction with *N*-methylimidazole at 80 °C proceeded very fast in 30 minutes only and resulted in the formation of the imidazolium chloride **17** as brown glass. Crystallization from anhydrous acetonitrile gave **17** as colourless crystals, that were further subjected to anion metathesis with $LiN(Tf)_2$ in H_2O to yield the imidazolium triflimide **18** as very viscous light yellow oil.

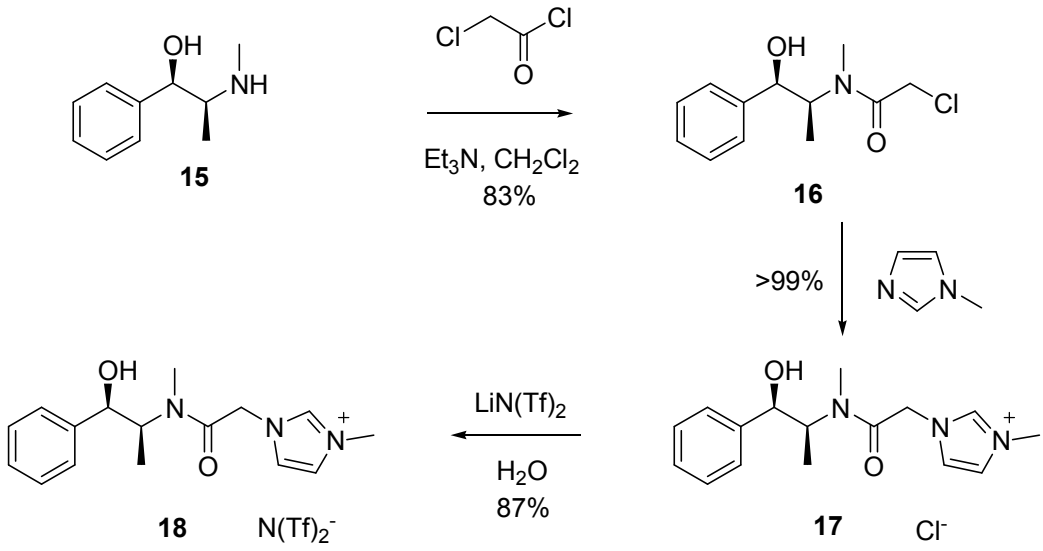

Figure 33: Synthesis of hydroxy amido chiral ionic liquids from (1R, 2S)-ephedrine

This knew CIL revealed a high potential for non-covalent interaction: π–π-stacking of the phenyl ring and -although weaker- of the imidazolium unit is possible. Furthermore, strong OH-bonding and weaker dipole-dipole interactions of the amid linking unit can take place. Additionally, ion-ion interactions are likely due to the imidazolium cation.

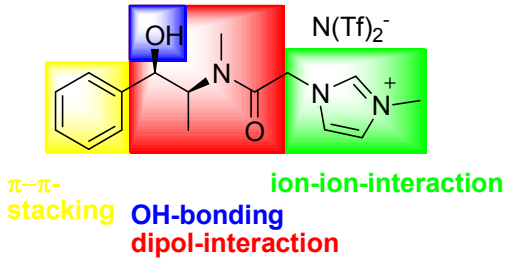

Figure 34: Possible interactions of hydroxy amido chiral ionic liquid 18

NMR-analysis of the amide **16** as well as of the imidazolium salts **17** and **18** showed a mixture of two products in a ratio of 1:1.8 that could be revealed as isomers derived from the hindered rotation of the amide N-C bond.

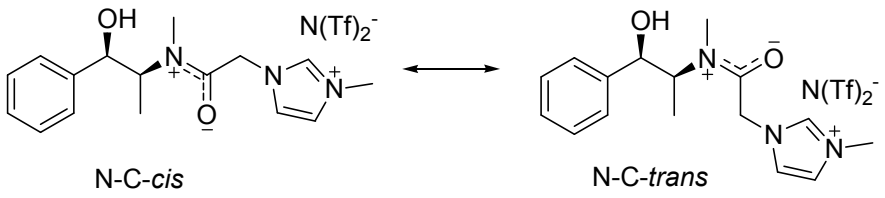

Figure 35: Rotameres of chiral ionic liquid 18

High-temperature NMR of the salt **18** showed a thermal equilibrium and therefore proved the presence of two rotameres.

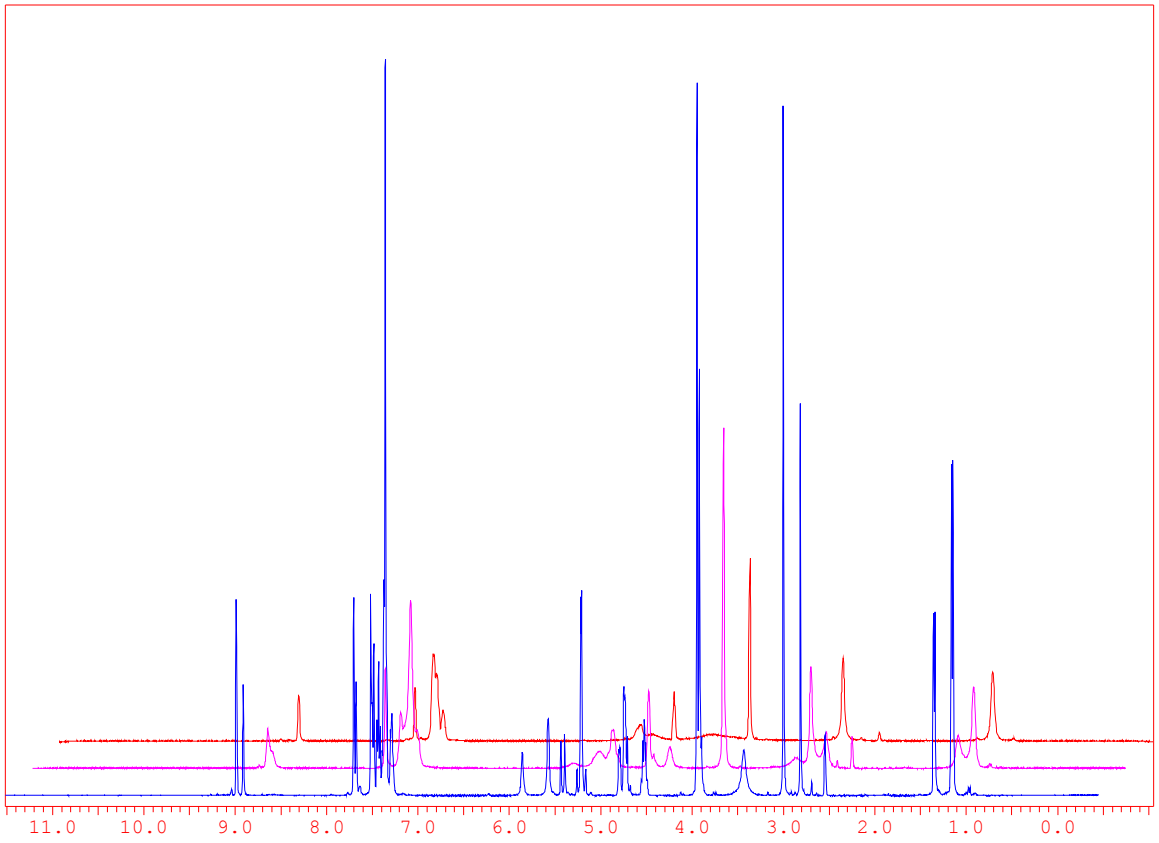

Figure 36: Thermal equilibrium of chiral ionic liquid 18 measured at 25 °C (blue), 85 °C (purple) and 130 °C (red).

This simple 3-step synthesis could be applied to various secondary amino alcohols: To further investigate the influence of stereochemistry, the diastereomeric (1*S*, 2*S*)-pseudoephedrine **19** was used for the same synthetic sequence (Figure 37).

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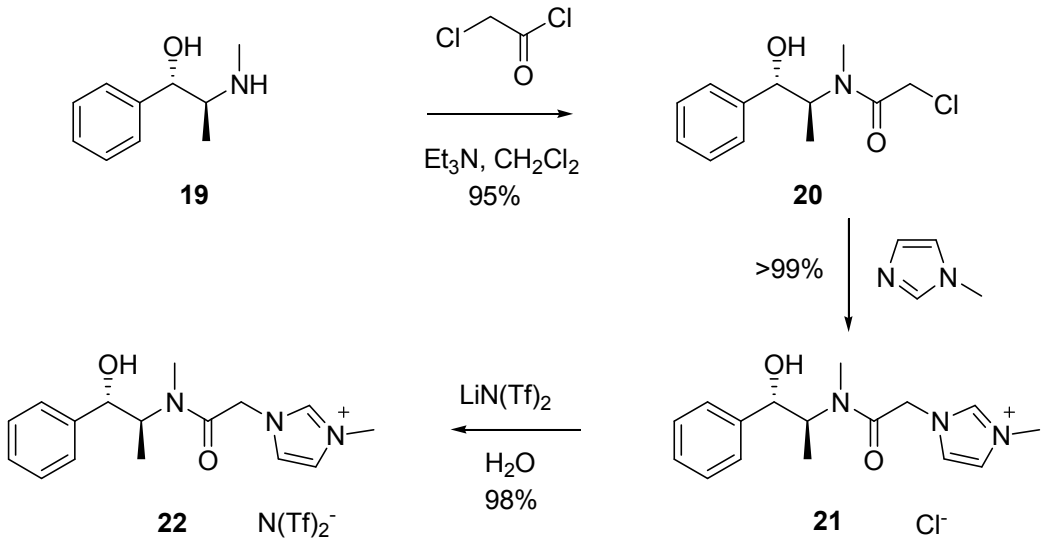
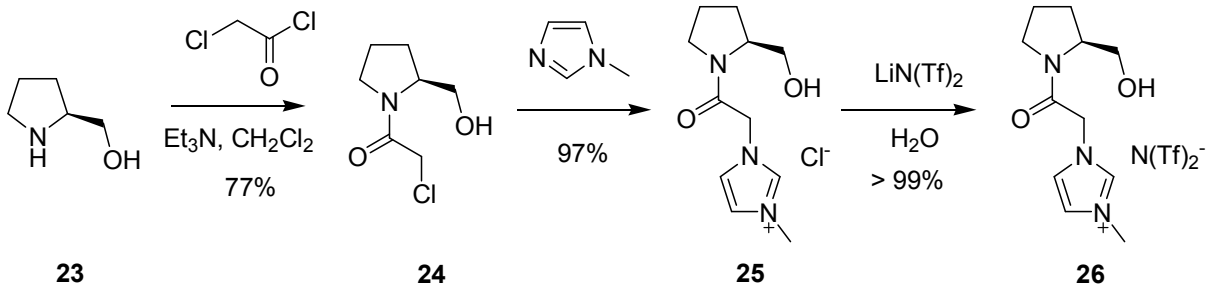


Figure 37: Synthesis of a hydroxy amido chiral ionic liquid from (1S, 2S)-pseudoephedrine

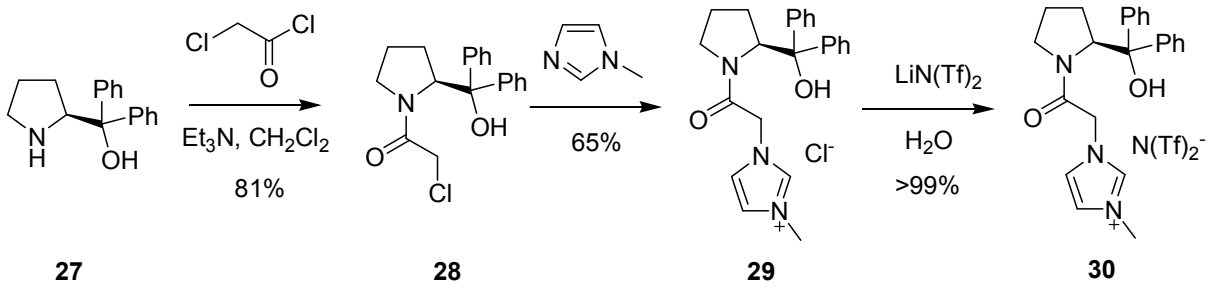
The same pathway was applied to the amino acid-derived amino alcohol (*S*)-prolinol **23** and CIL **26** was obtained as colourless oil in good overall yield (Figure 38).



23 **24** **25** **26**

Figure 38: Synthesis of hydroxy amido chiral ionic liquids from (S)-prolinol

In order to prepare a sterically more hindered CIL, the same sequence was run starting from (*S*)-diphenylprolinol **27**, a chiral amino alcohol that is well known as chiral precursor for the Corey-Bakshi-Shibata (CBS)-reduction of ketones with boranes and usually providing excellent selectivities.[80] Despite the high tendency for crystallization of diphenylprolinol derivatives, imidazolium salt **30** was obtained as colourless glass (Figure 39).



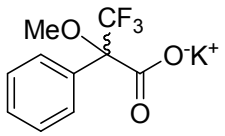
27 **28** **29** **30**

Figure 39: Synthesis of hydroxy amido chiral ionic liquids from (S)-diphenylprolinol

[80] (a) Corey, E. J.; Helal, C. J. *Angew. Chem.; Int. Ed.* **1998**, *37*, 1986. (b) Walbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

4.2.2 Investigation in diasteromeric interaction

To evaluate the chiral recognition ability of these new functionalized CILs the diastereomeric interactions between the CIL and a cationic racemic substrate were investigated. Thus, the potassium salt of racemic Mosher's acid **31** was mixed with various amounts of the enantiopure imidazolium salts (Figure 40).



31

Figure 40: Mosher's acid potassium salt

To trap the potassium cation, one equivalent of the crown ether 18C6 was added. The mixture was dissolved in CD_2Cl_2 and the resulting clear solution was examined by ^{19}F NMR spectroscopy. In case of diastereomeric interactions, a splitting of the CF_3 signal at -70.15 Hz was observed, whose chemical shift difference could be directly related to the tightness of the diastereomeric interactions (Figure 41).

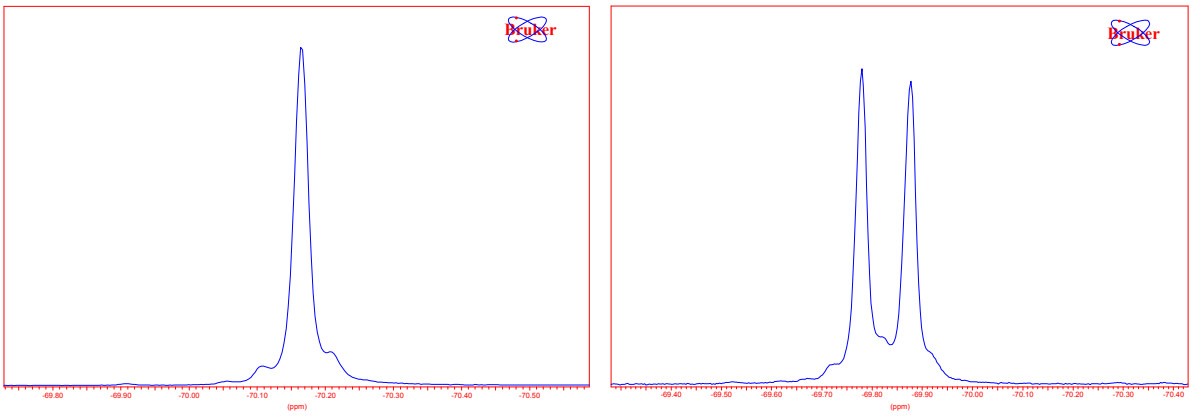


Figure 41: ^{19}F NMR signals of CF_3 group of Mosher's acid potassium salt (a) without chiral ionic liquids (left) and (b) in the presence of 3 eq. of 18 (right).

Surprisingly, no splitting was observed in the presence of one equivalent of the (*S*)-diphenylprolinol derivative **30**, although a certain broadening of the peak shape revealed the presence of some diastereomeric interactions. A distinct chemical shift difference of 10 Hz was observed in the presence of the prolinol derived CIL **26**, and the strongest interactions were observed with the ephedrine derivative **18**, indicating a large influence of the second chiral centre present in the CIL **18**.

Similar experiments were carried out in the presence of 3, 5 and 10 equivalents of each CIL, to further investigate the concentration effect of the CILs on the Δδ value.

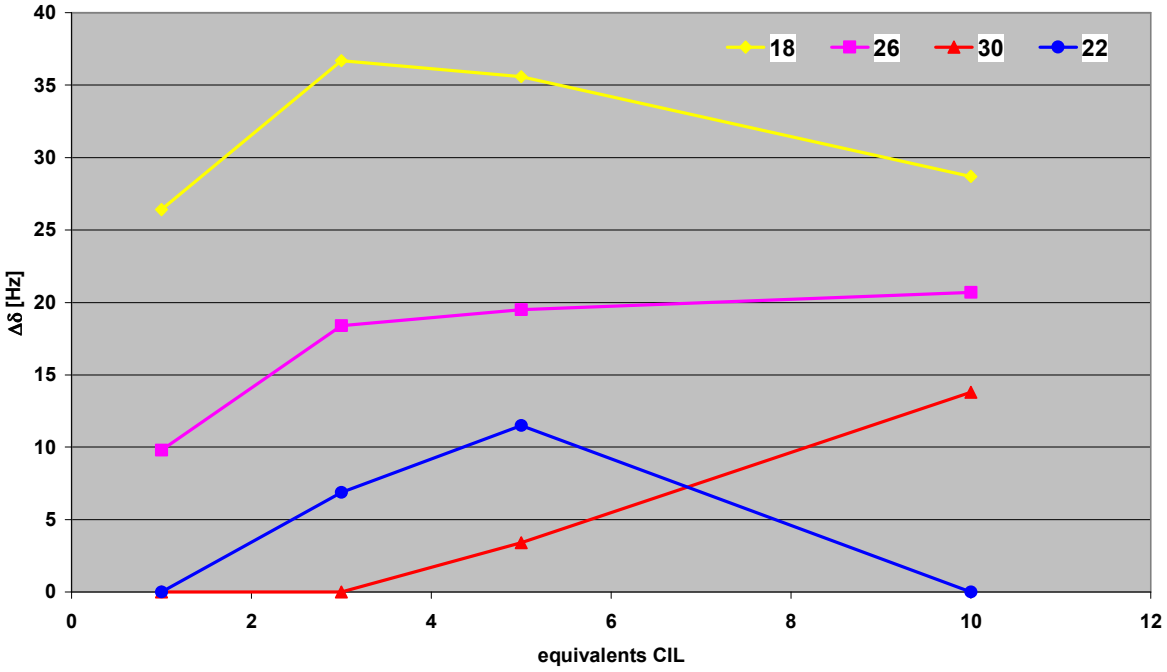


Figure 42: Concentration effect of CILs 18, 22, 26 and 30 on the chemical shift difference of the CF_3 signal (^{19}F NMR, 376.5 MHz) of racemic Mosher's acid carboxylate.

Interestingly, a maximum splitting of 37 Hz for the CF_3-signal was observed with a 3-fold excess of CIL **18**, whereas a stronger excess led to a decrease of the diastereomeric interactions. The same concentration effect was observed for the pseudoephedrine derivative **22**, although weaker interactions were present. On the contrary, in case of (*S*)-prolinol CIL **26** and (*S*)-diphenylprolinol derivative **30**, the splitting of the CF_3 group of Mosher's acid potassium salt is constantly growing with increasing amounts of CIL.

This NMR measurement clearly indicates that the functionalized CIL **18** can indeed interact with racemic substrates and expresses excellent chiral recognition ability. In order to demonstrate the application as chiral shift reagent for the determination of an enantiomeric excess, an enantioenriched sample of Mosher's acid potassium salt with 33% ee was synthesized. This sample was mixed with ephedrine derivative **18** under the same conditions previously optimized. Integration of the two signals obtained in ^{19}F spectroscopy gave a ratio of 2:1 and thus proved the applicability of CILs with an amido alcohol structure as chiral shift reagent.

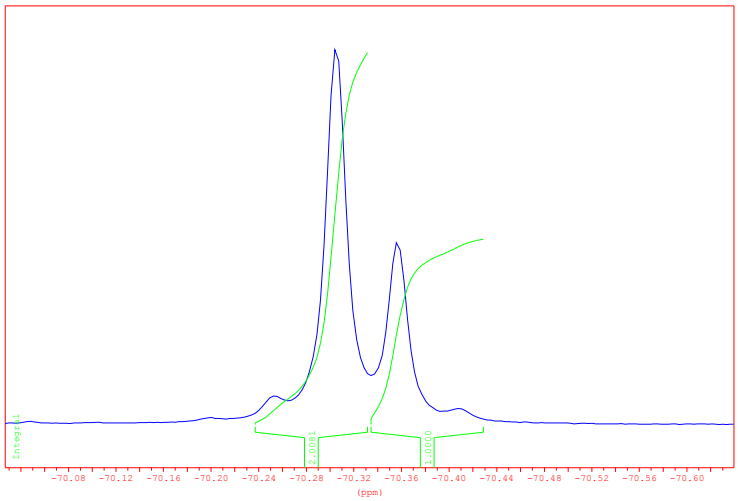


Figure 43: ^{19}F NMR spectrum of an (S)-enantioenriched sample of Mosher's acid potassium salt in the presence of chiral ionic liquid 18.

4.3 Chiral ionic liquids with an amino alcohol structure

4.3.1 Amino alcohols in asymmetric synthesis

1,2-Amino alcohols of both acyclic and cyclic derivatives are successfully used as auxiliaries or ligands in asymmetric synthesis in an immense variety.[81] In addition to being useful compounds to affect a wide range of transformation, the amino alcohol functionality is also present in a relatively large number of natural products.

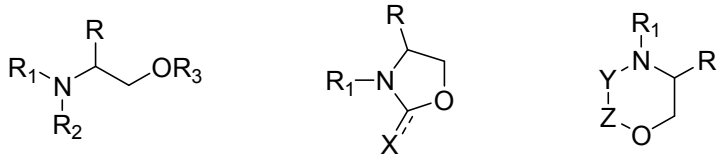


Figure 44: 1,2-Amino alcohols and their cyclic derivatives

A simple set of 19 chiral 1,2-amino alcohols is easily accessible via reduction of native α-amino acids with $LiAlH_4$ in THF.[82] When borane reagents are applied, protocols include the use of boran methyl sulphide in the presence of boron trifluoride etherate[83], of sodium borohydride-sulfuric acid systems[84], of lithium borohydride/trichloromethyl silane[85] or of sodium borohydride-iodine.[86] However, in many cases more complex and sterically demanding systems are required and functionalization of *N*-protected amino acid derivatives with Grignard reagents is hence done before the reducing step is performed.[87] Other methods described for the preparation of chiral 1,2-amino alcoholes include reduction of α-amino carbonyls, alkoxy carbonyls or cyanohydrins, the ring opening of epoxides or cyclic sulfates or the oxyamination or oxymercuration of alkenes.

Further transformations of simple chiral 1,2-amino alcohols lead to cyclic derivatives like oxazolidines, oxazines, oxazolidinons and oxazolines which are mainly used as auxiliaries.

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[81] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

[82] (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (b) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth.* **1990**, *Coll Vol. 7*, 530.

[83] Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *40*, 3527.

[84] Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.

[85] Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.

[86] McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

[87] Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1994**, *59*, 4680.

4.3.2 1,2-Amino alcohol mediated asymmetric alkylation of carbonyls

The catalytic enantioselective addition of organometallic reagents to carbonyl groups is one of the most useful methods for the preparation of chiral secondary alcohols and therefore has been studied extensively.[88] Several metal organyls in combination with a large number of chiral ligands have been published, making this strategy superior to the comparative enantioselective reduction of ketones. Of all organometallic reagents, dialkylzinc organyls might be the most useful and are frequently used, since a chemoselective alkylation of functionalized carbonyls is possible and high enantioselectivities can be achieved.[89,90]

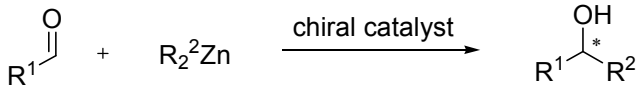

Figure 45: Addition of dialkylzinc reagents to carbonyls

There are two general mechanisms for the enantioselective addition of dialkylzinc reagents to aldehyds: (*i*) chiral Lewis base mediated asymmetric alkylation and (*ii*) Lewis acid promoted addition (Figure 46).

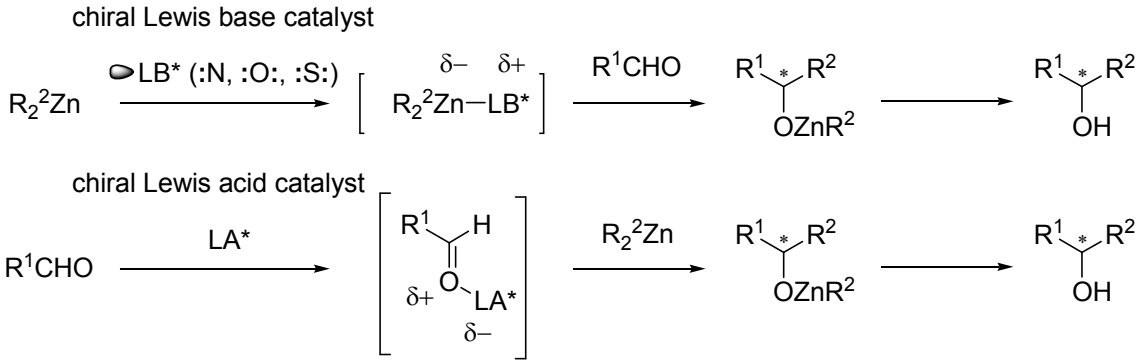

Figure 46: Lewis base and Lewis acid promoted asymmetric alkylation with dialkylzinc reagents

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[88] (a) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, 911. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5.

[89] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

[90] Noyori, R.; Kitamura, M. *Angew. Chem.; Int. Ed.* **1991**, *30*, 49.

Except few examples, dialkylzinc itself is not reactive enough to alkylate aldehyds in the absence of catalysts. However, they can be activated as zincates by the addition of catalytic amounts of Lewis bases like amino alcohols.[91] Alternatively, Lewis acids enhance the eletrophilicity of aldehyds by coordination and facilitate the attack of the zinc organyl. In both cases, the alkylation of the aldehyde is not only promoted, but enantioselectivity can be induced using chiral Lewis acids or bases.

The first example of a Lewis base catalyzed enantioselective alkylation of benzaldehyde with diethylzinc dates to the year 1984, when Oguni and Omi used (*S*)-leucinol as catalyst and reported a moderate enantioselectivity of 49% ee.[92] The first highly enantioselective process was published in 1986 by Noyori *et al.* who used (-)-3-*exo*-dimethylaminoisoborneol [(-)-DAIB] as catalyst.[93] In the presence of 2 mol% (-)-DAIB, alkylation of benzaldehyde with dimethylzinc in toluene at 0 °C gave (*S*)-1-phenylethanol in excellent yield with up to 95% ee.

Since then an impressive variety of highly efficient amino alcohols has been published, covering not only simple cyclic or acyclic amine based amino alcohols, but three-, four-, five- and six-membered rings, multicyclic rings, pyridinyl and iminyl alcohols, carbohydrate-based amino alcohols, axially chiral derivatives, ferrocene complexes, amino alcohols with η^6-arene chromium and oxazolines.[94]

As an alternative to amino alcohols, amine thiols, disulfides, diselenids, diamines or diols, and titanium sulfonamide and phosphoramide complexes have been reported to successfully catalyze the enantioselective addition of dialkylzinc to aldehydes. Recent publications deal with the application of macromolecules, including polymer-anchored chiral ligands, main chain chiral polymer catalysts and dendrimer ligands in organozinc addition.[94]

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[91] Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.

[92] (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841.

[93] Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

[94] (a) Evans, D. A. *Science* **1988**, *240*, 420. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (c) Noyori, R.; Kawai, S. K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597. (d) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

Extensive investigations on the reaction mechanism of the amino alcohol catalyzed addition of dialkylzinc to aldehyds were done by Noyori and co-workers, which resulted in the following mechanism (Figure 47):[88,94c,95]

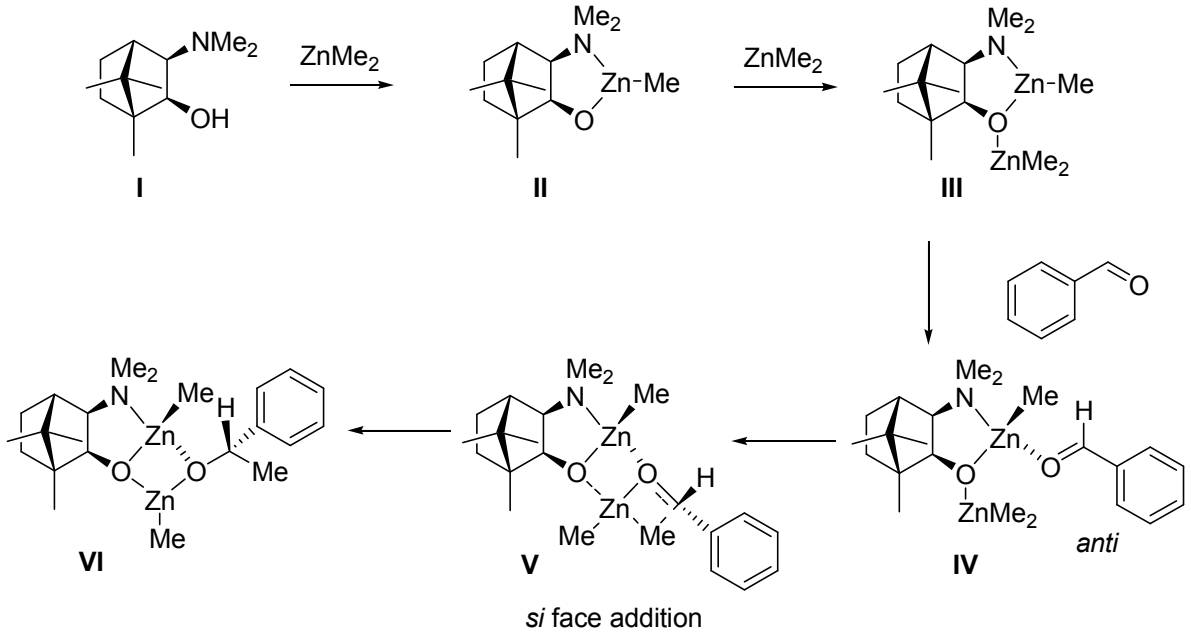


Figure 47: Mechanism of the amino alcohol-catalyzed asymmetric alkylation of benzaldehyde with dimethylzinc

In the first step, dimethylzinc reacts with the hydroxyl group of the amino alcohol to form the alkylzinc alkoxide **II** and liberates methane. This alkylzinc complex, however, is not able to transfer the methyl group to the aldehyde, which indicates that two zinc atoms per amino alcohol unit are needed for the alkyl transfer. A second molecule of dimethylzinc coordinates to the alkoxy-oxygen (**III**) and activates the (-)-DAIB-attached zinc atom to coordinate to benzaldehyde (**IV**). Various bi- and tricyclic assemblies are possible for the transition state, but *ab initio* and density functional calculations indicate that the presence of the 5/4/4 tricyclic transition state **V** is most favourable.[96] This transition state involves transfer of the bridging methyl group to the *si*-face of the aldehyde to form complex **VI** that further dissociates with another molecule of diethylzinc to (*S*)-1-phenylethoxy-ZnMe and regenerates **III**.

[95] (a) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128. (b) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, 117, 6327.

[96] (a) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (b) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77. (c) Kaufmann, E.; Schleyer, P. von R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560.

The importance of the presence of dimeric compounds was recognized by Oguni and co-workers in 1988, who observed a non-linear relation between the enantiomeric purity of the chiral auxiliary and the enantiomeric excess of the alkylated product.[97] The origin of this amplification of chirality is based on the equilibrium between monomer and dimer and the presence of diastereomeric dimeric complexes that react remarkably different.[98]

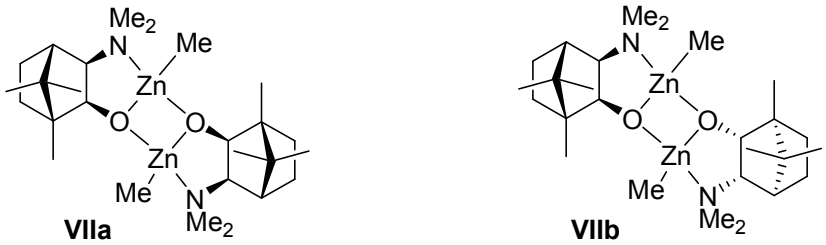


Figure 48: Homo- and heterodimeric zinc complexes

The zinc complex **II** forms the homodimer **VIIa**, whereas combination with its -minor-enantiomer generates the considerable more stable heterodimer **VIIb** (Figure 48). Thus, the less stable homodimer dissociates much faster to alkylate the aldehyde, but the more stable heterodimer consumes the minor and undesired enantiomer of the ligand, leading to the observed positive non-linear effect.[99]

[97] Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.

[98] (a) Girard, C.; Kagan, H. B. *Angew. Chem.; Int. Ed.* **1998**, *37*, 2922. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997.

[99] (a) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (b) Kitamura, M.; Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1171

4.3.3 Synthesis of amino alcohol chiral ionic liquids

Though chiral amino alcohols are highly useful as versatile reagents in asymmetric synthesis, a major drawback is that they are not easy to recover when applied as chiral catalysts for asymmetric alkylation. Usually 10 mol% of the chiral amino alcohol, that has to be previously prepared in a multi-step synthesis, is applied and lost during the reaction.

The careful design of CILs bearing an amino alcohol functionality should allow the use of this systems as catalysts for the enantioselective addition of diethylzinc to benzaldehyde or other amino alcohol catalyzed asymmetric reactions. Furthermore, it is not necessary to use the CIL as solvent and create a chiral environment as usually done. In fact, it is much more convenient and economical to apply the CIL in catalytic amounts in the sense of IL-supported catalysts or IL-supported ligands that can be recycled after product separation.

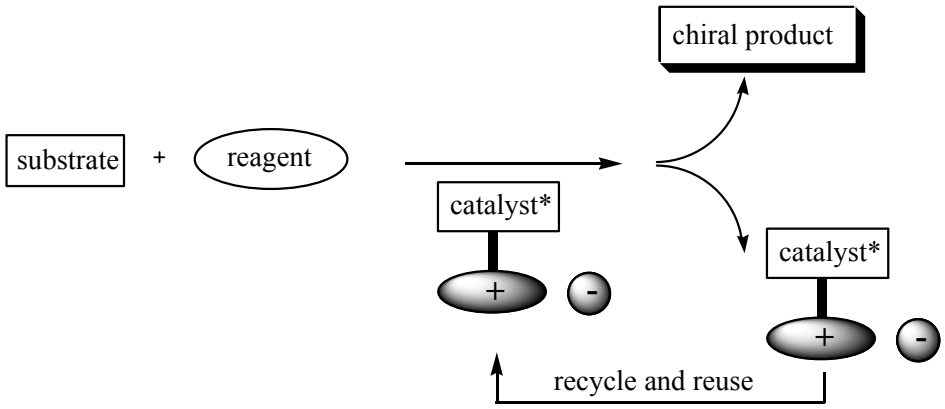


Figure 49: General concept of chiral ionic liquid-supported catalysis

Therefore, IL supported chiral amino alcohols were designed to achieve highly coordinating CILs which could be used as ligands, catalysts and auxiliaries similar to chiral amino alcohols. Considering the higher basicity of amines compared to amides, these amino alcohol CILs should show even better interaction and coordination ability than the previously prepared amido alcohol CILs (4.2).

In a general strategy, a nitrogen-containing IL precursor is grafted into a chiral 1,2-amino alcohol L* to obtain tridentate ligands (Figure 50). Alkylation of one nitrogen unit should enable access to highly coordinating basic CILs that can be applied not only as chiral reaction media, but also show the possibility for direct interaction with substrates or metals.

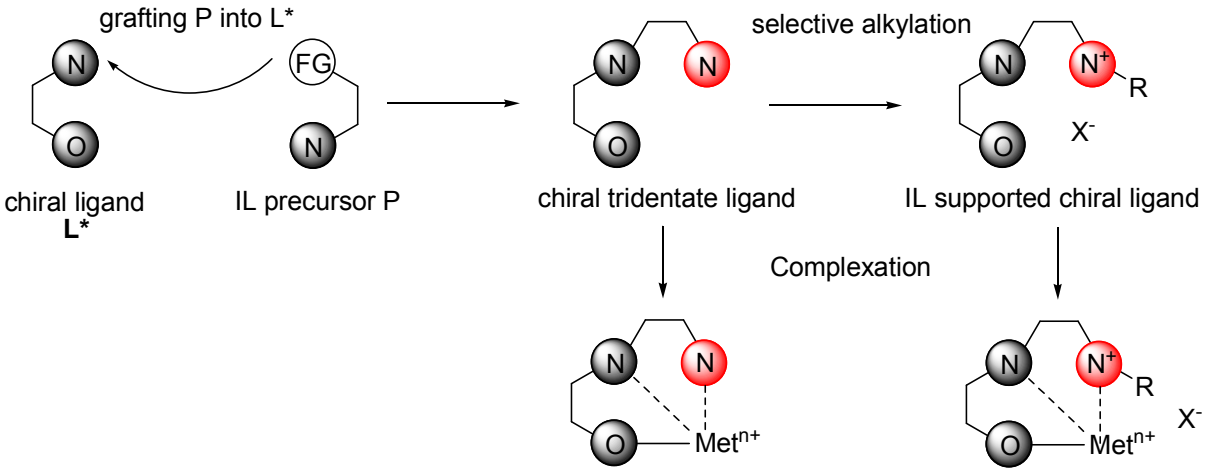


Figure 50: Grafting strategy for the synthesis of chelating chiral ionic liquids

The major problem in the design of basic CILs bearing an amino alcohol unit is the selective alkylation of the ionic liquid part in the presence of the amino alcohol functionality that has to be kept unsubsituted. Alternatively, protecting groups may be used or the alkylation has to be performed on a precursor that is further transformed to an amino alcohol CIL.

The most elegant way, however, is to tune the reactivity of both nitrogenes towards nucleophilic substitution and selectively alkylate the IL precursor. Additionally, a grafting strategy is necessary that allows selective linkage of the chiral amino alcohol L* nitrogene with the ionic linking precursor P without reaction of the alcohol.

In a first step, reductive alkylation of the chiral primary 1,2-amino alcohol (1*S*,2*R*)-norephedrine **32** with pyridine-3-carboxaldehyde was performed. Reaction in the presence of freshly activated molecular sieve in anhydrous methanol gave a complex mixture of two isomeric imines and the N,O-acetale that were directly reduced with sodium borohydride without isolation to yield the secondary amino alcohol **33** as single product (Figure 51).

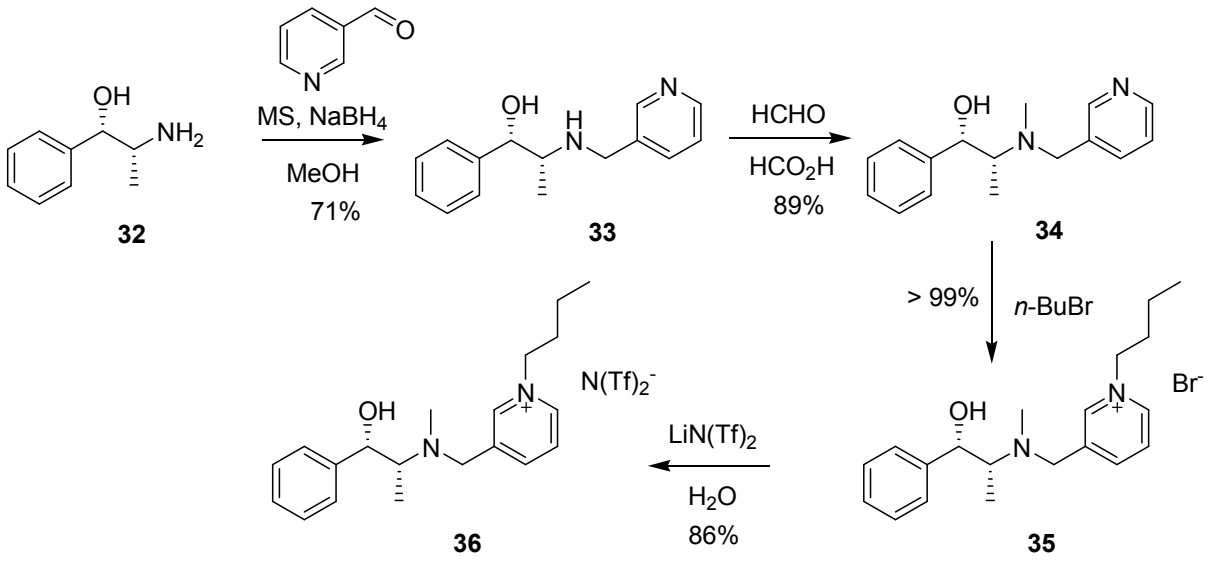


Figure 51: Synthesis of (1S,2R)-norephedrine-derived amino alcohol chiral ionic liquids

It was necessary to use an exact stoichiometric amount of freshly distilled pyridine-3-carboxaldehyde to achieve satisfying yields. If an excess was used, the formed by-product pyridine-3-methanole was almost impossible to separate via chromatographic purification or distillation. Further *N*-methylation using the classical Leukart-Wallach protocol gave the tridentate ligand **34** in good overall yield.

Selective alkylation of the terminal pyridine was best done with *n*-butyl bromide at 60 °C overnight under solvent-free conditions. Despite the higher basicity of tertiary amines compared to pyridine, alkylation can be selectively performed on the pyridine moiety which might be explained by sterical reasons and an easier accessibility for alkylation. Even with a 3-fold excess of alkyl bromide, a selective alkylation of the pyridine took place and no substitution of the amino group was observed. In fact, the only way to force double alkylation is to reflux amino alcohol **34** with an excess of the very reactive alkylation reagent methyl iodide. In this case, a quantitative formation of the di-cation **37** was observed (Figure 52). In contrast, selective monoalkylation with methyl iodide could not be performed, since only starting material **34** was obtained after refluxing in the presence of one equivalent of methyl iodide in anhydrous ethanol overnight.

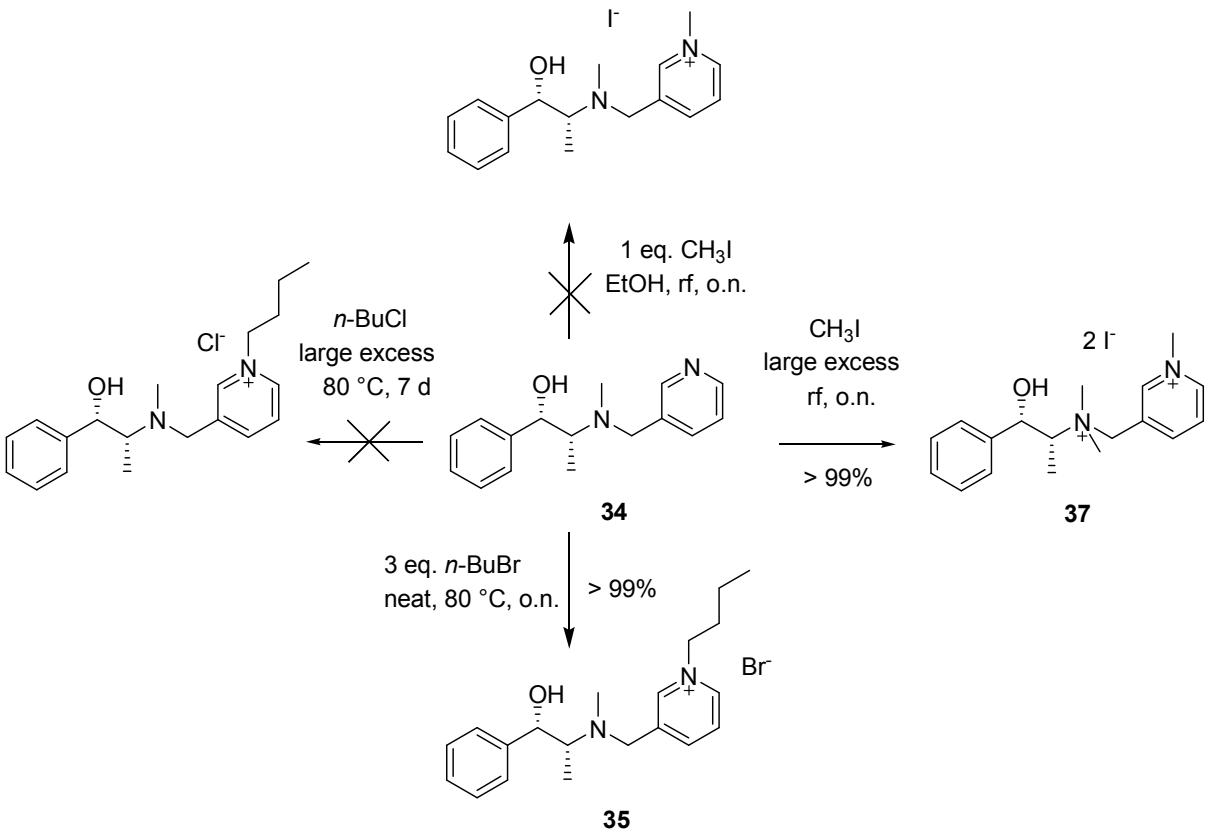


Figure 52: Selective alkylation of tridentate ligand 34.

When the less reactive *n*-butyl chloride was used as alkylation reagent instead of *n*-butyl bromide, no conversion could be obtained even under rough conditions (neat, 80 °C, 7 days). The crude imidazolium bromide was washed with anhydrous ethyl acetate to remove remaining *n*-butyl bromide. Unfortunately, the imidazolium bromide **35** was obtained as brown oil and crystallization for X-ray analysis failed so far. However, crystal structures could be obtained from compounds **34** and **37**. The norephedrine-derivative **34** crystallized from *n*-hexane/ethyl acetate in the chiral and polar space group $P2_1$.

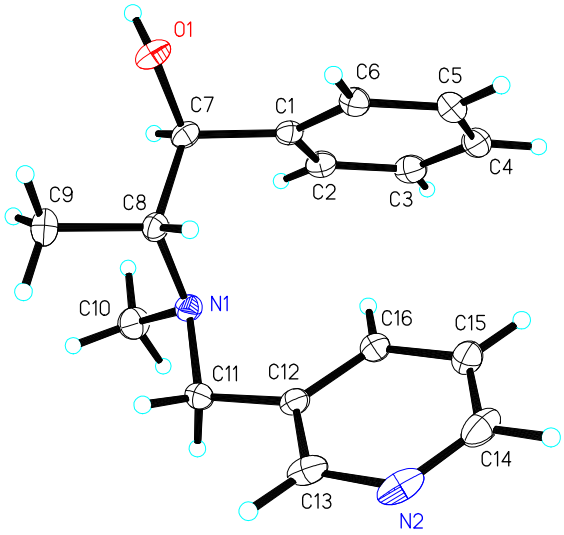


Figure 53: ORTEP plot of norephedrine derivative 34

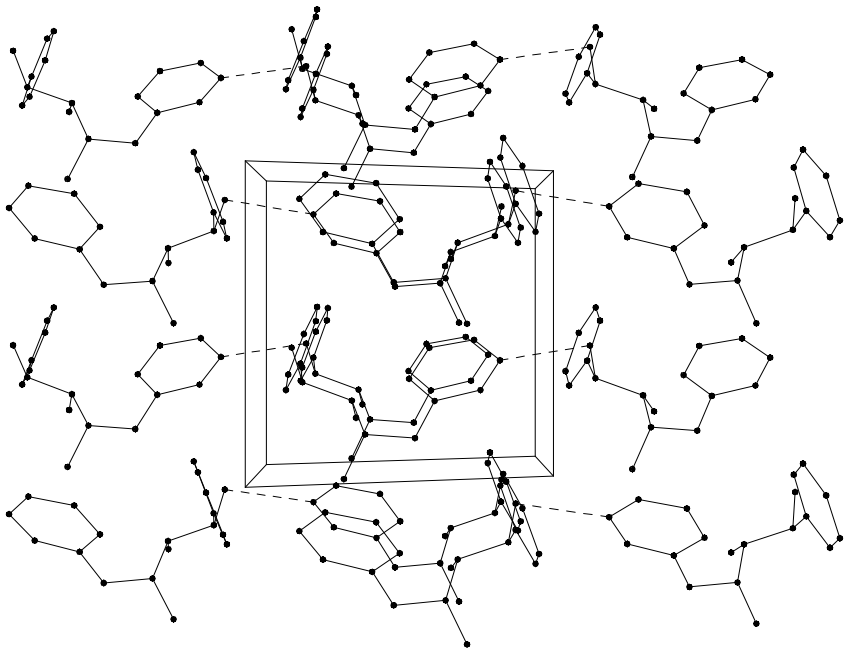


Figure 54: Packing diagram of norephedrine derivative 34

The diiodide salt **37** could be crystallized from ethanol/H_2O to give large plate-like crystals with remarkable triangular structure which reflects the polar character of the solid state structure.

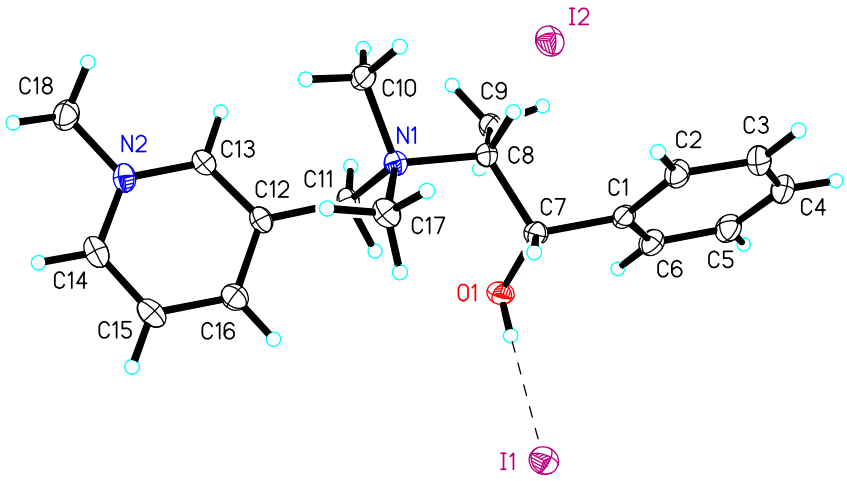


Figure 55: ORTEP plot of 1-Methyl-3-[[[dimethyl[(1R,2S)-2-hydroxy-1-methyl-2-phenyl]ethyl]ammonio] methyl]pyridinium diiodide 37

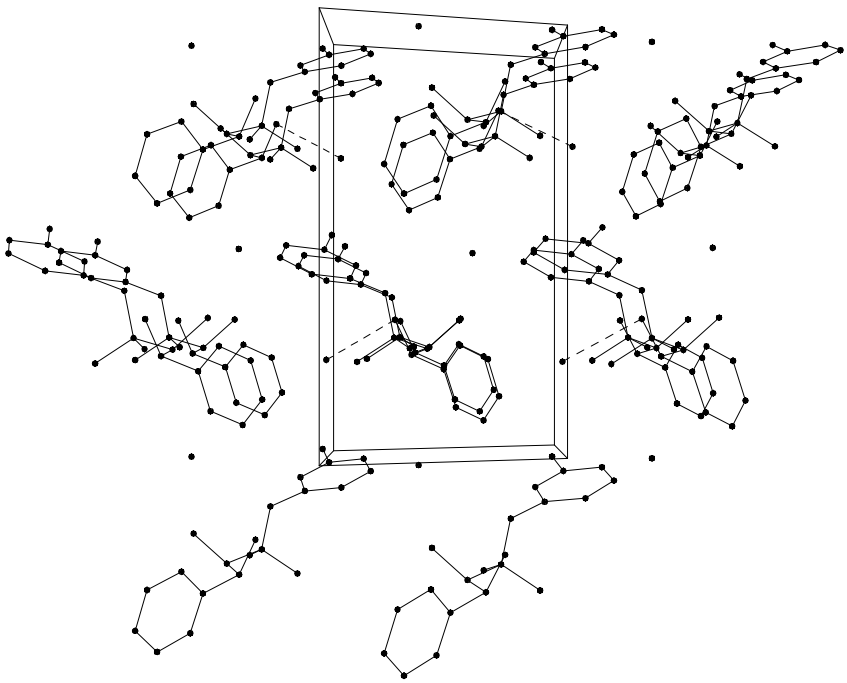


Figure 56: Packing diagram of 1-Methyl-3-[[[dimethyl[(1R,2S)-2-hydroxy-1-methyl-2-phenyl]ethyl]ammonio] methyl]pyridinium diiodide 37

The absolute configuration of diiodide salt **37** could be determined as (1*S*,2*R*) and is in accordance with the starting material norephedrine **32**.

The same synthesis pathway could be applied to the primary 1,2-amino alcohols (*S*)-leucinol **38** (Figure 57) and *exo*-aminoisoborneol **43** (Figure 58) as well as to the secondary amino acid derived 1,2-amino alcohol (*S*)-prolinol **23** (Figure 59), and several amino alcohol functionalized CILs could be synthesized.

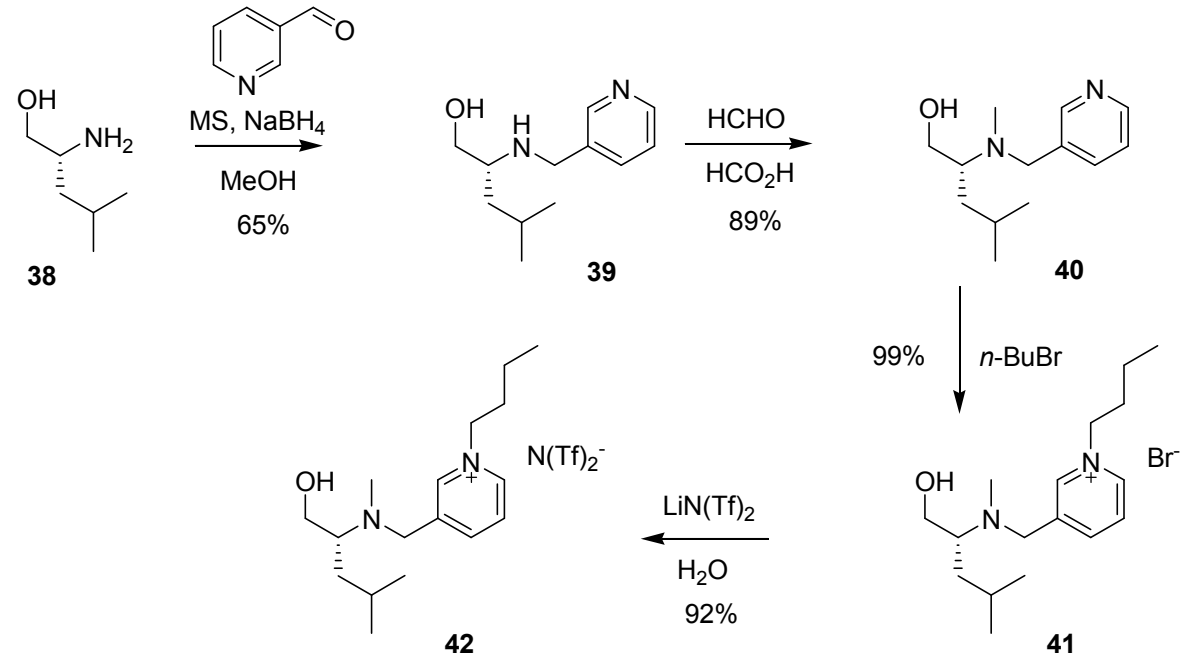


Figure 57: (S)-Leucinol-derived amino alcohol chiral ionic liquids

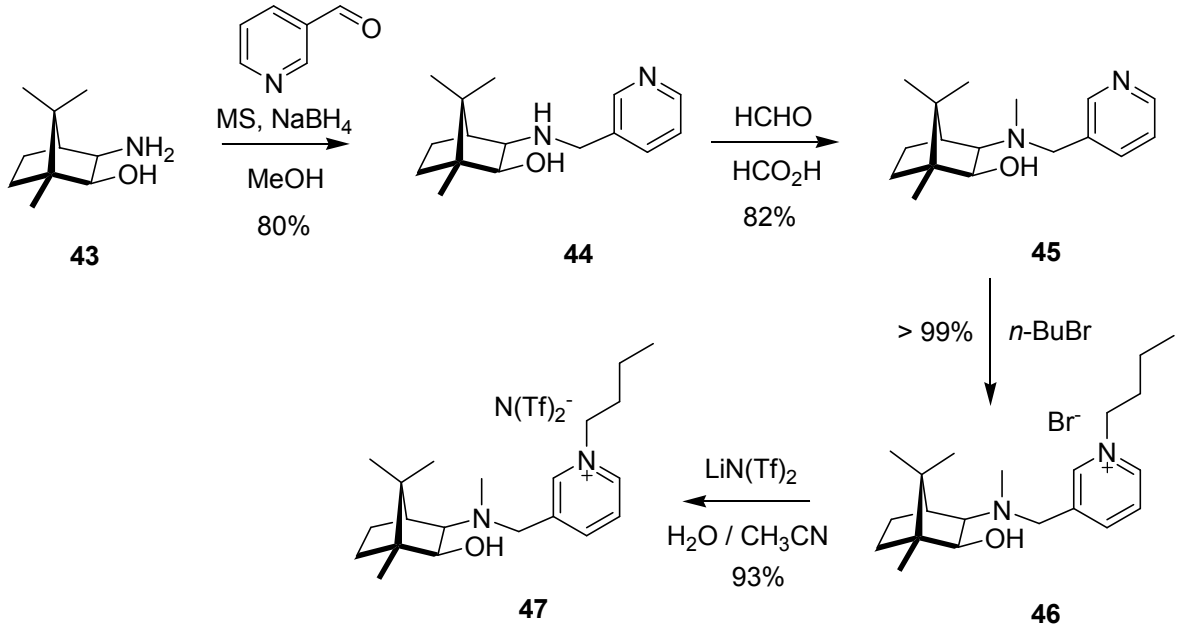


Figure 58: exo-Aminoisoborneol-derived amino alcohol chiral ionic liquids

It is noteworthy that imidazolium bromide **46** is a rare example of a pyridinium halide that is insoluble in water. Thus anion metathesis with $Li(NTf)_2$ was performed in a mixture of acetonitrile and H_2O to maintain homogeneous conditions.

When the secondary amino alcohol (*S*)-prolinol **23** was applied, simple refluxing in acetonitrile with equimolar amounts of pyridine-3-carbaldehyde gave the cyclic *N,O*-acetale that could be further reduced with sodium borohydride to yield the corresponding tridentate ligand **48** (Figure 59). Similarly to the primary amino alcohol derived CILs, alkylation with *n*-butylbromide occurred selectively on the pyridine system without substitution of the pyrrolidine ring.

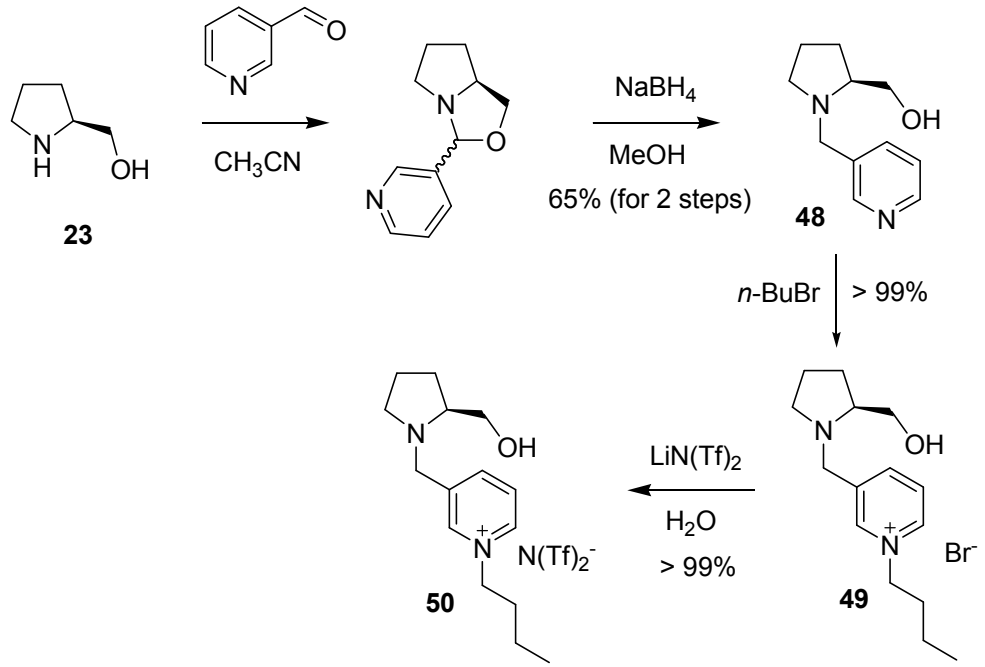


Figure 59: (S)-Prolinol-derived amino alcohol chiral ionic liquids

4.3.4 Application of tridentate ligands in diethylzinc addition

During the synthesis of functionalized CILs **36**, **42**, **47** and **50** intermediate1,2-amino alcohols were obtained which show high potential for the use as tridentate ligands. The presence of 3 heteroatoms O, N and N in the reasonable distance of 3 and 4 C-C-bonds should allow efficient coordination to metals. Indeed, the X-ray structure of the crystalline amino alcohol **34** revealed bond lengths that should allow multiple tethering to metal cations (Figure 53).

To investigate to catalytic abilities of these ligands, the enantioselective addition of diethylzinc to benzaldehyde **51** was investigated (Figure 60).

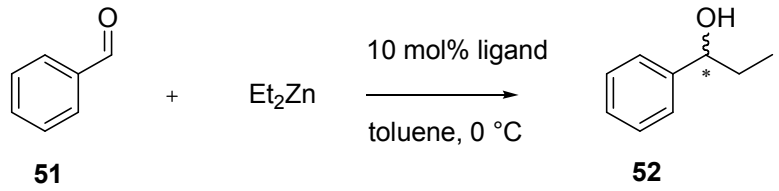
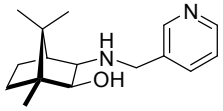
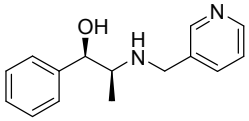
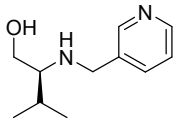
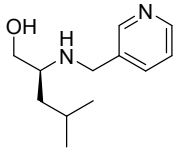
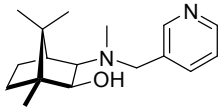
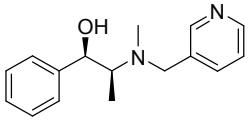
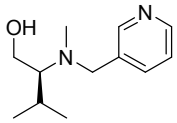
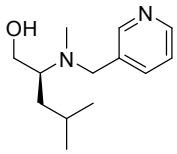


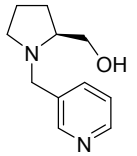
Figure 60: Asymmetric alkylation of benzaldehyde with diethylzinc

A catalytic amount of ligand (10 mol%) was dissolved in toluene and reacted with a 1 M solution of diethylzinc in hexane at 0 °C. Freshly distilled benzaldehyde was added at 0 °C and the reaction was left to stir at room temperature for 24 hours. Hydrolyzation with diluted hydrochloric acid followed by standard extractive work-up gave 1-phenyl-1-propanol **52** that was further analyzed via chiral HPLC after chromatographic purification.

All ligands **33**, **39**, **44** and **53** that were initially screened did successfully catalyze the addition of diethylzinc to benzaldehyde and excellent yields of 1-phenyl-1-propanol **52** could be achieved (Table 14, entries 1-4). However, only modest enantiomeric excess up to 45% ee in case of norephedrine derivative **33** could be observed (entry 2). The camphor derived (-)-DAIB analogue **44** completely failed to induce selectivity (entry 1). When *n*-hexane was applied as solvent instead of toluene, the yield dropped to 59%.

Table 14: Asymmetric addition of diethylzinc to benzaldehyde 51 catalyzed by various tridentate ligands

Entry [a]	Ligand	Yield [%] [b]	ee [%] [c,d]
1	 **44**	85	1 (*S*)
2	 **33**	94	45 (*S*)
3	 **53**	93	16 (*R*)
4	 **39**	84	16 (*R*)
5	 **45**	77	98 (*S*)
6	 **34**	79	77 (*S*)
7	 **54**	99	14 (*R*)
8	 **40**	84	25 (*S*)

9	 **48**	93	2 (*R*)

[a] All reactions were performed with 2 mmol benzaldehyde **51**, 4.4 mmol of a 1 M solution of Et_2Zn in hexane and 0.2 mmol ligand at 0 °C for 24-48 hrs. [b] Isolated yield of **52** after flash column chromatography. [c] Determined by HPLC using a DAICEL Chiralcel OD-H column. [d] Absolute configuration determined by optical rotation and comparison with literature values

The low enantioselectivity obtained compared to literature known ligands like *N*-methylephedrine or (-)-DAIB led to the conclusion that the formation of a conformational rigid aggregate was prevented by the presence of a secondary amine. Therefore the *N*-methylation step was introduced in the synthetic pathway and the tertiary amino alcohol ligands **34**, **40**, **45**, **48** and **54** were screened again (Table 14, entries 5-9).

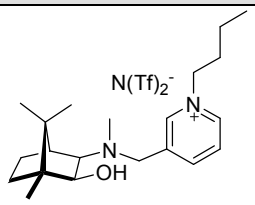
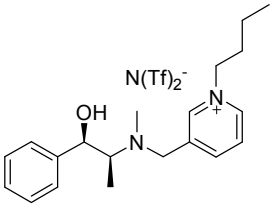
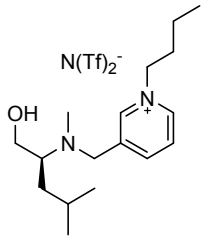
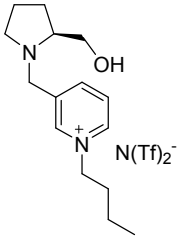
A dramatic influence of the *N*-methylation could be proved: An increase of selectivity from 45 to 77% ee for the norephedrine derivative **34** was observed and almost complete enantioselectivity could be obtained with the *exo*-aminoisoborneol derived ligand **45** that completely failed before *N*-methylation (entries 5, 6). However, the (*S*)-prolinol derived ligand still failed, although a tertiary amine structure is present (entry 9). Surprisingly, a reverse of selectivity was observed in case of the (*S*)-leucinol derivative **39** that induced the (*R*)-enriched product compared to the (*S*)-enriched alcohol derived from ligand **40** (entry 4 *vs.* 8). This indicates a completely different form of coordination and aggregation, and that the presence of a tertiary amine is necessary for stereocontrol in the addition reaction.

Although quite similar in structure, this effect was not observed with the (*S*)-valinol derivatives **53** and **54**, that were synthesized similarly to the (*S*)-leucinol ligands: The use of the *N*-methylated ligand led to a slight decrease in selectivity but yielded a product with the same configuration as the norligand in the asymmetric alkylation of benzaldehyde (entry 3 *vs.* 7).

4.3.5 Applications of chiral ionic liquids in diethylzinc addition

In comparison to the tridentate ligands **34**, **40**, **45**, **48** and **54** previously examined, solubility behaviour of the amino alcohol CILs is completely different since ILs are usually not soluble in toluene or hexane. To evaluate optimal reaction conditions, different solvents were chosen and homogeneous and heterogeneous systems examined. A catalytic amount of amino alcohol CIL (10 mol%) was reacted with a 1 M solution of diethylzinc in hexane and benzaldehyde at 0 °C. In case of toluene as solvent, the obtained yield was strongly dependent on the solubility of the CILs. Surprisingly, the *exo*-aminoisoborneol derived CIL **47** was soluble in 4 ml of anhydrous toluene, and thus a similar yield of 83% and a slight decrease of enantioselectivity to 80% compared with ligand **45** could be obtained (Table 15, entry 1). Considerable lower yield and a drop of selectivity were observed for the norephedrine derivative **36**, and no conversion was observed with the CILs **42** and **50** which turned out to be completely insoluble in toluene (entries 2, 3 & 4).

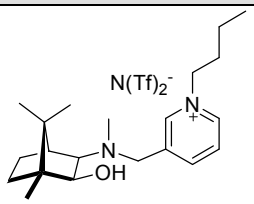
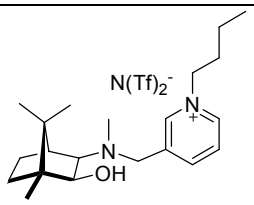
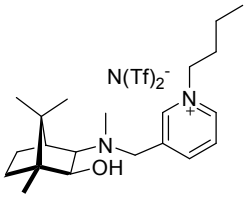
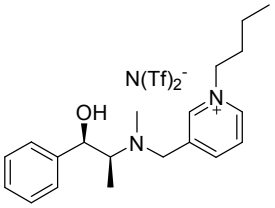
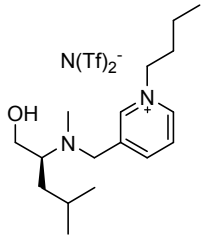
Table 15: Asymmetric addition of diethylzinc to benzaldehyde 51 catalyzed by basic chiral ionic liquids in toluene

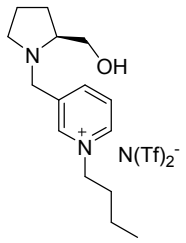
Entry [a]	CIL	Solvent	Yield [%] [b]	ee [%] [c,d]
1	 **47**	toluene	83	80 (*S*)
2	 **36**	toluene	25	33 (*S*)
3	 **42**	toluene	< 1 [e]	n. d.
4	 **50**	toluene	< 1 [e]	n. d.

[a] All reactions were performed with 2 mmol benzaldehyde **51**, 4.4 mmol of a 1 M solution of Et_2Zn in hexane and 0.2 mmol ligand in 4 ml of toluene at 0 °C for 24-48 hrs. [b] Isolated yield of **52** after flash column chromatography. [c] Determined by HPLC using a DAICEL Chiralcel OD-H column. [d] Absolute configuration determined by optical rotation and comparison to literature values. [e] No conversion according to GC-MS analysis.

In order to obtain homogeneous conditions, acetonitrile and dichloromethane were examined as co-solvent. An excellent yield and a selectivity almost similar to the tridentate ligands were obtained with the *exo*-aminoisoborneol CIL **47** (Table 16, entry 1) in dichloromethane.

Table 16: Asymmetric addition of diethylzinc to benzaldehyde 51 catalyzed by basic chiral ionic liquids under homogenous conditions

Entry [a]	CIL	Solvent	Yield [%] [b]	ee [%] [c,d]
1	 **47**	CH_2Cl_2	90	95 (*S*)
2	 **47**	acetonitrile	22	5 (*S*)
3	 **47**	CH_2Cl_2 + $Ti(OiPr)_4$ [e]	74	2 (*S*)
4	 **36**	CH_2Cl_2	81	74 (*S*)
5	 **42**	CH_2Cl_2	72	20 (*R*)

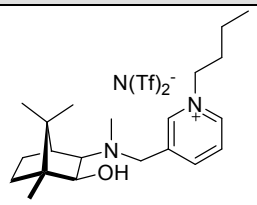
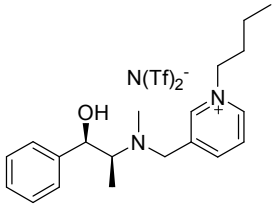
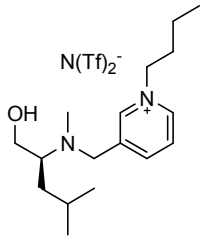
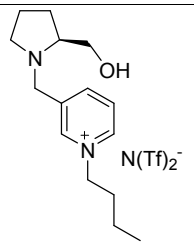
6	 **50**	CH_2Cl_2	45	39 (*S*)

[a] All reactions were performed with 2 mmol benzaldehyde **51**, 4.4 mmol of a 1 M solution of Et_2Zn in hexane and 0.2 mmol ligand in 4 ml of solvent at 0 °C for 24-48 hrs. [b] Isolated yield of **52** after flash column chromatography. [c] Determined by HPLC using a DAICEL Chiralcel OD-H column. [d] Absolute configuration determined by optical rotation and comparison to literature values. [e] 2.4 mmol of $Ti(OiPr)_4$ were added.

A significant drop of yield and enantiomeric excess was observed when acetonitrile was used (entry 2). The addition of the Lewis acid $Ti(OiPr)_4$ in dichloromethane resulted in a decrease of yield to 74% and in a complete loss of selectivity (entry 3). Good conversion could be obtained in both CILs **36** and **42** in dichloromethane, but the (*S*)-leucinol derivative **42** only gave low selectivity of 20% ee whereas the ephedrine derived CIL **36** induced high selectivity of 80% ee (entries 4 & 5). Interestingly, the (*S*)-prolinol derived CIL **50** showed a modest enantioselectivity of 39%, although the precursor ligand **48** completely failed to induce selectivity before quaternization (entry 6).

Alternatively, that reaction was performed using 1 g of the IL 1-buty-3-methylimidazolium hexafluorophosphate bmim-PF_6 as solvent (Table 17).

Table 17: Asymmetric addition of diethylzinc to benzaldehyde 51 catalyzed by basic chiral ionic liquids in the ionic liquid bmim-PF_6 as co-solvent

Entry [a]	CIL	Solvent	Yield [%] [b]	ee [%] [c,d]
1	 **47**	bmim-PF_6	77	52 (*S*)
2	 **36**	bmim-PF_6	93	62 (*S*)
3	 **42**	bmim-PF_6	< 1 [e]	n. d.
4	 **50**	bmim-PF_6	48	15 (*S*)

[a] All reactions were performed with 2 mmol benzaldehyde **51**, 4.4 mmol of a 1 M solution of Et_2Zn in hexane and 0.2 mmol ligand in 1 g of bmim-PF_6 at 0 °C for 24-48 hrs. [b] Isolated yield of **52** after flash column chromatography. [c] Determined by HPLC using a DAICEL Chiralcel OD-H column. [d] Absolute configuration determined by optical rotation and comparison to literature values. [e] no conversion according to GC-MS analysis.

Although imidazolium salts possess an acidic proton in position 2, it has been described in literature that the basicity of zinc organyls is not enough to deprotonate the imidazolium salt and form the corresponding carbine.[100] All chiral amino alcohol CILs were readily soluble in bmim-PF_6 and a biphasic system was obtained when a solution of diethylzinc in hexane was added. After hydrolyzation with hydrochloric acid, a three-phase system was obtained and 1-phenyl-1-propanol **52** was isolated from the upper ethereal layer. Except for the (*S*)-leucinol derivative **42**, modest to excellent conversion was observed, but enantioselectivities always remained below those obtained in toluene or dichloromethane as solvent (Table 17).

4.3.6 Mechanistical considerations

When tridentate ligands are reacted with diethylzinc, a rigid trivalent transition state is possible that can further determine the approach of benzaldehyde and thus influence selectivity. The proposed binding model for this type of ligand is depicted in Figure 61.

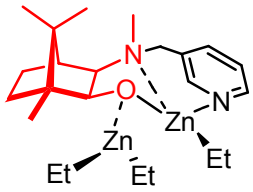


Figure 61: Proposed binding model for tridentate ligand 45

In comparison to the transitions state of the tridentate ligands, the alkylated nitrogen of the pyridine ring is not free for coordination anymore. For this reason, a bidentate transition state with coordination of the 1,2-amino alcohol system that is in equilibrium with the corresponding dimer is more likely (Figure 62).

[100] Law, M. C.; Wong, K.-Y.; Chan T. H. *J. Org. Chem.* **2005**, *70*, 10434.

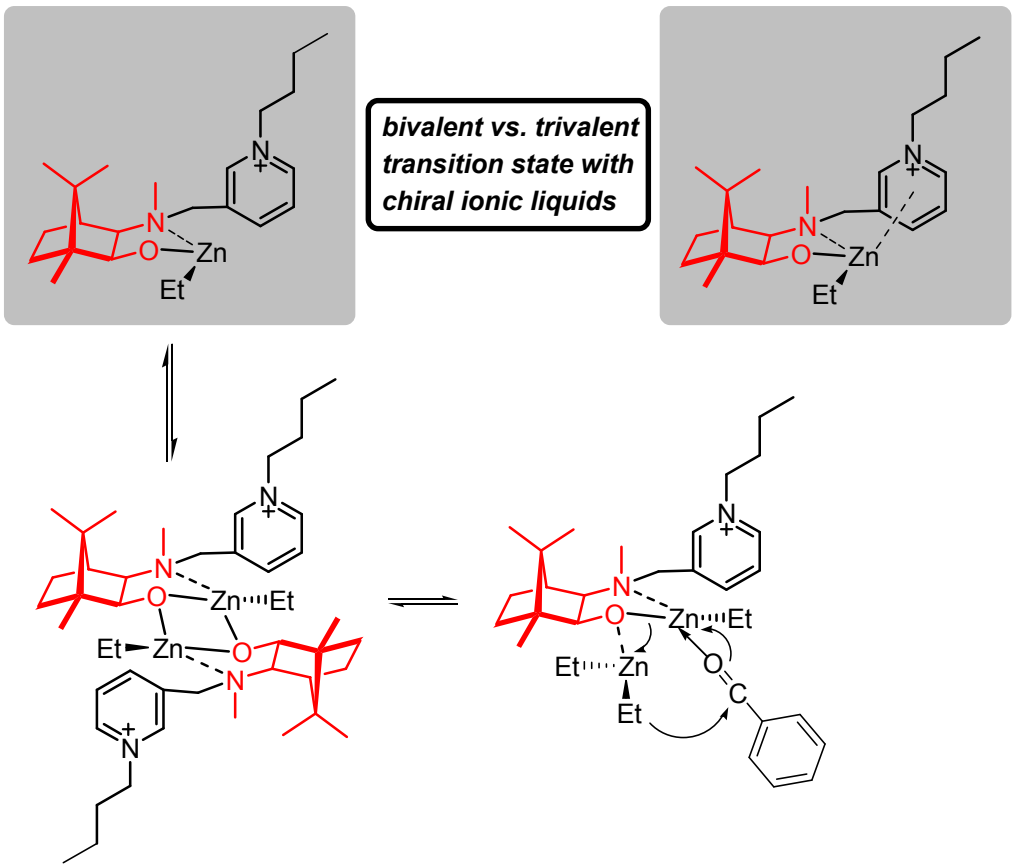


Figure 62: Bivalent (left) and trivalent (right) transition state for chiral ionic liquid 45.

However, there are some examples of d-π-interactions between metal cations and the π-electrons of pyridinium or other IL salts present in literature, although no specific example on zinc salts is described.[101] Additionally to the chelating 1,2-amino alcohol group, a third interaction of the pyridinium ring with the zinc cation is therefore possible. These multiple interactions could influence the relative stabilities of the transition structures as well as the approach of benzaldehyde and therefore have a significant influence on the observed selectivity transfer of chirality.[102]

[101] Mataga, S.; Mataga, N. *Z. Physik. Chem.* **1962**, *33*, 374.

[102] Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.

4.4 Metal-containing ionic liquids

4.4.1 The principle of ionic liquid catalysts

When dealing with CILs, little attention is paid to the corresponding non-chiral counter ion. However, it would be interesting to introduce anions that show catalytic properties beyond their potential of forming common ILs.

This can easily be realized by incorporating transition metals in the accompanying anion to form metal-containing ILs. Dealing with metal-containing ILs, it is particularly interesting to extend the application of ILs beyond their use as mere reaction media and develop ILs serving as catalysts themselves (Figure 63), thus giving access to stable and recyclable catalysts with ionic structures.

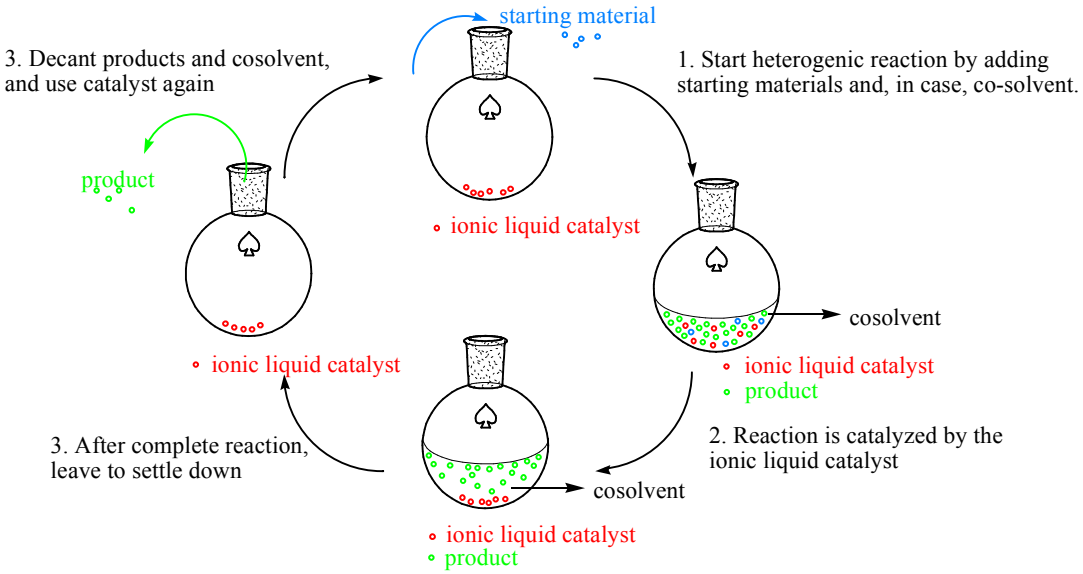


Figure 63: Ionic liquid catalysts in biphasic organic synthesis

- To satisfy both economical and ecological aspects, the expensive transition metal catalyst can easily be recovered after simply decanting the product layer and successfully recycled.
- Since the ionic liquid catalyst is only used in traces, the required amounts of ILs can be significantly reduced. Even though ILs have become commercially available, they are still relative expensive compared to traditional solvents.
- Large amounts of volatile organic solvents can be spared since only catalytic amounts of ILs are needed and the product can be simply isolated by decanting the upper phase without further extraction or washing.

4.4.2 Synthesis of metal-containing ionic liquids

In general, ILs incorporating a metal in the anion can be easily prepared from imidazolium, ammonium or any other organic halide salt and the corresponding Lewis acid MX_n, usually the chloride.

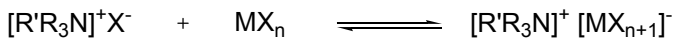


Figure 64: General synthesis of metal-containing ionic liquids

Probably the best-established ILs of this type are chloroaluminate melts that are present in literature since 1978 as "first-generation ILs" and have been studied exhaustively. Care has to be taken considering the stoichiometric ratio of organic halide and Lewis acid, since several species are often present in an equilibrium depending on the ratio [cation]X:MX_n.
Despite chloroaluminate salts the scope of accompanying metallic anions is huge, and therefore many catalytically active transition metals can be used (e.g. Fe(II), Fe(III), Cu(II), Pd(II)). Some examples of ILs that can be prepared by the reaction of a Lewis acid and the organic halide salt are summoned in Table 18.

Table 18: Examples of ionic liquids that can be synthesized by the reaction of a halide with a Lewis acid

Ionic liquid [a]	Established anion	Ref.
[cation]Cl/$AlCl_3$	Cl^-, $AlCl_4^-$, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$	[103]
[cation]Cl/$AlEtCl_2$	$AlEtCl_3^-$, $Al_2Et_2Cl_5^-$	[104]
[cation]Cl/BCl_3	Cl^-, BCl_4^-	[105]
[cation]Cl/CuCl	$CuCl_2^-$, $CuCl_3^-$, $Cu_3Cl_4^-$	[106]
[cation]Cl/$SnCl_2$	$SnCl_3^-$, $SnCl_5^-$	[107]

[103] (a) Karpinski, Z. J.; Osteryoung, R. A. *Inorg. Chem.* **1984**, *23*, 1491. (b) Abdul-Sada, A. A. K.; Greenway, A. M.; Seddon, K. R.; Welton, T. *Org. Mass Spectrom.* **1993**, *28*, 759.

[104] Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res.* **1995**, *34*, 1149. (b) Gilbert, B.; Chauvin, Y.; Olivier, H.; DiMarco-Van Tiggelen, F. *J. Chem. Soc., Dalton Trans. 1* **1995**, 3867.

[105] Williams, S. D.; Schoebrechts, J. P., Selkirks, J. C.; Mamantov, G. *J. Am. Chem. Soc.* **1987**, *109*, 2218.

[106] Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *25*, 26.

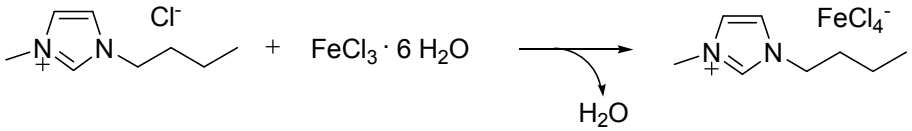
[107] (a) Parshall, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 8716. (b) Waffenschmidt, H. Wasserscheid, P. *J. Mol. Catal. A* **2000**, *164*, 61.

[cation]Cl/$FeCl_3$	$FeCl_4^-$, $Fe_2Cl_7^-$	70,108
[cation]Cl/$NiCl_2$	$NiCl_4^-$	109
[cation]Cl/$PtCl_2$	$PtCl_4^{2-}$	110
[cation]Cl/$TiCl_5$	$TiCl_5^-$	111

[a] cation = pyridinium, imidazolium

Since iron is one of the most inexpensive and non-pollutant metals on earth, the scope for iron-catalyzed chemistry is of substantial interest and the synthesis and application of iron-containing ILs in organic synthesis is further investigated.

The iron-containing ionic liquid 1-butyl-3-methylimidazolium tetrachloroferrate **55** (bmim-$FeCl_4$) was easily prepared in a solid state reaction by mixing commercially available solid bmim-Cl **12** and $FeCl_3 \cdot 6\ H_2O$, yielding the hydrophobic ionic liquid as a lower phase, and water, which can be easily separated. [70b]



54 **55**

Figure 65: Biphasic synthesis of the iron-containing ionic liquid bmim-$FeCl_4$ 55

Alternatively, anhydrous iron(III) chloride can be used, although care has to be taken since both bmim-Cl **12** and the iron salt are very hygroscopic and the exact measurement of stoichiometric amounts might be more demanding.

[108] Zhang, Q.; Yang, J.; Lu, X.; Gui, J.; Huang, M. *Fluid Phase Equilib.* **2004**, *226*, 207.

[109] (a) Zhong, C; Sasaki, T; Tada, M; Iwasawa, Y. *J. Catal.* **2006**, *242*, 357. (b) Carmichael, A. J.; Hardacre, C.; Holbrey, J. D.; Nieuwenhuyzen, M.; Seddon, K. R. *Anal. Chem.* **1999**, *71*, 4572.

[110] Hasan, M.; Kozhevnikov, I. V.; Siddiqui, M. R. H.; Femoni, C.; Steiner, A.; Winterton, N. *Inorg. Chem.* **2001**, *40*, 795.

[111] Bonnet, P; Lacroix, E.; Schirmann, J.-P. WO Patent 081353, 2001.

4.5 Iron-containing ionic liquids for Kumada cross-coupling

4.5.1 Iron-catalyzed Kumada-Corriu cross-coupling

Transition metal-catalyzed cross-coupling-reactions are one of the most powerful methods for the formation of carbon-carbon or carbon-heteroatom bonds.[112] The field of Kumada-Corriu Grignard cross-coupling is largely dominated by the use of nickel and palladium complexes as catalysts.[113] Only recently, the use of iron as cheap, benign and non-toxic precatalyst has been recognized as rewarding field of research.[114]

Initial work on this topic was performed by Kochi *et al.* in 1971, who noticed that alkenyl halides undergo stereoselective cross-coupling with Grignard reagents in the presence of catalytic amounts of FeX_3.[115] Cahiez and Avedissian later introduced the use of NMP as co-solvent and could thus develop stereo- and chemoselective cross-coupling of alkenyl halides even in the presence of functional groups.[116] The catalyst system $FeCl_3$/stoichiometric TMEDA was also described by Nakamura *et al.*; nevertheless slow addition of the Grignard reagent via a syringe pump was necessary.[117]

Nagano and Hayashi showed the utility of $Fe(acac)_3$ in the coupling of $C(sp^3)$-X-compounds[118], whereas Fürstner used $Fe(acac)_3$ and anhydrous $FeCl_3$ for the coupling of aryl halides as well as iron-salen catalysts[119] and the tetrakisferrate complex

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[112] (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, 2002; Vol. 219. (c) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3; 481.

[113] *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002.

[114] For a review: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Shinokobu, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (c) Fürstner, A.; Rubén, M. *Chem. Lett.* **2005**, *34*, 624.

[115] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971,** *93,* 1487. (b) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971,** *44,* 3063. (c) Tamura, M.; Kochi, J. K. *Synthesis* **1971,** 303. (d) Kochi, J. K. *Acc. Chem. Res.* **1974,** *7*, 351. (e) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975,** *40,* 599. (e) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976,** *41,* 502. (f) Kochi, J. K. *J. Organomet. Chem.* **2002,** *653,* 11.

[116] Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

[117] Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004,** *126,* 3686.

[118] Nagano, T.; Hayashi, T. *Org. Lett.* **2004,** *6,* 1297.

[119] (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002,** *124,* 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem.; Int. Ed.* **2003,** *42,* 308.

$[Li(tmeda)_2]Fe(C_2H_4)_2$.[120] Further studies on the use of various iron-salen catalysts were performed by Bedford *et al.*, who also discovered the concept to use anhydrous $FeCl_3$ in combination with appropriate amine ligands in order to diminish β-elimination.[121]

Several papers of Fürstner *et al.* dealt with the $Fe(acac)_3$ catalyzed coupling of aryl triflates[122] and enol triflates[123] as well as of acid chlorides.[123,124] Alkenyl phosphates, -sulfones and allyl phosphates were also found to be suitable substrates and react well in the presence of iron catalysts.

Although considerable effort has been made, the mechanism of the iron-catalyzed Grignard cross-coupling is still not fully explored. Different iron species are proposed as catalytically active, including Fe(0), Fe(+I), Fe(+II) and Fe(-II) species .[125] It is proved that $FeCl_2$ reacts with 4 equivalents of an alkyl Grignard reagents to form an "inorganic Grignard reagent" bearing a formally negative charge at iron with the formal composition $[Fe(MgX)_2]$.[126] As by-products, a mixture of hydrocarbons from homocoupling, β-elimination and β-hydrid transfer are observed.

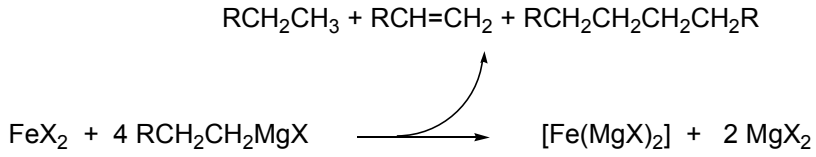

Figure 66: Formation of the „inorganic Grignard reagent"

A catalytic cycle was proposed by Fürstner *et al.*, in which the highly nucleophilic entity $[Fe(MgX)]_2$ undergoes oxidative addition of an aryl halide.[119]

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[120] Martin, R.; Fürstner, A. *Angew. Chem.; Int. Ed.* **2004,** *43,* 3955.

[121] Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005,** 4161.

[122] Seidel, D.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950.

[123] (a) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (b) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Tenson, J. *Angew. Chem.; Int. Ed.* **2003**, *42*, 5358.

[124] Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett*. **1984**, *25*, 4805. (b) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett*. **1987**, *28*, 2053.

[125] (a) Lehr, G. F.; Lawler, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 4048. (b) Kauffmann, T. *Angew. Chem.; Int. Ed.* **1996**, *35*, 386 and literature cited therein.

[126] Bogdanovic, B.; Schwickardi, M. *Angew. Chem.; Int. Ed.* **2000**, *39*, 4610.

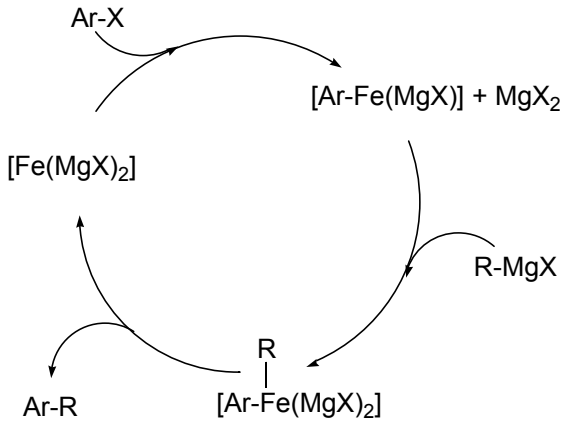


Figure 67: Proposed catalytic cycle of iron-catalyzed Kumada-Corriu cross-coupling

The resulting organometallic iron compound is further alkylated by a second Grignard molecule. Reductive elimination forms the desired cross-coupling product and regenerates the active Fe(-II) species.

4.5.2 Iron-containing imidazolium ionic liquids as catalysts

The iron-containing ionic liquid 1-butyl-3-methylimidazolium tetrachloroferrate **55** (bmim-$FeCl_4$) has been described in literature as catalyst for Friedel-Crafts acylation, but no application in cross-coupling chemistry neither as catalyst nor as a solvent has been reported so far.[127] It was therefore interesting to evaluate the potential of ILs as a completely different kind of iron-precatalyst for Grignard cross-couplings. In contrast to the other iron precatalysts that have been applied in Kumada-Corriu cross-couplings, bmim-$FeCl_4$ **55** is not soluble in the solvent and thus the reaction has to be performed under biphasic conditions.

For initial screening of catalytic activity, an alkyl halide bearing β-hydrogens was chosen and the coupling between dodecyl bromide **56** and 4-fluorophenylmagnesium bromide **57** using 10 mol% of bmim-$FeCl_4$ **55** as catalyst was examined (Figure 68).

[127] Valkenberg, M. H.; deCastro, C.; Holderich, W. F. *Appl. Catal. A* **2001,** *215,* 185.

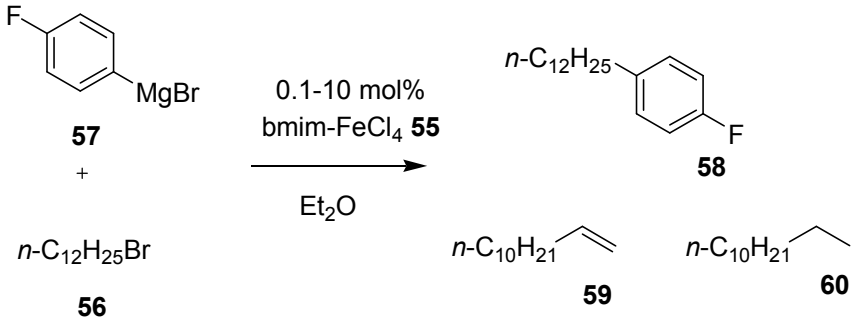


Figure 68: Bmim-$FeCl_4$ 55 catalyzed cross-coupling of dodecyl bromide 56 and 4-fluorophenylmagnesium bromide 57.

The biphasic reaction was initially run in dry diethyl ether as co-solvent, but later studies showed that there is no difference using technical instead of anhydrous ether. Furthermore, the reaction proved to be completely air and moisture stable and could be carried out without inert atmosphere. Since addition of the Grignard solution was rather exothermic, cooling with an ice bath during the addition is recommended, although higher temperature did not have any negative influence on the yield.

Table 19: Influence of the catalyst concentration on the bmim-$FeCl_4$ 55 catalyzed cross-coupling of 4-fluorophenylmagnesium bromide 57 and dodecyl bromide 56.

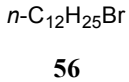
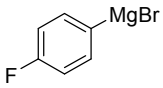
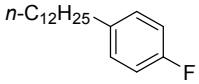
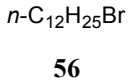
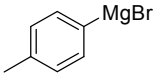
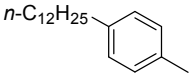
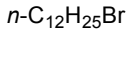
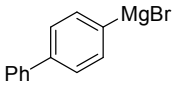
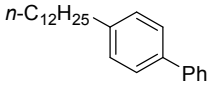
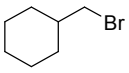
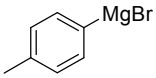
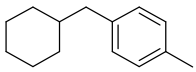
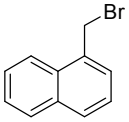
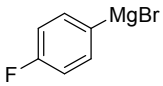
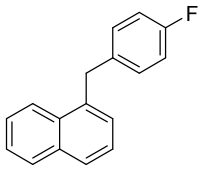
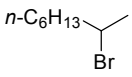
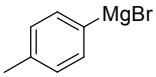
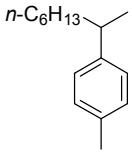
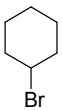
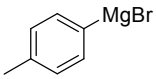
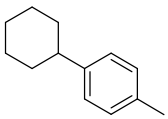
		Yield		
Entry [a]	**bmim-$FeCl_4$ 55 [mol%]**	**58 [b] [%]**	**59 [b] [%]**	**60 [b] [%]**
1	10	88.3	7.6	3.5
2	5	89.8	6.7	3.0
3	1	80.3	9.9	4.9
4	0.5	79.4	9.8	6.1
5	0.1	<0.1	0.5	0.4

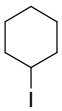
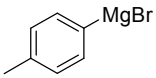
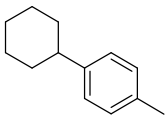
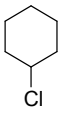
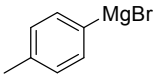
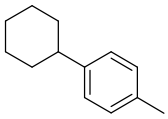
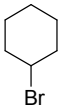
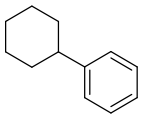
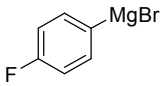
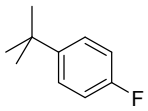
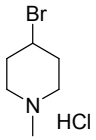
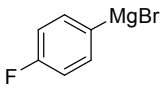
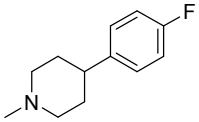
[a] All reactions were carried out in Et_2O at 0 °C with 2 mmol R-X, 3 mmol ArMgX under air. [b] Determined by GC-MS using *n*-hexadecane as internal standard.

Reactions proceeded very fast and gave product **58** in 88% yield and only small amounts of by-products from β-elimination (**59**) and reductive elimination (**60**) (Table 19, entries 1 and 2) compared to analogous $Fe(acac)_3$-catalyzed reactions reported in the literature.[118] Best results were obtained with a catalyst concentration of 5 mol% giving 90% yield whereas a lower catalyst concentration resulted in a slight increase of by-products **59** and **60** and a decrease of the desired coupling product **58** (entries 3, 4 & 5).

Changing the Grignard reagent to the electron rich *p*-tolylmagnesium bromide **61** as well as to 4-biphenylmagnesium bromide **63** the reaction proceeded also favourably, although with lower yields of 73 and 60%, respectively (Table 20, entries 2 & 3).

Table 20: Results of various aryl Grignard cross-couplings catalyzed by bmim-$FeCl_4$ 53

Entry [a]	RX	Ar-Met	Product	Yield [b]
1	 **56**	 **57**	 **58**	86
2	 **56**	 **61**	 **62**	73
3	 **56**	 **63**	 **64**	60
4	 **65**	 **61**	 **66**	64
5	 **67**	 **57**	 **68**	60
6	 **69**	 **61**	 **70**	84
7	 **71**	 **61**	 **72**	89

8	 **73**	 **61**	 **72**	79
9	 **74**	 **61**	 **72**	75
10	 **71**	 **75**	 **76**	20 [c]
11	 **77**	 **57**	 **78**	0 [d]
12 [e]	 **79**	 **57**	 **80**	79

[a] All reactions were carried out in Et_2O at 0 °C with 2 mmol R-X, 3 mmol ArMgX under air. [b] Isolated yield after flash chromatography, if not otherwise stated. [c] Yield calculated from GC-MS of crude product using *n*-hexadecane as internal standard. [d] No product could be observed on GC-MS analysis. [e] 5 mmol of ArMgX **57** used.

Moving to secondary alkyl halides, we observed a selective formation of the desired coupling product **70** and **72** without any occurrence of β-elimination nor reductive elimination.

Thus it was possible to achieve considerably higher yields in the coupling of 2-octyl bromide **69** and cyclohexyl bromide **71** with Grignard reagent **61** (entries 6 & 7) than reported in literature for $Fe(acac)_3$ as a catalyst.[118] Both cyclohexyl iodide **73** and chloride **74** turned out to be suitable for the cross-coupling even though the isolated yields of the coupling product **9** are slightly lower (entries 8 & 9).

The use of phenyl lithium **75** instead of an aryl Grignard reagent lead to a significant drop in yield, and for the first time the homocoupling product 1,1'-dicyclohexyl was detected in

almost equal amount (entry 10). Tertiary alkyl halides are less reactive: As already Nagano and Hayashi have reported for $Fe(acac)_3$ as catalyst[118], no conversion at all could be detected using *tert*-butyl bromide **77** (entry 11). Secondary alkyl halides incorporating a heterocyclic 1-methylpiperidinyl structural motif like **79** also performed satisfyingly, yielding 79% of coupling product **80** (entry 12).

When *p*-tolylmagnesium bromide **61** was coupled with *n*-dodecyl bromide **56** a considerable amount of ~10% of *n*-dodecane **60** (t_R = 9.23 min) and *n*-dodecene **59** (t_R = 9.10 min) was formed, as shown in the crude GC-MS chromatogram in Figure 69.

In contrast, the same Grignard reagent coupled selectively to the secondary halide 2-bromooctane **69** without by-products from β-elimination or β-hydrogen transfer (Figure 69).

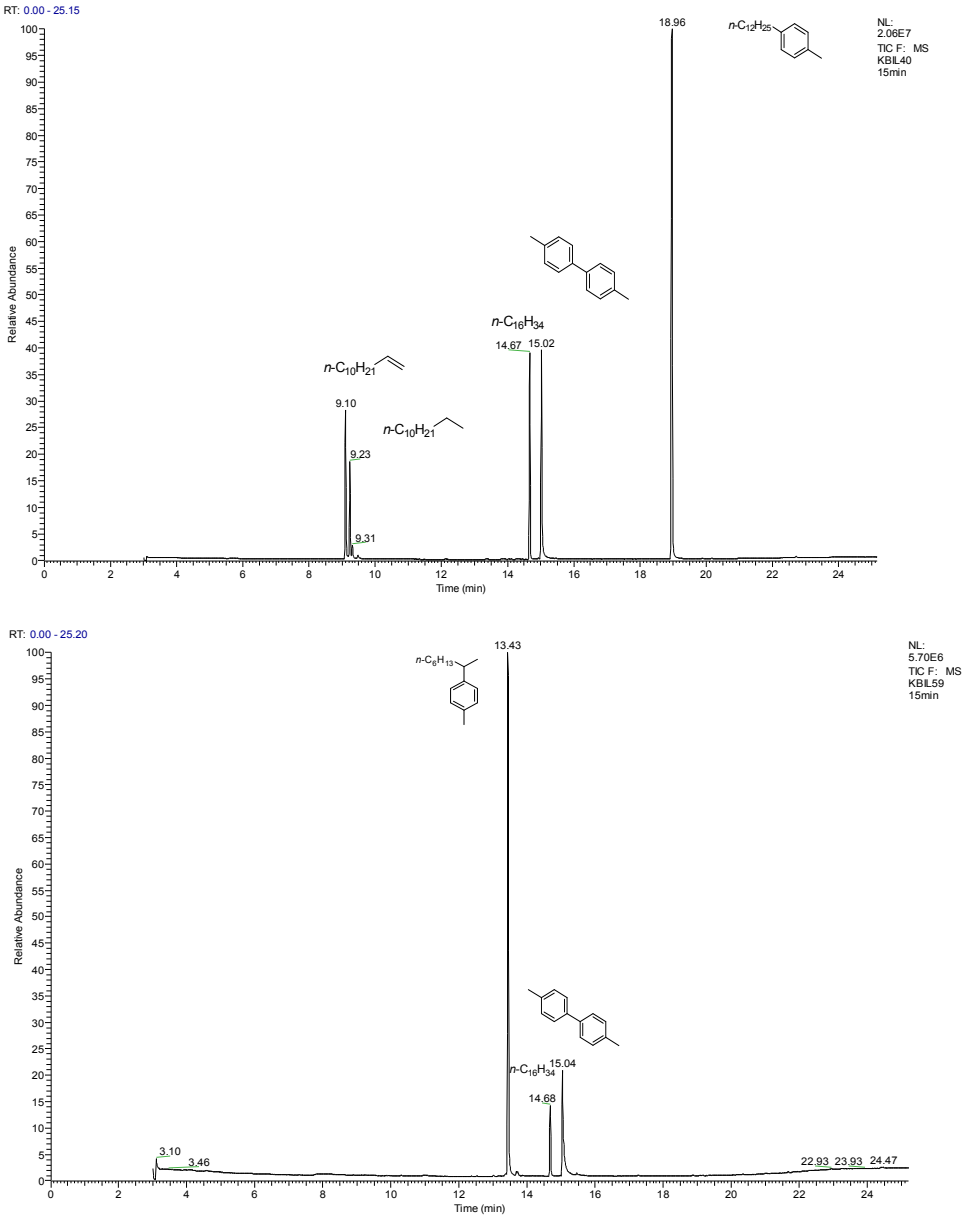


Figure 69: Comparison of GC-MS plot of crude product for (a) primary (top) and (b) secondary alkyl halide (bottom).

However, for both primary and secondary halides, a small amount of biphenyl-derivative (t_R = 15.04 min) is present in the crude reaction mixture. This leads to the conclusion that the formation of a biphenyl-derivative is necessary to form the activated iron species and to start the catalytic cycle. The color change and the dark precipitate obtained indicate the presence of low-valent iron-species (Figure 70).

Figure 70: Progress of the addition of 4-fluorophenylmagnesium bromide to the biphasic reaction mixture

Ionic liquids have proven to be excellent solvents for catalyst immobilization via liquid-liquid biphasic catalysis. In most cases products and remaining starting materials can be simply removed by decantation while the catalyst trapped in the IL can be reused. Starting with 5 mol% of bmim-$FeCl_4$ **55** and 0.5 ml of diethyl ether as co-solvent it was possible to recycle the iron-containing ionic liquid, surveying the initially optimized coupling of *n*-dodecyl bromide **56** and 4-fluorophenylmagnesium bromide **57**.

Table 21: Recycling of bmim-$FeCl_4$ 55 in the cross-coupling of 4-fluorophenylmagnesium bromide 57 and dodecyl bromide 56.

Entry [a]	Run	Conversion of 1 [%] [b]	Yield of 58 [%] [c]
1	1	>99	86
2	2	>99	n.a.
3	3	96	77
4	4	93	n.a.
5	5	92	76

[a] All reactions were carried out in Et_2O at 0 °C with 2 mmol R-X, 3 mmol ArMgX under air. [b] Conversion calculated from GC-MS of crude product using *n*-hexadecane as internal standard. [c] Isolated yield after flash chromatography.

After complete reaction the ionic liquid and formed $MgBr_2$ were left to settle, and the upper ethereal layer containing the product was decanted. Remaining product was extracted by washing the residue twice with 0.5 ml of diethyl ether each. Fresh alkyl halide, *n*-hexadecane as internal standard and 0.5 ml of diethyl ether as co-solvent were added to the remaining bmim-$FeCl_4$-layer which had turned from black to orange during the washing steps. Successive addition of Grignard reagent gave an immediate color change to black, and the catalytic cycle was found to be active again. Although conversion of the alkyl halide was almost complete, the isolated yield of the desired coupling product **58** slightly decreased from 86% in the first run to 76% after the fifth one (Table 21; entries 1-5). This may be explained by the fact that small amounts of iron are removed from the ionic liquid phase during extraction (compare with Table 19).

4.6 Iron-catalyzed Michael addition

Besides cross-coupling, the Michael addition is a classical and one of the most useful C-C bond-forming reactions and has wide applications in organic synthesis.[128,129] This reaction is usually catalyzed by strong bases such as alkali hydroxides or tertiary amines which often cause undesirable side reactions. Therefore, the catalysis via transition metals, that work under neutral and mild conditions, has attracted attention.[130]

The iron-catalyzed Michael addition of β-oxo esters to enones is one of the oldest known iron-catalyzed transitions. Athough various other transition metal catalysts have been investigated, iron almost always turns out to be the most efficient.[131] Several papers using $FeCl_3 \cdot 6\ H_2O$ as catalyst have been published[132], and various other iron(III) salts like $Fe(ClO_4)_3$, $Fe(acac)_3$ and Fe(III)-exchanged fluorotetrasilicic mica or Fe-exchanged montmorillonite K10 have been successfully used.[133,134]

Mechanistic studies on this reaction were done by Christoffers *et al.* who used DFT calculations as well as Raman, UV-VIS, EXAFS and XANES studies[135] and by Trage *et al.* who used electrospray mass spectroscopy to get insight into the catalytic species.[136]

There are also two papers dealing with ionic liquids as solvents for transition metal-catalyzed Michael addition, in which the influence of the ionic liquids' impurities on the catalytic

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[128] Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series: Pergamon, Oxford, 1992; Vol. 9.

[129] (a) Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419. (b) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 10486. (c) Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516. (d) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.

[130] (a) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246. (b) Brunner, H.; Kraus, J. *J. Mol. Catal.* **1989**, *49*, 133.

[131] (a) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259. (b) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3141. (c) Mekonnen, A.; Carlson, R. *Eur. J. Org. Chem.* **2006**, 2005 (d) Christoffers, J. *Synlett* **2001,** 723.

[132] Christoffers, J. *Chem. Commun.* **1997**, 943.

[133] Shimizu, K.; Miyagi, M.; Kan-no, T.; Kodama, T.; Kitayama, Y. *Tetrahedron Lett.* **2003**, *44*, 7421.

[134] Singh, D.; Singh, P.; Samant, S. *Synth. Commun.* **2006**, *36*, 1265.

[135] (a) Bauer, M.; Kauf, T.; Christoffers, J.; Bertagnollia, H. *Phys. Chem. Chem. Phys.* **2005**, *7*, 2664. (b) Pelzer, S.; Kauf, T.; van Wüllen, C.; Christoffers, J. *J. Organomet. Chem.* **2003**, *684*, 308.

[136] Trage, C.; Schröder, D.; Schwarz, H. *Chem. Eur. J.* **2005**, *11*, 619.

activity of the iron and nickel salts is discussed.[137] Recently, the use of the ionic liquid 1-butyl-3-methylimidazolium hydroxid (bmim-OH) as efficient reaction media has been reported.[138]

4.6.1 Ionic liquid-catalyzed Michael addition under thermic conditions

For initial studies, the reaction of methyl 2-oxocyclopentane-carboxylate **81** and methyl vinyl ketone **82** with the IL bmim-$FeCl_4$ **55** as solvent and as catalyst was investigated.

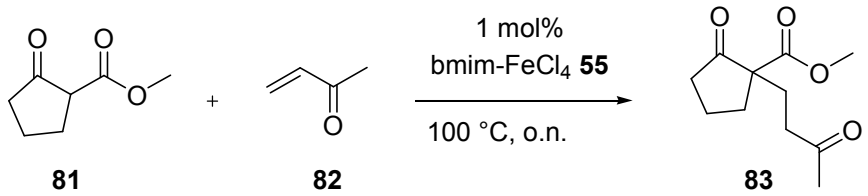

Figure 71: Iron-catalyzed Michael addition under thermal conditions

Both starting materials **81** and **82** were soluble in the solvent bmim-$FeCl_4$ **55**, and therefore the reaction could be run neat without addition of a co-solvent. The reaction proceeded smoothly in 2 hours at 100 °C and gave product **83** in 81% yield which could be easily separated by distillation of the non-volatile IL (Table 22, entry 1). Encouraged by this result the amount of bmim-$FeCl_4$ **55** was reduced from solvent conditions to a catalytic amount of 10 mol%. Good conversion was still obtained, and the isolated yield was only slightly decreasing to 77% (entry 2). Surprisingly, best yield was obtained with even lower catalyst loading of 1 mol% bmim-$FeCl_4$ **55**: Complete conversion of **81** could be achieved by heating the sample at 100 °C overnight with a slight excess of methyl vinyl ketone **82** and a good isolated yield of 89% was obtained (entry 3). This higher yield with lower catalyst loading was maybe due to less product remaining in the ionic liquid layer after distillation.

Several other β-oxo esters **84**, **86**, **88** were also converted under the same conditions, each giving good to excellent yields ranging from 72-94% (entries 4, 5 & 6).

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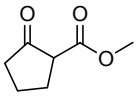
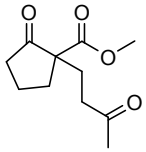
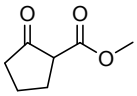
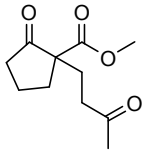
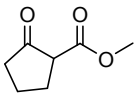
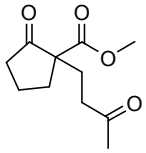
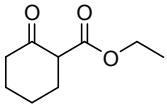
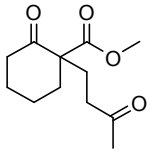
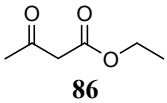
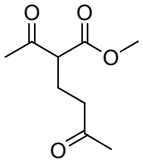
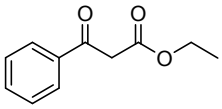
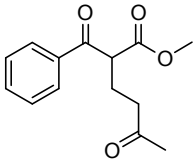
[137] (a) Dell'Anna, M. M.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *Chem. Commun.* **2002**, 434. (b) Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *J. Chem. Soc., Dalton Trans.1* **2002**, 4339.

[138] (a) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049. (b) Ranu, B. C.; Banerjee, S.; Jana, R. *Tetrahedron* **2006**, *63*, 776.

Table 22: Various Michael additions using bmim-$FeCl_4$ 55 as solvent or catalyst under thermal conditions

Entry [a]	bmim-$FeCl_4$	Starting material	Product	Yield [b]
1	2 g	 **81**	 **83**	81
2	10 mol%	 **81**	 **83**	77
3	1 mol%	 **81**	 **83**	89
4	1 mol%	 **84**	 **85**	94 [c]
5	1 mol%	 **86**	 **87**	72 [c]
6	1 mol%	 **88**	 **89**	91

[a] All reactions were performed using 5 mmol β-oxo ester and 7 mmol methyl vinyl ketone **82** at 100 °C. [b] Isolated yield after distillation. [c] Isolated yield after flash column chromatography.

As soon as the catalyst bmim-$FeCl_4$ **55** was mixed with β-oxo ester **81**, a deep purple colour was observed due to the immediate formation of an iron(III)-ato complex I (Figure 72, Figure 73). The significant colour of these Fe(III) complexes with 1,3-dicarbonyls is well known for over 100 years and has been utilized for the detection of β-keto esters or β-diketones (Figure 73).[139] Ligand exchange leads to coordination of methyl vinyl ketone **82** to the central metal

[139] *Gmelins Handbuch der Anorganischen Chemie*, Eisen, Vol. 59 B, Verlag Chemie: Berlin, 1932, 554.

(**II**) and holds the acceptor in proximity to the donor. Furthermore, Lewis acid activation of the Michael acceptor increases the reactivity towards nucleophilic addition. In the next step the activated carbon atom of the dionato complex is alkylated by the coordinating methyl vinyl ketone to form a bicyclic intermediate **III**. Liberation of the product via ligand exchange regenerates the catalytically active iron(III)-ato complex **I**.

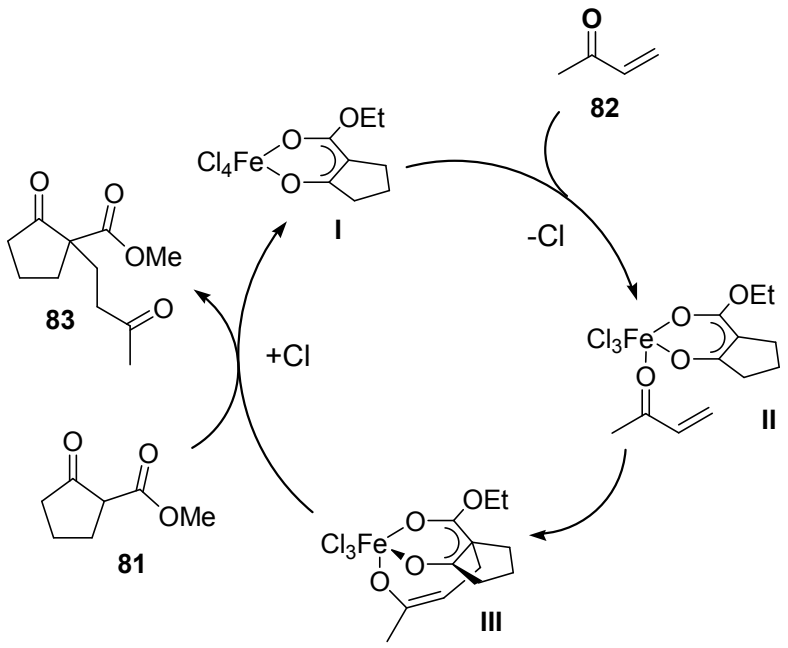


Figure 72: Proposed catalytical cycle for the bmim-$FeCl_4$ catalyzed Michael addition [135b]

Complete conversion could be easily recognized by a colour change from dark purple to a clear yellow solution, that was caused by the alkylated species and the Fe(III) salt (Figure 73).

Figure 73: Fe(III)-ato complex of bmim-$FeCl_4$ 55 and methyl 2-oxocyclopentane carboxylate 81 and colour change observed after complete conversion.

Since ionic liquids have proven to be excellent solvents for the immobilization of transition metal catalysis, it was particularly interesting to recycle the iron-containing ionic liquid **55** if used as catalyst itself without further immobilization. After the product **83** was isolated by

distillation, the remaining black residue was directly subjected to the next run without further work-up or purification. Fresh starting materials were added and the reaction was successfully run again showing only a minor decrease of yield from 89 to 86% in the second run and 83% in the third one, resp. (Table 23, entries 2 & 3). However, after the third run, conversion was dropping dramatically to 38% yield and only 11% could be isolated in the fifth run (entries 4 & 5). The accumulation of polymerized methyl vinyl ketone **82** that is formed as by-product could be responsible for this significant decrease of catalytical activity.

Table 23: Recycling of bmim-$FeCl_4$ 55 in the thermic Michael addition of β-oxo ester 81 and methyl vinyl ketone 82

Entry [a]	Run	Yield [b]
1	1	89
2	2	86
3	3	83
4	4	38
5	5	11

[a] All reactions were performed using 5 mmol β-oxo ester and 7 mmol methyl vinyl ketone at 100 °C. [b] Isolated yield of product **83** after distillation or flash column chromatography.

4.6.2 Microwave assisted Michael addition using ionic liquids as catalyst

Ionic liquids have recently attracted considerably attention as solvents or additives in microwave chemistry (4.1.5). Since they show high polarity which can be easily tuned depending on the cation and anion, ionic liquids have been successfully used as aids for microwave assisted heating of non-polar solvents.[76] Excessive studies of ionic liquid mediated microwave heating of various organic solvents were done by Leadbeater *et al.* and Ley and co-workers could significantly increase the reaction rate and yields of microwave assisted reactions run in toluene by adding a small quantity of an ionic liquid to the reaction mixture.[140,141] Thus, it was particularly interesting to run the bmim-$FeCl_4$ catalyzed Michael

[140] Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.

[141] Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans.1* **2001**, 358.

addition under microwave conditions: Due to the highly polar nature of the iron-containing ionic liquid, microwave irradiation should occur directly into the catalyst and thus lead to a strong acceleration of the reaction rate compared to thermal heating (Figure 74).

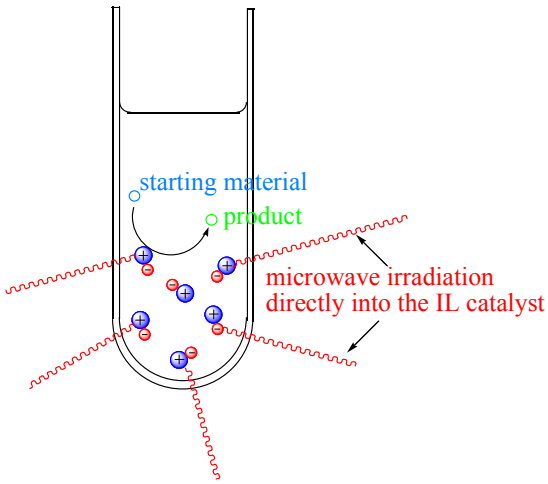
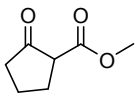
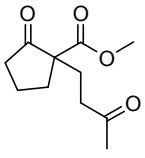
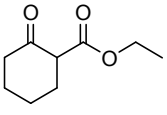
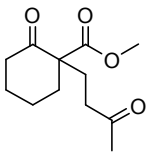
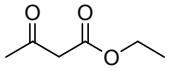
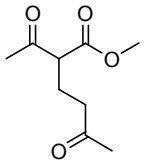
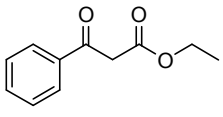
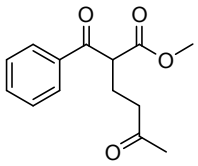
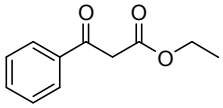
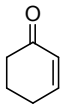
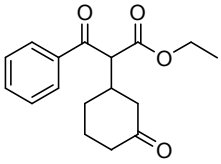
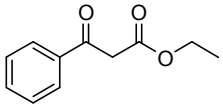
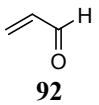
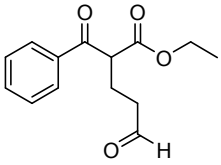


Figure 74: Microwave irradiation in ionic liquid catalyst

Reactions were performed in a CEM Explorer PLS microwave unit at a low power rate (50 W) to avoid initial overheating. A reaction temperature of 125 °C proved to be optimal since elevated temperature in some cases led to partial polymerization of methyl vinyl ketone **82** as side reaction. Various β-oxo esters **81**, **84**, **86** and **88** were tested as Michael donors, and each gave good to excellent yields (Table 24, entries 1-4).

Table 24: Various Michael additions using 1 mol% of 55 as catalyst under microwave conditions

Entry [a]	β-Keto ester	Enone	Conditions	Product	Yield [b]
1	 **81**	 **82**	125 °C/15 min	 **83**	94
2	 **84**	 **82**	125 °C/30 min	 **85**	89

3	 **86**	 **82**	125 °C/30 min	 **87**	71
4	 **88**	 **82**	125 °C/90 min	 **89**	79
5	 **88**	 **90**	125 °C/90 min	 **91**	88
6	 **88**	 **92**	125 °C/90 min	 **93**	52

[a] All reactions were performed in a CEM Explorer PLS microwave unit using 5 mmol β-oxo ester and 7 mmol enone. [b] Temperature control via external IR sensor [c] Hold times [d] Isolated yield after flash column chromatography.

When the enone component was changed to cyclohexenone **90** instead of methyl vinyl ketone **82**, a good yield of 88% was achieved (entry 5). Acrolein **92** was also suitable as Michael acceptor; however, the isolated yield was significantly lower which probably is a result of polymerization of the α,β-unsaturated aldehyde (entry 6).

To get insight in the influence of microwave irradiation, the reaction between β-oxo ester **81** and methyl vinyl ketone **82** was further investigated Samples with 1 and 10 mol% catalyst loading were irradiated at 125 °C/50 W and the conversion was monitored by GC-MS. To be able to compare the obtained results with those measured under thermal conditions the same samples were subjected to a preheated oil bath. In both cases (10 and 1 mol% catalyst, resp.) a strong acceleration of the reaction rate was observed: After a reaction time of 1 minute using 1 mol% of bmim-$FeCl_4$ **55**, the conversion in case of thermal heating was only 1%, whereas 17% conversion could be observed using microwave irradiation. The difference is even bigger in case of 10 mol% catalyst: After 1 minutes a conversion of 5% was obtained under thermal

condition, in case of microwave heating, the conversion after 1 minute is already 65%, and the reaction is finished after 5 minutes only (Figure 75).

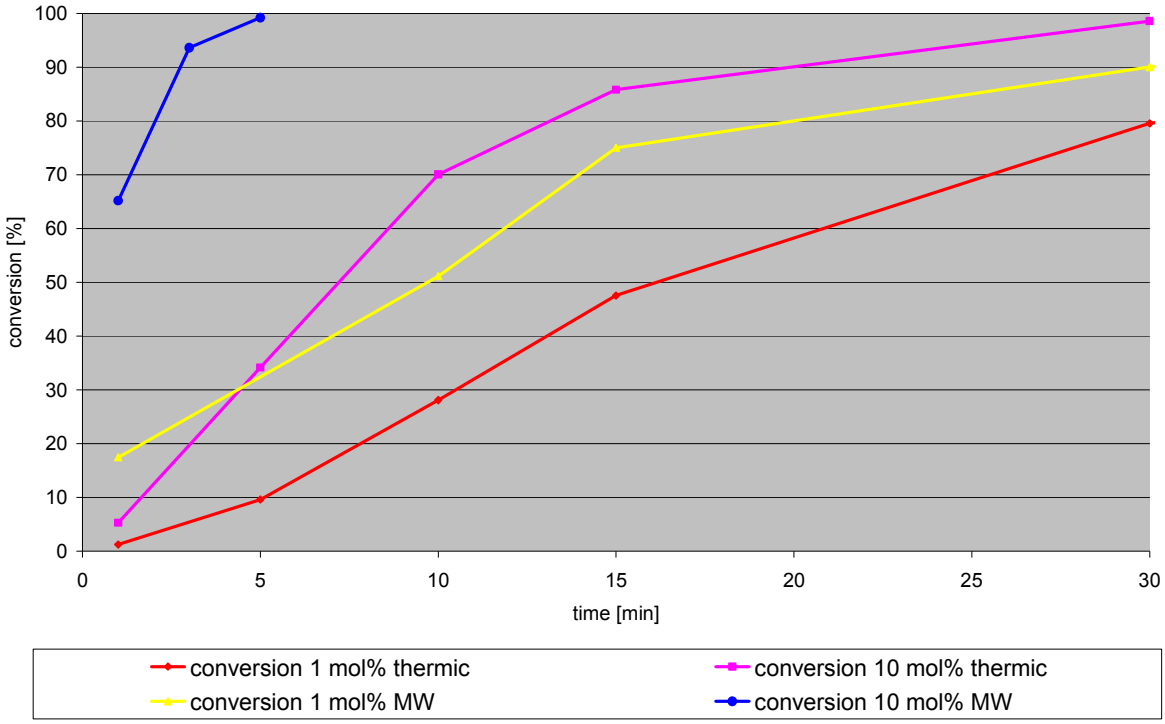


Figure 75: Comparison of conversion under microwave and thermal conditions

4.6.3 Monitoring of Fe(III) catalyzed reactions via ATR-FTIR

One of the major drawbacks of iron-catalyzed reactions is their difficult monitoring, particularly in case of iron(III), because its paramagnetic behaviour complicates spectroscopic techniques like NMR. However, a method to investigate the progress of iron-catalyzed Michael addition could be established: ATR-FTIR spectra of the reaction of β-keto ester **81** and methyl vinyl ketone **82** in the presence of 10 mol% bmim-$FeCl_4$ **55** as catalyst were recorded. Significant changes in the mid-IR spectral region could be used to calculate a concentration profile using multivariant curve resolution (MCR), a chemometric technique which can be applied to the analysis of a global instrumental response such as a set of spectra recorded from a chemical reaction over time.[142] To resolve the concentration profiles the following constraints were applied: non-negativity and unimodality in the concentration domain and non-negativity in the spectral domain. As initial estimates for the iterative process, the measured reference spectra of **81**, **82**, **83** and **55** were used. Figure 76 shows the FTIR spectra in the wavenumber region between 1850 and 1500 cm^{-1}. The IR spectrum of methyl vinyl ketone **82** exhibits two C=O stretching bands at 1701 and 1678 cm^{-1} due to the presence of *s-cis* and *s-trans* rotational isomers. On the other hand, the band located at 1617 cm^{-1} is due to the C=C stretching. Characteristic group frequencies for **81** are 1752 and 1723 cm^{-1} for C=O stretching. It can also be shown that the main carbonyl stretching bands in the product **83** spectra are located at 1746 and 1713 cm^{-1}. The spectrum of the catalyst used in the reaction has an intense absorption band at 1705 cm^{-1}.

[142] (a) de Juan, A.; Taluer, R. *Anal. Chim. Acta* **2003**, *500*, 195. (b) Tauler, R. *Chemom. Intell. Lab. Syst.* **1995**, *30*, 133. (c) Jaumot, J.; Gargallo, R.; de Juan, A.; Tauler, R. *Chemom. and Intel. Lab. Syst.* **2005**, *76,* 101.

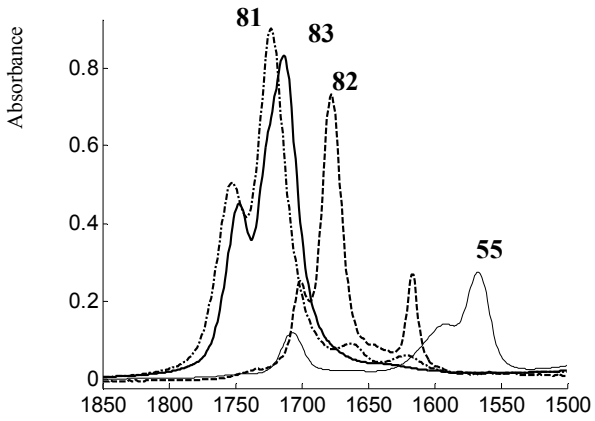


Figure 76: Reference ATR-FTIR spectra of 81, 82, 83 and 55 in the wavenumber region between 1850 and 1500 cm^{-1}

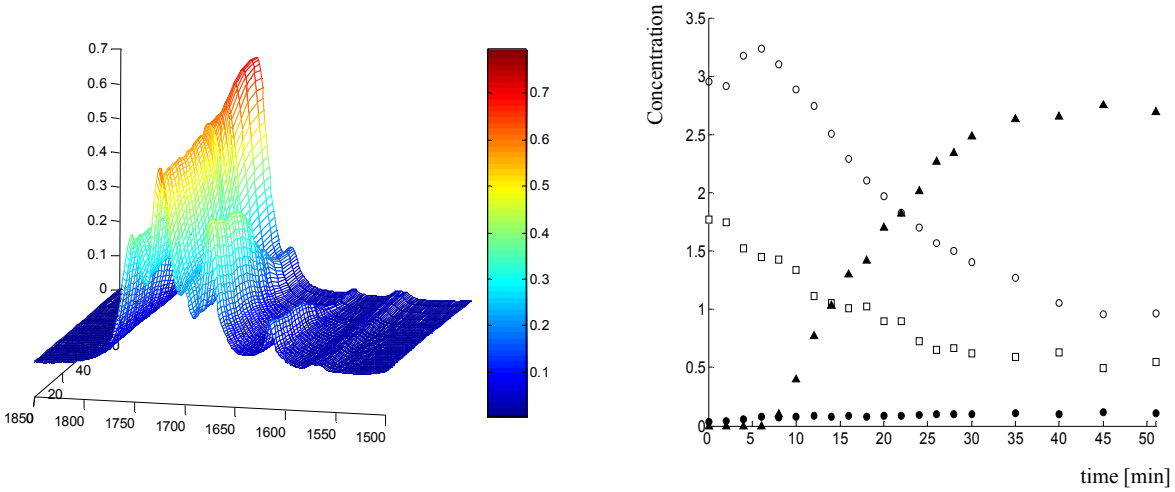


Figure 77: (a) Entire ATR-FTIR spectral data set used in the monitoring of the catalysed reaction between 81 and 82 (left) (b) Optimized pure concentration profiles for 81 (○),82 (□), 55 (●) and product 83 (▲) calculated by MCR analysis of the spectral data (right)

Figure 77 shows the reaction progress via time-resolved FTIR spectra and the calculated concentration profiles. FTIR spectrometry in combination with chemometric data analysis has thus proven to be a powerful technique to monitor this type of chemical reactions involving iron catalysis in ionic liquids.

4.7 Iron-catalyzed hydroxymethylation in aqueous media

Aldol reaction with the one-carbon electrophile formaldehyde is a classical C-C bond-forming reaction and one of the most useful procedures for the introduction of a C1-moiety.[143,144] Hydroxymethylation of 1,3-dicarbonyl compounds has broad applications in organic synthesis and many biologically active compounds contain an α-hydroxymethyl carbonyl unit as structural motif.[145] However, many C1 homologation reactions are limited by the use of gaseous formaldehyde, solid paraformaldehyde or trioxane which has to be depolymerized prior use. Therefore, the use of aqueous formaldehyde solution combined with transition metal catalysis would be highly beneficial and enable neutral, mild and environmentally benign conditions. Recent advances in the iron-catalyzed hydroxyformylation include the work of Lecomte and Bolm who described iron(III)-catalyzed tandem sequentional methanol oxidations and Aldol coupling and of Ogawa and Kobayashi who described surfactant-promoted hydroxymethylation of various 1,3-dicarbonyls in water.[146,147] Large catalyst amounts (10 and 5 mol%, resp.) where used, and in case of tandem oxidation/hydroxylation a substoichiometric amount of aldehyde was added.

The application of a metal-containing IL in this reaction showed some crucial advantages compared to common iron catalysts previously used (Figure 78):

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[143] (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, 527. (b) Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667. (c) Angelo, J.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 7114. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3244. (e) Lucast, D. H.; Wemple, J. *Synthesis* **1976**, 724. (f) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

[144] (a) Palomo, C.; Oiarbide, M.; Garćia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem*. **2002**, 1595.

[145] (a) Shiraga, Y.; Okano, K.; Akira, T.; Fukaya, C.; Yokoyama, K.; Tanaka, S.; Fukui, H.; Tabata, M. *Tetrahedron* **1988**, *44*, 4703. (b) Frampton, G. A.; Hannah, D. R.; Henderson, N.; Katz, R. B.; Smith, I. H.; Tremayne, N.; Watson, R. J.; Woollam, I. *Org. Process Res. Dev.* **2004**, *8*, 415. (c) Watson, R. J.; Batty, D.; Baxter, A. D.; Hannah, D. R.; Owen, D. A.; Montana, J. G. *Tetrahedron Lett.* **2002**, *43*, 683. (d) Jin, Y. *Synlett* **1998**, 1189. (e) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729. (f) Chan, T. H.; Schwerdtfeger, A. E. *J. Org. Chem.* **1991**, *56*, 3294.

[146] Lecomte, V.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 1666.

[147] Ogawa, C.; Kobayashi, S. *Chem. Lett.* **2007**, *36*, 56.

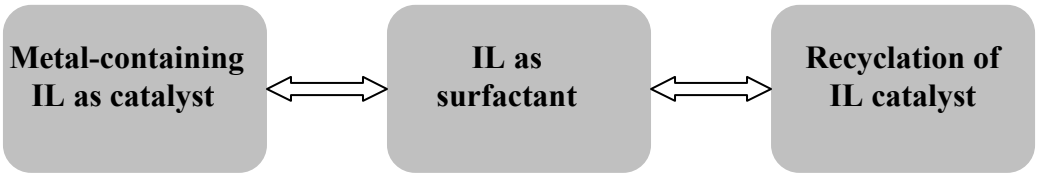
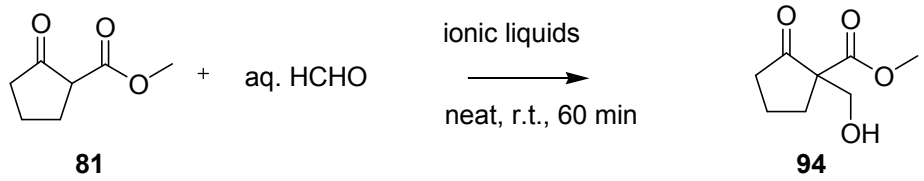


Figure 78: Multiple properties of ionic liquids in aqueous hydroxymethylations

The metal-containing IL should not only act as catalyst for hydroxymethylations of β-oxo esters under mild conditions, but recyclation of the IL should also be possible. Furthermore, ILs do also possess surfactant properties, therefore the catalytic amount of IL should promote the reaction between the aqueous formaldehyde solution and β-oxo esters that are not soluble in water.[148]

For initial screening the reaction of β-oxo ester **81** and aqueous formaldehyde solution with 10 mol% of various metal-containing ILs as catalysts was investigated.



81 **94**

Figure 79: Ionic liquid catalyzed hydroxymethylation using aqueous formaldehyde

Interestingly, the hydroxymethylated β-oxo ester methyl-1-(hydroxymethyl)-2-oxocyclopentane carboxylate **94** has been described as intermediate for anti-HIV drugs.[149]

[148] (a) Evans, K. O. *Colloids and Surf., A* **2006**, *274*, 11. (b) Dietz, M. L.; Dzielawa, J. A.; Jensen, M. P.; Firestone, M. A. *ACS Symposium Series* **2003**, *856* (Ionic Liquids as Green Solvents), 526. (c) Hoffman, M. M.; Heitz, M. P.; Carr, J. B.; Tubbs, J. D. *J. Dispersion Sci. Technol.* **2003**, *24*, 155.

[149] (a) Kuwano, H.; Haraguchi, K.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C.; Kato, K. *Nucleoside, Nucleotides Nucleic Acids* **2005**, *24*, 73. (b) Cheng, Y.; Tanaka, H.; Baba, M. U.S. Patent 167096, 2004.

Table 25: Screening of metal-containing ILs as catalysts for hydroxymethylation

Entry [a]	Catalyst	Yield [b]
1	bmim-$FeCl_4$	90
2	$bmim_2$-$CoCl_4$	77
3	$bmim_2$-$NiCl_4$	76
4	bmim-$TiCl_5$	32
5	$bmim_2$-$CuCl_4$	44

[a] All reactions were carried out at room temperature for 60 minutes with 5 mmol β-oxo ester **81**, 6 mmol 37 % aqu. HCHO solution and 0.05 mmol ionic liquid. [b] Isolated yield of **94** after flash column chromatography.

No co-solvent was necessary since homogenous conditions were observed even after addition of the aqueous formaldehyde solution. Furthermore, less formaldehyde solution (1.2 eq.) had to be used compared to the surfactant-promoted hydroxymethylation which was run with 1.5 up to 10 equivalents. In each case, the desired reaction was observed, but among those, Fe(III), Ni(II) and Co(II) ILs proved superior and gave product **94** in good yield, whereas Cu(II) and Ti(IV) salts gave considerably lower yields (Table 25, entries 1-5). Especially in case of Ti(IV) salts, extensive polymerization of formaldehyde at elevated temperature was observed as side reaction. Best results could be obtained with the iron-containing IL bmim-$FeCl_4$ **55**, which showed complete conversion within 5 minutes.

In consequence, the iron-catalyzed reaction was investigated in detail and the catalyst concentration was reduced: If 1 mol% of the iron salt **55** was used, the reaction proceeded smoothly within 15 minutes at room temperature and gave an isolated yield of 87% (Table 26, entry 2). Further reduction of the catalyst loading up to 0.1% resulted in longer reaction times and stirring over night was necessary to achieve complete conversion and maintain the yield of 88%. Nevertheless, this problem could be easily dealt with by elevating the reaction temperature: The reaction proceeded in 15 minutes only if run at 80 °C and gave an excellent isolated yield of 92% (Table 26, entries 3 & 4).

Table 26: Optimization of catalyst concentration

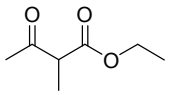
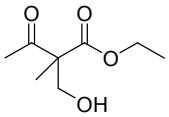
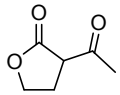
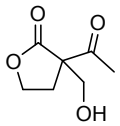
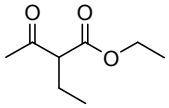
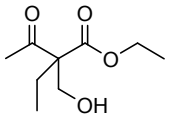
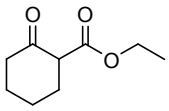
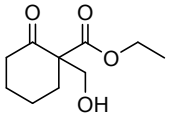
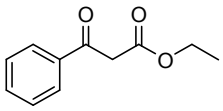
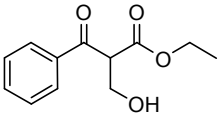
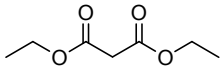
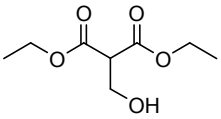
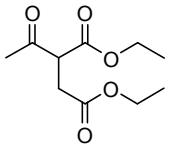
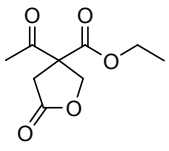
Entry [a]	bmim-$FeCl_4$ **55**	Conditions	Yield [b]
1	10 mol%	r.t., 5 min	90
2	1 mol%	r.t., 15 min	87
3	0.1 mol%	r.t., 16 h	88
4	0.1 mol%	80 °C, 15 min	92

[a] All reactions were carried out with 5 mmol β-oxo ester **81** and 6 mmol 37 % aqueous HCHO solution. [b] Isolated yield of **94** after flash column chromatography.

Further studies showed that the use of aqueous formaldehyde solution is indeed necessary to ensure conversion: When treated with paraformaldehyde or trioxane in the presence of 1 mol% bmim-$FeCl_4$ **55**, no conversion of β-keto ester **81** was observed neither at room temperature nor after heating to 80 °C overnight.

When β-keto ester **95** was applied, longer reaction times were necessary, nevertheless 83% of **96** could be isolated after stirring overnight (Table 27, entry 1). The β-keto esters **84**, **88** and 2-acetylbutyrolactone **97** also gave good to excellent yields of 70-87%, whereas β-keto ester **99** only showed slow conversion and a considerable lower yield of 33% (entries 2-5). Unfortunately, almost no conversion was observed when diethyl malonate **103** was applied (entry 6). In case of diethyl acetylsuccinate **105**, only very slow conversion was observed at room temperature using 1 mol% of catalyst **55**. On the other hand, when heated to 80 °C in the presence of 10 mol% of bmim-$FeCl_4$ **55** complete conversion was observed within 2 hours. Hydroxymethylation followed by *in-situ* lactonization gave lactone **106** as single product in 85% isolated yield (entry 7).

Table 27: Results of various iron-catalyzed hydroxymethylations

Entry [a]	Starting material	Product	Yield [c]
1	 **95**	 **96**	83
2	 **97**	 **98**	87
3	 **99**	 **100**	33
4	 **84**	 **101**	73
5	 **88**	 **102**	70
6	 **103**	 **104**	< 1
7 [b]	 **105**	 **106**	85

[a] Reactions were carried out at room temperature with 5 mmol β-keto ester, 6 mmol 37% aqu. HCHO solution and 0.05 mmol bmim-$FeCl_4$ **55**. [b] Reaction was performed at 80 °C using 0.5 mmol bmim-$FeCl_4$ **55**. [c] Isolated yield after flash column chromatography.

After product isolation via Kugelrohr distillation, the remaining black residue was directly subjected to the next run without further work-up or purification. Fresh β-oxo ester **81** and aqueous formaldehyde solution were added and the reaction was successfully run again showing only a minor decrease of yield from 87 to 78% after 5 runs (Table 28, entries 1-5). However, reaction times had to be increased.

Table 28: Recycling of bmim-$FeCl_4$ 55 in the hydroxymethylation of ketoester 81

Entry [a]	Run	Conditions	Yield [b]
1	1	r.t., 15 min	87
2	2	r.t., 15 min	81
3	3	r.t., 30 min	88
4	4	r.t., 60 min	75
5	5	r.t., 240 min	78

[a] Reactions were carried out at room temperature with 5 mmol β-oxo ester **81**, 6 mmol HCHO solution and 0.05 mmol bmim-$FeCl_4$ **55**. [b] Isolated yield of **94** after Kugelrohr distillation.

5. Summary

5.1 Chiral ionic liquids – Design, synthesis and application

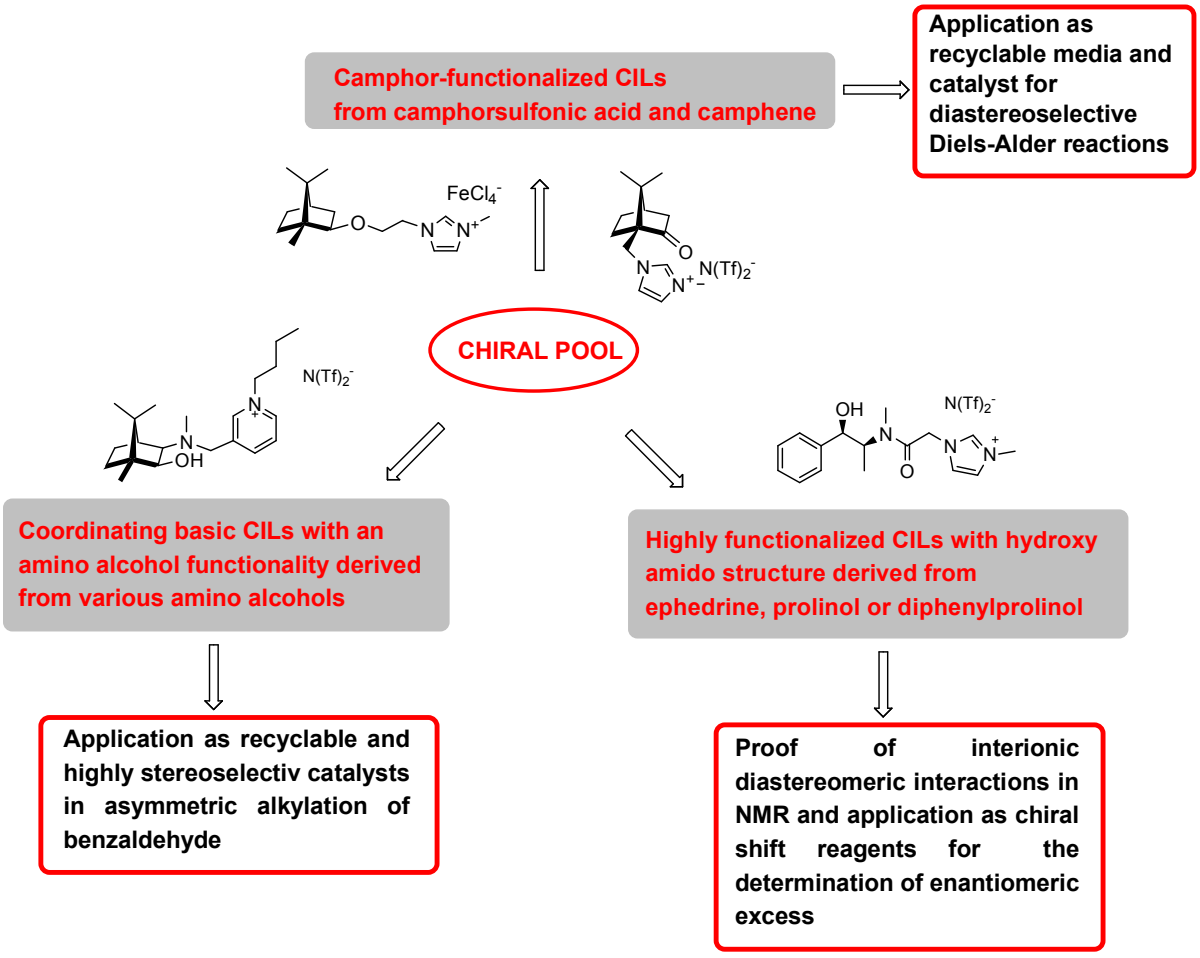


Figure 80: Synthesis and applications of chiral ionic liquids - Summary

In summary, two new kinds of CILs bearing a bornyl moiety were synthesized in good overall yield from inexpensive chiral pool precursors. Particularly the synthesis of the chiral RTILs **8a-d** is interesting from green chemistry focus, giving a straightforward synthesis in three steps only and avoiding the use of solvents except water and the use of highly toxic alkylation reagents. Furthermore, a useful procedure for the microwave assisted synthesis of imidazolium salts to diminish long reaction times was developed.

These camphor-functionalized CILs are a suitable and fully recyclable reaction media for Diels-Alder reactions and give good diastereoselectivities and excellent yields without further addition of Lewis acid, although no enantiomeric excess could be achieved.

In a second approach, a set of highly functionalized CILs was synthesized starting from commercially available amino alcohols. An amide functionality was introduced to link the amino alcohol to the ionic liquid moiety. The strong interionic diastereomeric interactions with racemic

substrates were visualized via ^{19}F-NMR spectroscopy and the application as shift reagent for the determination of enantiomeric excess was demonstrated.

Finally, a synthetic strategy for basic and highly coordinating CILs with an amino alcohol unit was developed and could be applied to various chiral 1,2-amino alcohol.

Despite of the ionic liquid pyridinium moiety two non functionalized coordination sites are free and therefore best conditions for high selectivity should be disclosed. Indeed, when tested as chiral ligands in the enantioselective alkylation of benzaldehyde with diethylzinc, excellent yields and high enantioselectivities of up to 95% ee were observed with camphor-derived CILs. In fact, these results are among the best selectivities ever obtained with CILs in asymmetric synthesis (2.1) and by far the most convincing in asymmetric alkylation (2.1.3).

5.2 Metal-containing ionic liquids as recyclable catalysts for C-C-bond formation

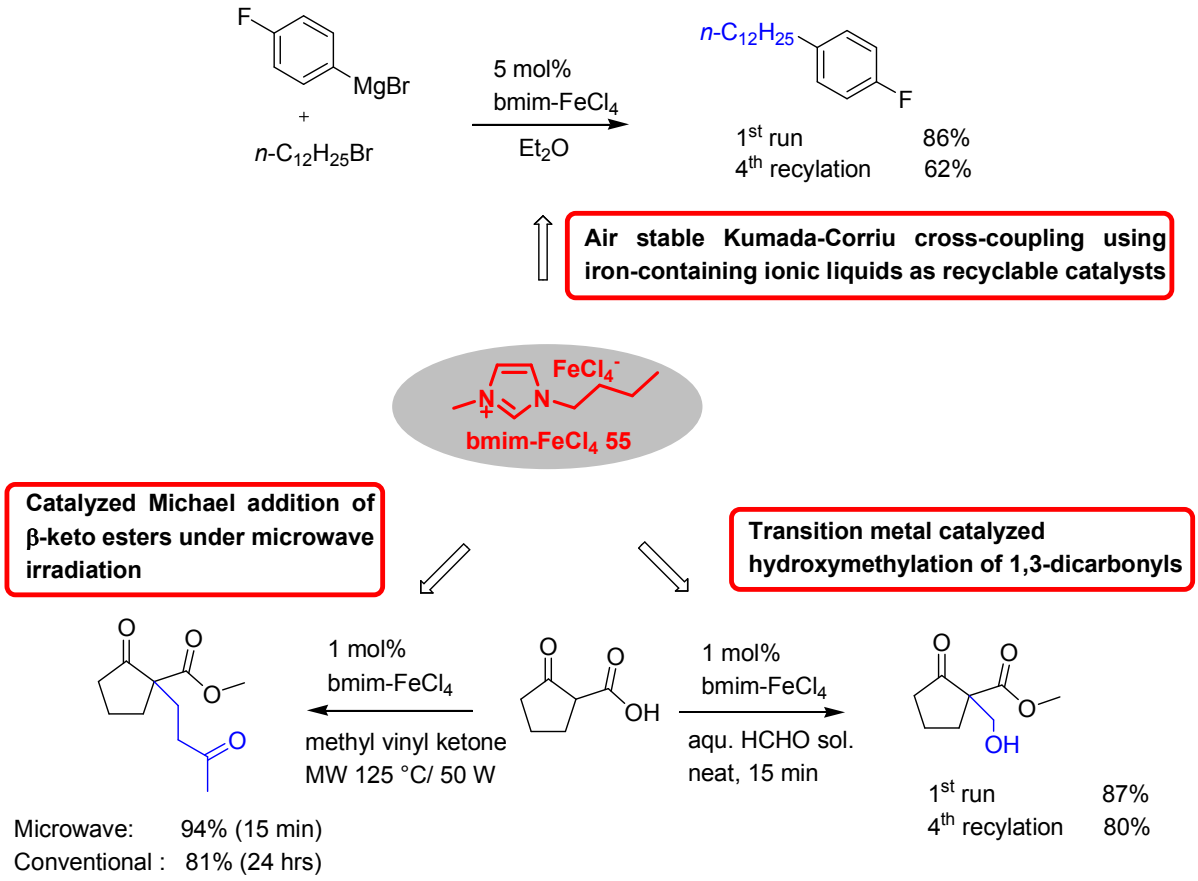


Figure 81: Metal-containing ionic liquids as catalysts for C-C-bond formation - Summary

The IL 1-butyl-3-methylimidazolium tetrachloroferrate (bmim-$FeCl_4$) was established as a very effective and completely air stable catalyst for the biphasic Grignard cross-coupling with primary and secondary alkyl halides bearing β-hydrogens. After simply decanting the product in the ethereal layer, the IL catalyst was successfully recycled four times.

Further investigations dealing with iron-catalyzed Michael addition proved that bmim-$FeCl_4$ also is a very efficient catalyst for microwave assisted synthesis, giving a strong acceleration of the reaction rate compared to thermal heating.

Hydroxymethylation of various 1,3-dicarbonyl compounds also proceeded extremely satisfying since only a very low catalyst loading - up to 0.1% - had to be applied. Various other metal-containing ILs [Cu(II), Ti(IV), Co(II) and Ni(II)] were examined, but cheap and environmentally benign iron proved to be superior. In this case, the IL did not only work as catalyst, but also as phase-transfer catalyst and allowed to perform the reaction under aqueous conditions without additional surfactants. Again, the catalyst could be successfully recycled for four cycles.

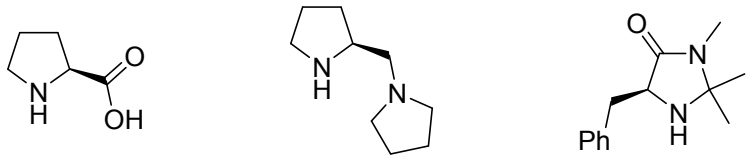
In summary, the concept of metal-containing IL catalysts worked exceptionally well and showed several advantages for all reactions examined:

- In each case, the IL could be used catalytically and low catalyst loading proved to be sufficient.
- Enhanced yields and selectivities compared to common iron(III) catalysts were observed.
- Large amounts of solvents for extraction of the product from an IL layer could be spared.
- In order to satisfy both economic as well as ecologic aspects, the transition metal catalyst could be easily recycled after decanting the product layer or after distillation of the product.

6. Outlook

6.1 Chiral ionic liquids in organocatalysis

Organocatalysis of asymmetric reactions by simple metal-free organic molecules has recently received much attention and has become a rewarding alternative to transition metal-catalyzed asymmetric synthesis.[37] A proline-like cyclic five-membered secondary amine structure has been recognized as privileged organocatalyst, and a variety of pyrrolidine or imidazoline based systems is now available for a constantly growing pool of reactions like asymmetric Aldol, Mannich, Michael and Diels-Alder reaction.



107

Figure 82: Privileged organic catalysts

Despite the fact that expensive and often toxic metals can be avoided, the need of substantial quantities of organic catalyst (approx. 30 mol%) and of highly polar solvents like DMSO which make the reaction work-up and catalyst recycling difficult are major drawbacks in asymmetric organocatalysis. It is therefore obvious that CILs might be an interesting alternative to overcome these limitations. Another major drawback in organocatalysis is the necessity of significant amounts of usually toxic and very corrosive trifluoroacetic acid to form a protic intermediate that can further interact with a carbonylic substrate for catalysis.

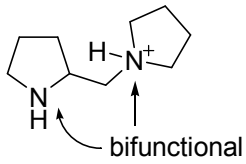


Figure 83: Protic intermediate of (S)-1-(2-Pyrrolidinylmethyl)pyrrolidine

This led to the design of an IL-supported chiral organocatalyst in which the protonated nitrogen was replaced by an alkylated ammonium functionality.

The CIL analogue of chiral diamine **107** was synthesized in a simple and high yielding synthesis starting from (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **107**. Quaternization of the benzyloxycarbonyl-(Cbz-) protected diamine **108** with dimethyl sulfate and *in situ* anion exchange gave intermediate **109** that was further deprotected using hydrogen and palladium on charcoal to give the CIL **110** as colourless liquid.

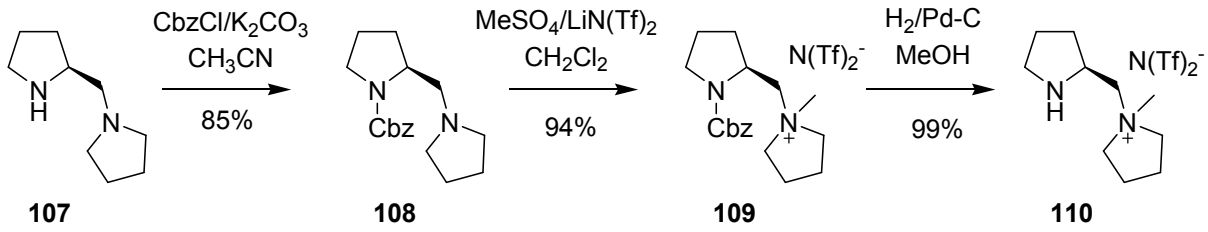


Figure 84: Synthetic strategy for a (S)-1-(2-pyrrolidinylmethyl)pyrrolidine derived chiral ionic liquid

First investigations in the catalytic activity were very promising: The organocatalytic acid-free Aldol reaction of 4-nitrobenzaldehyde **111** and cyclohexanone **112** could be performed with 15 mol% CIL only and gave the product **113** in a complete diastereoselective way and with an enantiomeric excess of 83% ee.

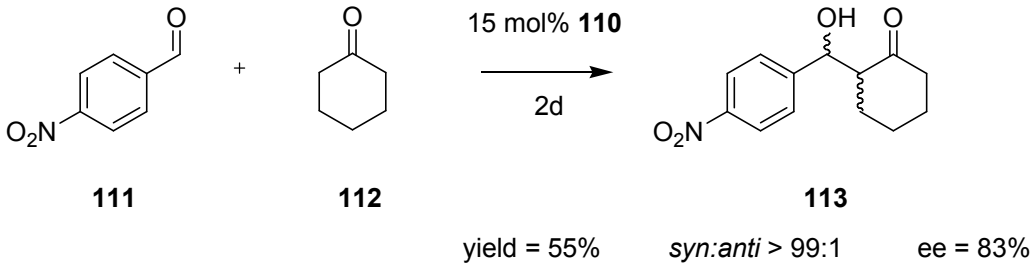


Figure 85: Chiral ionic liquid catalyzed asymmetric Aldol reaction

This early result indicates that it is indeed possible to perform acid-free organocatalysis and that this CIL bears a high potential for organocatalysis. However, full characterization of CIL **110**, the application in various transformations and further investigation in mechanistic details are still to be explored and will be subject of future work.

6.2 Chiral metal-containing ionic liquids

It is further interesting to combine the principles of metal-containing ionic liquids as recyclable catalyst and of chiral ionic liquids as reaction media, catalyst or ligand for asymmetric synthesis. Bifunctional CIL composed of two catalytically active parts can induce chirality with the cationic part, whereas the metal-containing anion can act as transition metal catalyst.

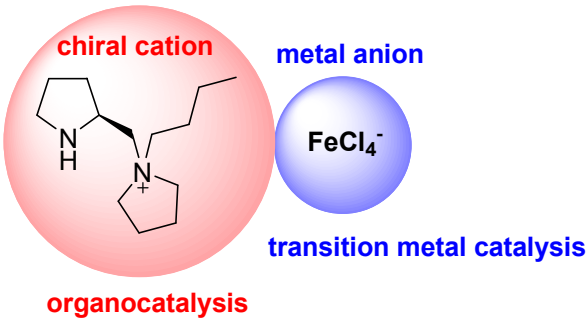


Figure 86: Organo-transition metal ionic liquid catalyst

In this case, a completely new strategy for asymmetric synthesis would be possible, combining both advantages of transition metal catalysis and chiral organocatalysis in an ionic liquid hybrid catalyst.

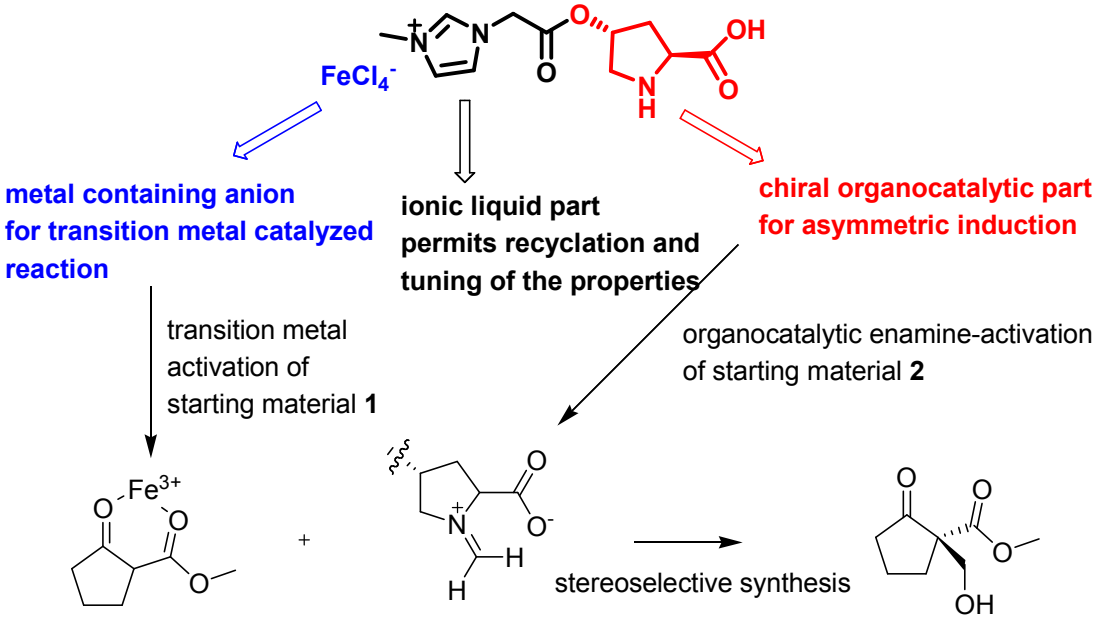


Figure 87: Principle of double catalysis shown at the example of stereoselective iron-catalyzed hydroxymethylation

A set of various chiral metal-containing CILs has been synthesized so far, however complete analysis and the application as chiral organo- and transition metal hybrid catalysts is still under investigation.

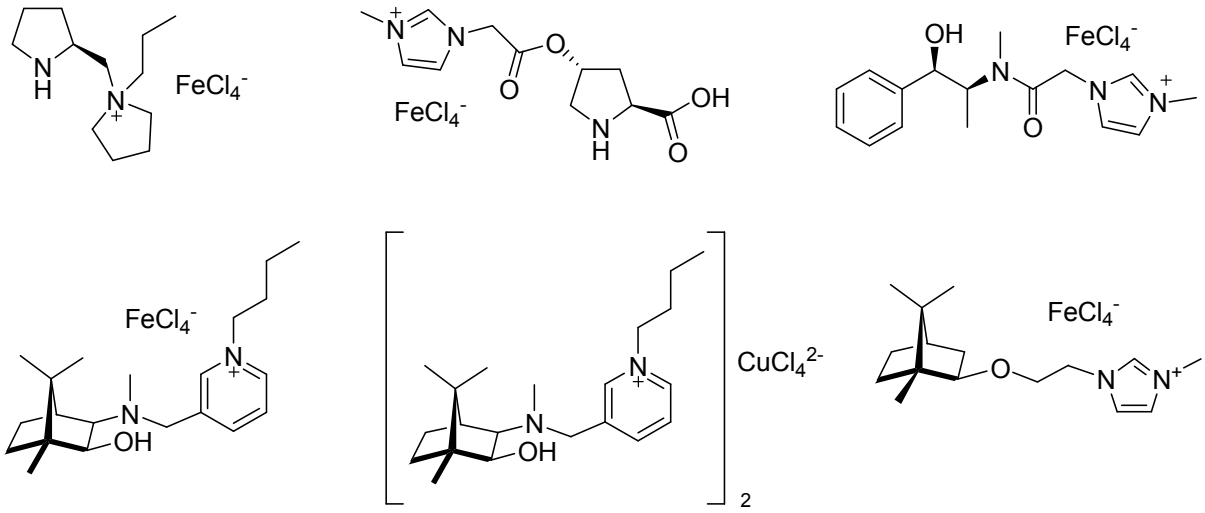


Figure 88: Chiral metal-containing ionic liquid catalysts synthesized so far

7. Experimental

7.1 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. Dry toluene, diethyl ether, THF and 1,4-dioxane were predried over KOH and distilled from Na/benzophenone. Dry chloroform, dichloromethane, acetonitrile and ethyl acetate were distilled from P_2O_5. Anhydrous acetone was dried over molecular sieve 4 Å. Grignard reagents were prepared according to standard protocols and titrated using 1,10-phenantroline and *sec*-BuOH in toluene.[150]

^{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 DEPT were referred as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

GC-MS analysis 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 film thickness) cross-bonded dimethyl polysiloxane capillary column. The electron energy was set to 70 eV and the ion source temperature to 200 °C. 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.

GC analysis were performed on ThermoFinnigan Trace chromtograph equipped with a BGB 175 column (30 m × 0.25 mm ID, 0.25 μm film). The temperature program was set to 80 °C (2 min)//5 °C/min//160 °C (1 min))//10 °C/min//220 °C (8 min); 2 ml/min He; 230 °C FID; 220 °C Inlet.

Infrared spectra were recorded on a Bruker Equinox 55 FTIR spectrometer (Bruker Optik GmbH, Ettlingen, Germany) equipped with a 3 bounce diamond attenuated total reflection (ATR) unit and a narrow band mercury cadmium telluride (MCT). The scanner of the interferometer operated at a HeNe laser modulation frequency of 180 kHz, the spectral resolution was set to 2 cm^{-1}.

[150] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

Time-resolved FT-IR spectroscopy was recorded against an air background with 50 scans coadded for each spectrum. For data acquisition and treatment the OPUS software (Bruker, Ettlingen, Germany) version 5.0 has been used. Chemometric analysis of the data was run under Matlab 7.0 (MathWorks, Natick, USA, version 7.0, 2004) using a MCR-ALS Matlab code.

Raman spectra were recorded on a LabRAM HR spectrometer (Jobin Yvon, Benzheim, Germany) using a 632.8 nm HeNe laser line.

Microwave synthesis was performed on a CEM Explorer PLS microwave unit with an external IR sensor for temperature control. Given reaction times are hold times.

TLC-analysis was done with precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck). Compounds were visualised by spraying with 5% phosphomolybdic acid hydrate in ethanol 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 and are uncorrected. Melting points of roomtemperature ILs were determined on a Netzsch STA 409 PC/PG under helium by heating samples precooled to -90 °C with a rate of 5 °C/min.

Specific rotations were measured on a Perkin-Elmer 241 polarimeter.

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

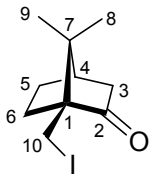
High resolution mass spectroscopy was perfomed on a Thermo Electron LTQ Orbitrap Hybrid Mass Spectrometer with a Finnigan nanospray ionization (NSI) source.

HPLC analysis was performed on Thermo Finnigan Surveyor chromatograph with a PDA plus detector (190-360 nm). A DAICEL Chiralcel OD-H column (250 × 4.60 mm) was used as stationary phase with *n*-hexan/*i*-propanol as solvent and a flow of 0.7 ml/min; detection at 254 and 219 nm.

7.2 Synthesis of camphor-derived chiral ionic liquids

7.2.1 (1*S*, 4*R*)-(1-(Iodomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 2

(1*S*)-(+)-Camphor sulfonic acid **1** (10.0 g, 43 mmol), triphenylphosphine (56.5 g, 215 mmol) and iodine (21.8 g, 86 mmol) were dissolved in 300 ml anhydrous toluene under nitrogen and heated at reflux for 18 hours. The resulting solution was evaporated to dryness and the black slurry was dissolved again in 300 ml ethyl acetate. Insoluble by-products were removed via filtration and the filtrate was washed successively with a saturated solution of sodium thiosulfate, water and brine. The organic phase was dried with sodium sulphate, filtered and the solvent removed in vacuum. In order to remove triphenylphosphine by-products, the crude product was dissolved in 100 ml ether and stirred for 5 minutes. The suspension was filtered and the filtrate was evaporated. VFC (400 g silica, light petrol:acetone 30:1) yielded pure **2** as colourless crystals (10.6 g, 89%).

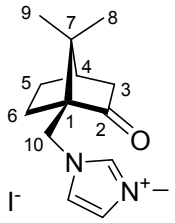


2
$C_{10}H_{15}IO$
278.13 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 3.30/3.10 (2d, J = 10.56 Hz/J = 10.76 Hz, 2H), 2.39 (ddd, J_1 = 18.34 Hz, J_2 = 4.94 Hz, J_3 = 2.01 Hz, 1H), 1.93-1.85 (m, 3H), 1.59 (m, 1H), 1.38 (m, 1H), 1.06 (s, 3H), 0.88 (s, 3H).
Analytical data were in accordance with literature values.[66]

7.2.2 1-Methyl-3-[(1*S*, 4*R*)-(2-oxo-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]imidazolium iodide 3

10-Iodocamphor **2** (3.04 g, 10.9 mmol) and *N*-methylimidazole (1.12 g, 13.7 mmol) (freshly distilled over KOH) were mixed in a round bottom flask under an atmosphere of dry nitrogen, sealed and stirred for 14 days at 80 °C. The crude product was washed several times with anhydrous ethyl acetate and dried by stirring under high vacuum and 80 °C for 24 hours to give **3** as very viscous oil (3.84 g, 97%). An analytical sample was crystallized from a mixture of anhydrous ethyl acetate and acetonitrile.



3
$C_{14}H_{21}IN_2O$
360.23 g/mol

$[\alpha]_{365}^{20}$ = -59.0 ($CHCl_3$, c = 1.09).

mp 118-120 °C (from ethyl acetate/acetonitrile).

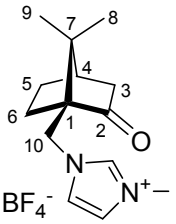
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 10.08 (s, 1H, -NCHN-), 7.79/7.50(2s, 2H, -NCHCHN-), 4.51/4.39 (2d, J = 14.28 Hz, 2H, H-10), 4.07 (s, 3H, CH_3N-), 2.41 (ddd, J_1 = 18.73 Hz, J_2 = 3.96 Hz, J_3 = 2.39 Hz, 1H), 2.25-1.97 (m, 3H), 1.89 (d, J = 18.58 Hz, 1H), 1.47-1.28 (m, 1H), 1.21-1.10 (m, 4H, therein 1.21 (s, H-10)), 0.88 (s, 3H, H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 217.0 (s, C-2),137.8 (d, -NCHN-), 124.5/123.0 (2d, -NCHCHN-), 60.4 (s, C-1), 48.0 (t, C-10), 47.1 (s, C-7), 43.8 (q, CH_3-), 42.9 (t, C-3), 37.0 (d, C-4), 26.5 (t, C-5), 25.7 (t, C-6), 20.1/19.9 (2q, C-8/C-9).

Anal. Calcd. for $C_{14}H_{21}IN_2O$: C, 46.68; H, 5.88; N, 7.78. Found: C, 46.43; H, 5.65; N, 7.65.

7.2.3 1-Methyl-3-[(1*S*, 4*R*)-(2-oxo-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]imidazolium tetrafluoroborate 4a

Cmp. **3** (1.00 g, 2.8 mmol) and $NaBF_4$ (0.40 g, 2.91 mmol) were suspended in dry acetone under an atmosphere of dry nitrogen and stirred for 20 hours. Inorganic salts were filtered over a short pad of silica and washed with dry acetone. The filtrate was evaporated to dryness, dissolved again in 30 ml of dichloromethane and washed twice with 5 ml of H_2O_{dest}. The organic phase was dried over $MgSO_4$, filtered, evaporated and dried on high vacuum to yield **4a** as yellow crystals (0.65 g, 67%). An analytical sample was crystallized from anhydrous ethanol.



4a
$C_{14}H_{21}BF_4N_2O$
320.13 g/mol

$[\alpha]_{365}^{20}$ = -24.1 ($CHCl_3$, c = 1.00).

mp 88-91 °C (from EtOH).

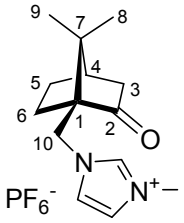
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.50 (s, -NCHN-), 7.68/7.49 (2m, 2H, -NCHCHN-), 4.34 (s, 2H, H-10), 3.98 (s, 3H, CH_3N-), 2.35 (ddd, J_1 = 18.63 Hz, J_2 = 4.64 Hz, J_3 = 1.81 Hz, 1H), 2.03 (m, 3H), 1.83 (d, J = 18.78 Hz, 1H), 1.34 (m, 1H), 1.18 (m, 1H), 1.11 (s, 3H, H-8), 0.82 (s, 3H, H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 216.8 (s, C-2), 137.4 (d, -NCHN-), 124.2/123.1 (2d, -NCHCHN-), 60.1 (s, C-1), 47.8 (t, C-10), 46.9 (s, C-7), 43.6 (q, CH_3-), 42.7 (t, C-3), 36.7 (d, C-4), 26.4 (t, C-5), 25.4 (t, C-6), 19.7/19.5 (2q, C-8/C-9).

HRMS (NSI+) m/z calcd for $C_{14}H_{21}N_2O$: 233.1649, found: 233.1646.

7.2.4 1-Methyl-3-[(1*S*, 4*R*)-(2-oxo-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]imidazolium hexafluorophosphat 4b

Cmp. **3** (1.00 g, 2.8 mmol) was dissolved in 10 ml of H_2O_{dest} and a 60% solution of HPF_6 in H_2O (0.81 g, 3.33 mmol) was added dropwise under stirring. A second phase separated immediately and was extracted with dichloromethane. The organic phase was washed with small portions of water until no more iodide-ions could be detected in the washings (checked by addition of an aqueous solution of $AgNO_3$). The organic phase was dried over $MgSO_4$, filtered and evaporated. Stirring at high vacuum and 80 °C yielded **4b** as slight yellow viscous oil which solidified upon long standing (0.89 g, 85%). Crystallization from ethanol gave **4b** as colourless needles.



4b
$C_{14}H_{21}F_6N_2OP$
378.29 g/mol

$[\alpha]_{365}^{20}$ = +123.5 ($CHCl_3$, c = 1.02).

mp 58-60 °C (from EtOH).

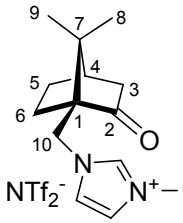
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.60 (s, 1H, -NCHN-), 7.54/7.28 (2s, 2H, -NCHCHN-), 4.36/4.11 (2d, J = 14.48 Hz, 2H, H-10), 3.89 (s, 3H, CH_3N-), 2.41 (ddd, J_1 = 18.78 Hz, J_2 = 4.30 Hz, J_3 = 2.54 Hz, 1H), 2.16 (t, J = 4.21 Hz, 1H), 1.96 (m, 2H), 1.89 (d, J = 18.78 Hz, 1H), 1.40 (m, 1H), 1.24-1.10 (m, 4H, therein 1.10 (s, 3H, H-8)), 0.87 (s, 3H, H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 217.1 (s, C-2), 137.2 (d, -NCHN-), 124.2/123.1 (2d, -NCHCHN-), 60.1 (s, C-1), 47.7 (t, C-10), 47.0 (s, C-7), 43.8 (q, CH_3-), 42.8 (t, C-3), 36.2 (d, C-4), 26.5 (t, C-5), 25.2 (t, C-6), 19.7/18.8 (2q, C-8/C-9).

Anal. Calcd. for $C_{14}H_{21}F_6N_2OP$: C, 44.45; H, 5.60; N, 7.41. Found: C, 44.49; H, 5.41; N, 7.43.

7.2.5 1-Methyl-3-[(1*S*, 4*R*)-(2-oxo-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]imidazolium bis(trifluoromethanesulfonyl)imide 4c

Cmp. **3** (3.84 g, 10.7 mmol) was dissolved in 20 ml of H_2O_{dest} and a solution of $Li[N(CF_3SO_2)_2]$ in 10 ml H_2O_{dest} was added dropwise under stirring. A second phase separated immediately and was washed with small portions of water until no more halide-ions could be detected in the washings (checked by addition of an aqueous solution of $AgNO_3$). Stirring at high vacuum and 80 °C yielded **4c** as slight yellow viscous oil in 92% yield.



4c
$C_{16}H_{21}F_6N_3O_5S_2$
513.48 g/mol

$[\alpha]_{365}^{20}$ = +80.2 ($CHCl_3$, c = 1.03).

mp -39.7 °C.

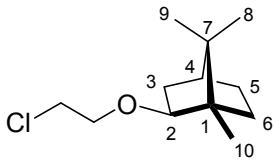
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.76 (s, 1H, -NCHN-), 7.59/7.27 (2m, 2H, -NCHCHN-), 4.37/4.13 (2d, J = 14.47 Hz, 2H, H-10), 3.90 (s, 3H, CH_3N-), 2.41 (ddd, J_1 = 18.73 Hz, J_2 = 4.54 Hz, J_3 = 2.88 Hz, 1H), 2.16-1.81 (m, 3H), 1.89 (d, J = 18.58 Hz, 1H), 1.40 (m, 1H), 1.17 (m, 1H), 1.10 (s, 3H, H-8), 0.87 (s, 3H, H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 216.9 (s, C-2), 137.2 (d, -NCHN-), 124.5/123.2 (2d, -NCHCHN-), 119.7 (q, J = 321.31 Hz, CF_3), 60.1 (s, C-1), 47.8 (t, C-10), 47.2 (s, C-7), 43.8 (q, CH_3-), 42.8 (t, C-3), 36.2 (d, C-4), 26.4 (t, C-5), 25.4 (t, C-6), 19.6/18.9 (2q, C-8/C-9).

Anal. Calcd. for $C_{16}H_{21}F_6N_3O_5S_2$: C, 37.43; H, 4.12; N, 8.18. Found: C, 37.59; H, 4.12; N, 7.97.

7.2.6 (1*S*, 2-*exo*)-2-(2-Chlorethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptane 6

Technical (80%) (+)-Camphene **5** (5.00 g, ~ 29 mmol), 2-chloroethanol (3.55 g, 44 mmol) and *p*-TsOH (0.30 g, 1.74 mmol) were stirred at 65 °C for 18 hours. Triethylamine (0.176 g, 1.74 mmol) was added. Vacuum distillation of the crude product at 112-115 °C/3 Torr using a 20 cm vigreux-column gave 6.01 g (94%) of **6** as colourless liquid.

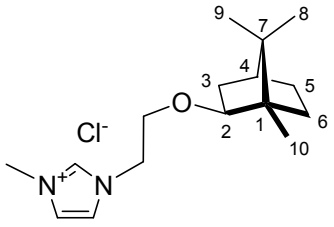


6
$C_{12}H_{21}ClO$
216.75 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 3.55 (m, 4H), 3.23 (dd, J_1 = 7.53, J_2 = 3.42, 1H), 1.83-1.44 (m, 5H), 0.98 (m, 5H), 0.89 (s, 3H), 0.80 (s, 3H).
Analytical data were in accordance with literature values.[68]

7.2.7 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium chloride 7

1-Chloro-2-isobornyloxyethan **6** (12.40 g, 57.2 mmol) and freshly distilled *N*-methylimidazole (4.93 g, 60.05 mmol) were mixed in a round bottom flask under an atmosphere of dry nitrogen, sealed and stirred for 4 days at 80 °C. Remaining starting material was removed under high vacuum at 80 °C for 24 hours to yield 15.40 g (90%) of **7** as a very hygroscopic solid.
Crystallization from a mixture of dry ethyl acetate and acetonitrile and filtration under dry nitrogene gave **7** as colourless crystals.



7
$C_{16}H_{27}ClN_2O$
298.85 g/mol

$[\alpha]_{365}^{20}$ = -1.36 ($CHCl_3$, c = 1.4).

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 10.31(s, 1H, -NCHN-), 7.58/7.36 (2m, 2H, -NCHCHN-), 4.49/4.36 (2ddd, J_1 = 14.13 Hz/14.18 Hz, J_2 = 6.11 Hz/6.74 Hz, J_3 = 3.06 Hz/2.93 Hz, 2H, -O$\underline{CH_2}CH_2$N), 3.98 (s, 3H, CH_3N-), 3.69/3.47 (2ddd, J_1 = 10.61 Hz/10.51Hz, J_2 = 6.21 Hz/6.89 Hz,

J_3 = 3.08/3.27 Hz, 2H, -$OCH_2\underline{CH_2}N$), 3.08 (dd, J_1 = 7.04 Hz, J_2 = 3.33 Hz, 1H, H-2_{endo}), 1.73-1.28 (m, 5H, H-4, H-3_{exo}, H-5_{exo}, H-3_{endo}, H-6_{exo}), 0.90-0.72 (m, 5H, therein 0.73(s, H-10)), 0.66 (s, 3H, H-8), 0.65 (s, 3H, H-9).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 137.6 (d, -NCHN-), 122.8/122.8 (2d, -NCHCHN-), 87.7 (d, C-2), 67.0 (t, -OCH_2-), 49.9 (t, -$CH_2\underline{CH_2}$N-), 49.0 (s, C-1), 46.1 (s, C-7), 44.6 (d, C-4), 37.7 (t, C-3), 36.2 (q, CH_3N-), 33. 9 (t, C-6), 26.8 (t, C-5), 19.9/19.8 (2 q, C-8/ C-9), 11.7 (q, C-10).

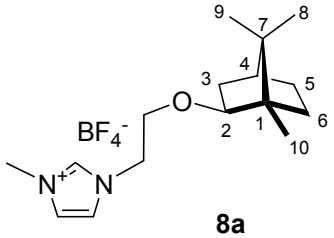
HRMS (NSI+) m/z calcd for $C_{16}H_{27}N_2O$: 263.2117, found: 263.2116.

7.2.8 Microwave-assisted synthesis of 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium chloride 7

1-Chloro-2-isobornyloxyethan **6** (1.08 g, 5 mmol) and freshly distilled *N*-methylimidazole (0.41 g, 5 mmol) were mixed in a microwave vial under nitrogen, sealed, and dissolved in 1 ml of anhydrous ethyl acetate. Irradiation in a CEM Explorer at 150 °C for 30 minutes hold time at 50 W gave **3** as a second layer. Ethyl acetate was decanted and the remaining crystals were washed with anhydrous ether and dried at high vacuum to yield **7** as colourless crystals (1.36 g, 91%).

7.2.9 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium tetrafluoroborat 8a

Preparation from **7** (3.84 g, 12.9 mmol) according to procedure 7.2.3 gave **8a** as yellow solid in 86% yield. An analytical sample was crystallized from anhydrous ethanol.



8a
$C_{16}H_{27}BF_4N_2O$
350.20 g/mol

$[\alpha]_{365}^{20}$ = -1.69 ($CHCl_3$, c = 1.01).

mp 46-48 °C (from EtOH).

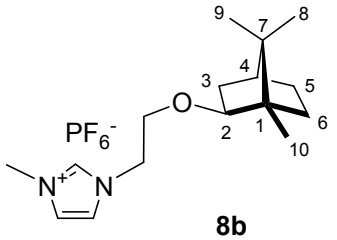
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 8.63 (s, 1H, -NCHN-), 7.36 (m, 2H, -NCHCHN-), 4.29 (m, 2H, -$O\underline{CH_2}CH_2$N), 3.89 (s, 3H, CH_3N-), 3.74/3.52 (2ddd, J_1 = 10.71 Hz/10.56 Hz, J_2 = 6.01 Hz/6.46 Hz, J_3 = 3.47/3.71 Hz, 2H, -$OCH_2\underline{CH_2}$N), 3.18 (m, 1H, H-2_{endo}), 1.63-1.37 (m, 5H, H-4, H-3_{exo}, H-5_{exo}, H-3_{endo}, H-6_{exo}), 0.99-0.85 (m, 5H) 0.80 (s, H-10), 0.75 (s, 3H, H-8), 0.74 (s, 3H, H-9).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 136.6 (d, -NCHN-), 123.1/123.0 (2d, -NCHCHN-), 87.7 (d, C-2), 66.6 (t, -OCH_2-), 50.2 (t, -$CH_2\underline{CH_2}$N-), 49.2 (s, C-1), 46.3 (s, C-7), 44.8 (d, C-4), 37.9 (t, C-3), 36.1 (q, CH_3N-), 34.1 (t, C-6), 27.0 (t, C-5), 20.0/19.9 (2q, C-8/C-9), 11.8 (q, C-10).

Anal. Calcd. for $C_{16}H_{27}BF_4N_2O$: C, 54.88; H, 7.77; N, 8.00. Found: C, 55.02; H, 7.51; N, 8.08.

7.2.10 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium hexafluorophosphat 8b

Preparation from **7** (0.64 g, 2.14 mmol) according to procedure 7.2.4 gave **8b** as colourless viscous oil in 94% yield.



8b
$C_{16}H_{27}F_6N_2OP$
408.36 g/mol

$[\alpha]_{365}^{20}$ = -0.3 ($CHCl_3$, c = 1.05).

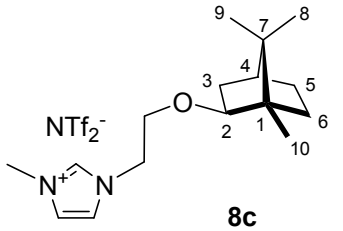
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 8.35 (s, 1H, -NCHN-), 7.28 (m, 2H, -NCHCHN-), 4.22 (m, 2H, -O$\underline{CH_2}CH_2$N), 3.82 (s, 3H, CH_3N-) 3.69/3.47 (2m, 2H, -$OCH_2\underline{CH_2}$N), 3.15 (m, 1H, H-2_{endo}), 1.61-1.29 (m, 5H, H-4, H-3_{exo}, H-5_{exo}, H-3_{endo}, H-6_{exo}), 0.97-0.83 (m, 5H) 0.78 (s, H-10), 0.72 (s, 3H, H-8), 0.71 (s, 3H, H-9).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 136.2 (d, -NCHN-), 123.0/123.0 (2d, -NCHCHN-), 87.7 (d, C-2), 66.4 (t, -OCH_2-), 50.2 (t, -$CH_2\underline{CH_2}$N-), 49.2 (s, C-1), 46.3 (s, C-7), 44.8 (d, C-4), 37.8 (t, C-3), 36.0 (q, CH_3N-), 34.1 (t, C-6), 27.0 (t, C-5), 20.0/19.9 (2q, C-8/ C-9), 11.7 (q, C-10).

Anal. Calcd. for $C_{16}H_{27}F_6N_2OP$: C, 47.06; H, 6.66; N, 6.86 Found: C, 47.15; H, 6.39; N, 6.96.

7.2.11 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium bis(trifluoromethanesulfonyl)imide 8c

Preparation from **7** (2.93 g, 9.8 mmol) according to procedure 7.2.5 gave **8c** as colourless liquid in 95% yield.



8c
$C_{18}H_{27}F_6N_3O_5S_2$
543.54 g/mol

$[\alpha]_{365}^{20}$ = -1.1 ($CHCl_3$, c = 1.05).

mp -54 °C.

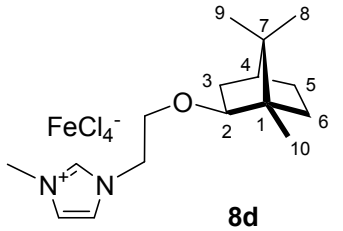
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H = 8.62 (s, 1H, -NCHN-), 7.36/7.29 (2m, 2H, -NCHCHN-), 4.30 (m, 4H, -O$\underline{CH_2}CH_2$N), 3.90 (s, 3H, CH_3N-), 3.75/3.53 (2ddd, J_1 = 10.66 Hz/10.51 Hz, J_2 = 5.96 Hz/6.41 Hz, J_3 = 3.42 Hz/3.86 Hz, 2H, -OCH$_2\underline{CH_2}$N), 3.20 (m, 1H, H-2$_{endo}$), 1.67-1.41 (m, 5H, H-4, H-3$_{exo}$, H-5$_{exo}$, H-3$_{endo}$, H-6$_{exo}$), 1.03-0.88 (m, 2H, H-5$_{endo}$, H-6$_{endo}$), 0.83 (s, H-10), 0.78 (s, 6H, H-8 and H-9).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 136.3 (d, -NCHN-), 123.2/123.1 (2d, -NCHCHN-), 119.7 (q, J = 321.19 Hz, CF_3), 87.9 (d, C-2), 66.5 (t, -OCH$_2$-), 50.3 (t, -CH$_2\underline{CH_2}$N-), 49.3 (s, C-1), 46.3 (s, C-7), 44.8 (d, C-4), 37.8 (t, C-3), 36.2 (q, CH_3N-), 34.1 (t, C-6), 27.0 (t, C-5), 20.0/19.9 (2q, C-8/C-9), 11.7 (q, C-10).

Anal. Calcd. for $C_{18}H_{27}F_6N_3O_5S_2$: C, 39.78; H, 5.01; N, 7.73. Found: C, 39.81; H, 4.75; N, 7.80.

7.2.12 1-Methyl-3-[(1*S*, 2-*exo*)-2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethyl]imidazolium tetrachloroferrate 8d

A mixture of **7** (2.59 g, 8.7 mmol) and $FeCl_3 \cdot 6\ H_2O$ (2.34 g, 8.7 mmol) was stirred for five minutes at room temperature. Almost immediately a dark coloured ionic liquid layer and an upper aqueous layer was formed. The aqueous layer was decanted and the remaining ionic liquid was dried for 24 hours at 100 °C at high vacuum under stirring to give **8d** as dark-yellow liquid (3.71 g, 93%).



8d
$C_{16}H_{27}Cl_4FeN_2O$
461.06 g/mol

$[\alpha]_{365}^{20}$ = +9885.1 (CH_2Cl_2, c = 0.015).

mp -44.9 °C.

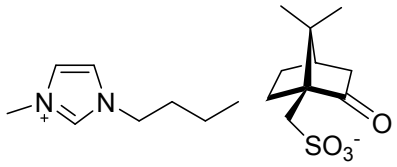
IR(ATR) = 3153, 3111, 2950, 2874, 1568, 1450, 1370, 1165, 1115, 1096, 830, 741, 695 cm^{-1}.

UV-VIS: λ_{max}= 746.5, 691.5, 532.5, 458.8, 364.5, 314.5, 243.0 cm^{-1}.

Anal. Calcd. for $C_{16}H_{27}Cl_4FeN_2O$: C, 41.68; H, 5.90; N, 6.08. Found: C, 41.98; H, 5.61; N, 6.17.

7.2.13 1-Butyl-3-methylimidazolium (1*S*)-camphorsulfonate 14

Potassium (1*S*)-(-)-camphorsulfonate **13** (2.00 g, 7.40 mmol) and 1-butyl-3-methylimidazolium chloride **12**[151] were dissolved in 20 ml of H_2O_{dest} and stirred overnight at room temperature. Water was removed under reduced pressure and the remaining residue was dissolved in dichloromethane, dried with $MgSO_4$, filtered and concentrated. The crude product was dissolved in 10 ml of anhydrous acetone, filtered over silica and again concentrated. Remaining volatile materials were removed under high vacuum and 50 °C to yield **14** as yellow viscous liquid in 99% yield.



14
$C_{18}H_{30}N_2O_4S$
370.51 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.79 (s, 1H), 7.90/7.83 (2s, 2H), 4.39 (t, J = 7.34 Hz, 1H), 4.06 (s, 3H), 3.18/2.66 (2d, J = 14.67 Hz, 2H), 2.83 (m, 1H), 2.29 (ddd, J_1 = 18.10 Hz, J_2 = 4.21 Hz, J_3 = 3.42 Hz, 1H), 2.05-1.79 (m, 6H), 1.59-1.26 (m, 4H), 1.14 (s, 3H), 0.91 (t, J = 7.24 Hz, 3H), 0.84 (s, 3H).

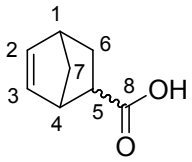
Analytical data were in accordance with literature.[13]

[151] Dupont, J.; Consort, C.; Suarez, P.; de Souza, R. *Org. Synth.* **2003**, *79*, 236.

7.2.14 Application in Diels-Alder reaction

General procedure for the Diels-Alder reaction in chiral ionic liquids

Freshly distilled acrylic acid **9** (144 mg, 2 mmol) and the CIL (1 g) were stirred at room temperature or 0 °C, resp. until a homogenous phase was obtained. Freshly monomerized cyclopentadiene **10** (397 mg, 6 mmol) was added and the reaction mixture was stirred at the indicated temperature for 90 minutes. The CIL phase was extracted 3 times with 5 ml diethyl ether each and the combined ethereal layers were back-extracted with a saturated solution of $NaHCO_3$. The aqueous layer was carefully acidified with concentrated HCl and extracted again with diethyl ether. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Remaining volatile materials were removed under high vacuum to yield norbornene carbonic acid **11** as colourless liquid in spectroscopic pure form.



11
$C_8H_{10}O_2$
138.16 g/mol

GC/EI-MS:

t_{R1} = 10.27 min (*exo*)

t_{R2} = 10.55 min (*endo*)

m/z = 138.03 (M^+, 3), 93.10 (2), 91.01 (6), 77.00 (5), 67.17 (4), 65.94 (100).

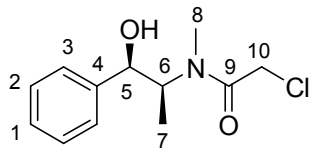
Analytical data were in accordance with literature values.[152]

[152] Arehart, S. V.; Pugh, C. *J. Am. Chem. Soc.* **1997**, *119*, 3027.

7.3 Synthesis of chiral ionic liquids bearing an amido alcohol unit

7.3.1 2-Chloro-*N*-[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*-methylacetamide 16

(1*R*,2*S*)-Ephedrine **15** (10.00 g, 60.5 mmol) and triethylamine (6.12 g, 60.5 mmol) were dissolved in 100 ml of anhydrous dichloromethane and cooled to 0 °C. Freshly distilled chloro acetyl chloride (6.83 g, 60.5 mmol) was added dropwise (violent reaction) and the resulting suspension was stirred at room temperature for 3 hours until TLC indicated complete conversion. The white precipitate was filtered and the residual solution was washed once with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over silica (CH_2Cl_2:MeOH 40:1) to yield **16** as colourless crystals in 83% yield.



16
$C_{12}H_{16}ClNO_2$
241.71 g/mol

R_f = 0.53 (CH_2Cl_2:MeOH 20:1).

$[\alpha]_{365}^{20}$ = +30.29 (EtOH, c = 1.09).

mp 75-76 °C.

Major rotamere:

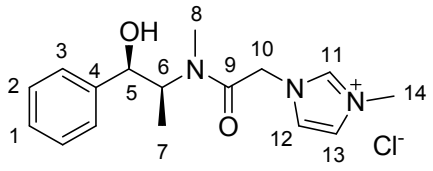
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 7.32 (m, 5H, H-arom.), 4.85 (m, 1H, H-5), 4.46 (m, 1H, H-6), 3.97 (s, 2H, H-10), 3.50 (s, 1H, OH), 2.84 (s, 3H, H-8), 1.18 (d, J = 7.04 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 167.2 (s, C-9), 141.5 (s, C-4), 128.0 (d, C-2), 127.4 (d, C-1), 125.8 (d, C-3), 75.1 (d, C-5), 57.2 (d, C-6), 41.7 (t, C-10), 32.4 (q, C-8), 11.3 (q, C-7).

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.81; H, 6.80; N, 5.80.

7.3.2 1-[[[(1*S*,2*R*)-(2-Hydroxy-1-methyl-2-phenylethyl)-methylamino]carbonyl]methyl]-3-methylimidazolium chloride 17

A mixture of **16** (5.84 g, 24.2 mmol) and freshly distilled *N*-methylimidazole (1.98 g, 24.2 mmol) were mixed in a round bottom flask and stirred for 30 minutes at 80 °C. Remaining volatile materials were removed under reduced pressure and 80 °C to yield **17** as glass-like solid in quantitative yield. Crystallization of an analytical sample from anhydrous acetonitrile gave colourless crystals.



17

$C_{16}H_{22}ClN_3O_2$

323.82 g/mol

$[\alpha]_{589}^{20}$ = -6.05 (EtOH, c = 1.01).

mp 143-146 °C (from acetonitrile).

Major rotamere:

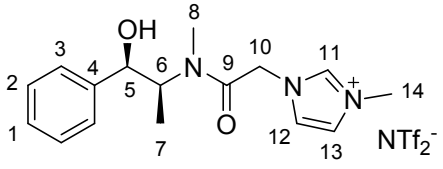
^{1}H-NMR (200 MHz, d_6-DMSO): δ_H = 9.17 (s, 1H, H-11), 7.76/7.62 (2s, 2H, H-12/H-13), 7.51-7.25 (m, 5H, H-arom.), 5.71 (m, 1H, H-5), 5.33 (s, 2H, H-10), 4.76 (m, 1H, H-6), 3.95 (s, 1H, OH), 3.05 (s, 3H, H-8), 1.08 (d, J = 7.04 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, d_6-DMSO): δ_C = 165.2 (s, C-9), 143.5 (s, C-4), 137.8 (d, C-11), 127.9 (d, C-2), 126.5 (d, C-1), 125.8 (d, C-3), 123.8/122.8 (2d, C-12/C-13), 73.6 (d, C-5), 55.3 (d, C-6), 50.4 (t, C-10), 35.8 (q, C-14), 30.2 (q, C-8), 11.0 (q, C-7).

Anal. Calcd. for $C_{16}H_{22}ClN_3O_2$: C, 59.35; H, 6.85; N, 12.98. Found: C, 59.09; H, 7.05; N, 12.81.

7.3.3 1-[[[(1*S*,2*R*)-(2-Hydroxy-1-methyl-2-phenylethyl)-ethylamino)carbonyl]methyl]-3-methylimidazolium bis(trifluoromethansulfonyl)imide 18

A solution of $LiN(Tf)_2$ (0.94 g, 3.27 mmol) in 3 ml of H_2O_{dest} was added dropwise to a solution of **17** (1.01 g, 3.11 mmol) in 5 ml of H_2O_{dest} and stirred for 30 minutes at room temperature. Water was decanted and the resulting second layer was washed 3 times with 2 ml H_2O_{dest} each until no more chloride ions could be detected in the washings (checked by $AgNO_3$). Drying for 24 hours at 80 °C and 0.01 Torr gave **18** as light yellow liquid in 98% yield.



18

$C_{18}H_{22}F_6N_4O_6S_2$

568.51 g/mol

$[\alpha]_{589}^{20}$ = -5.14 (EtOH, c = 1.48).

Major rotamere:

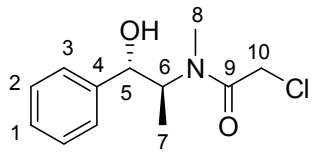
^{1}H-NMR (200 MHz, d_6-DMSO): δ_H = 8.97 (s, 1H, H-11), 7.70 (s, 1H, H-12), 7.51-7.24 (m, 6H, H-arom. + H-13), 5.57 (d, *J* = 4.70 Hz, H-5), 5.20 (2, 2H, H-10), 4.72 (m, 1H, H-6), 3.93 (s, 1H, OH), 2.99 (s, 3H, H-8), 1.13 (d, J = 7.04 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, DMSO): δ_C = 163.9(s, C-9), 142.6 (s, C-4), 137.3 (d, C-11), 127.2 (d, C-2), 126.4 (d, C-1), 125.6 (d, C-3), 123.2/122.6 (2d, C-12/C-13), 119.1 (q, J = 323.07 Hz, CF_3-), 74.0 (d, C-5), 56.0(d, C-6), 49.6 (t, C-10), 35.2 (q, C-14), 29.2 (q, C-8), 12.1 (q, C-7).

Anal. Calcd. for $C_{18}H_{27}F_6N_4O_6S_2$: C, 38.03; H, 3.90; N, 9.85. Found: C, 38.00; H, 3.80; N, 9.67.

7.3.4 2-Chloro-*N*-[(1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*-methylacetamide 20

Preparation from **19** (5.00 g, 30.3 mmol) according to procedure 7.3.1 gave **20** as colourless crystals in 95% yield.



20
$C_{12}H_{16}ClNO_2$
241.71 g/mol

R_f = 0.50 (CH_2Cl_2:MeOH 30:1).

$[\alpha]_{589}^{20}$ = + 85.79 (EtOH, c = 1.07).

mp 75-78 °C.

Major rotamere:

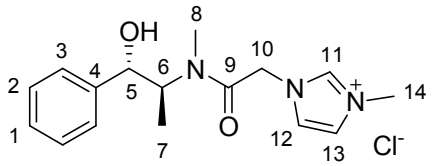
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 7.33 (m, 5H, H-1, H-2, H-3) 4.55 (m, 1H, H-5), 4.08-3.89 (m, 3H, H-6 and H-10a,b), 3.56 (s, 1H, OH), 2.90 (s, 3H, H-8), 1.02 (d, J = 3.72 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 168.1 (s, C-9), 141.5 (s, C-4), 128.4 (d, C-2), 127.9 (d, C-1), 126.6 (d, C-3), 75.7 (d, C-5), 59.1 (d, C-6), 42.0 (t, C-10), 27.4 (q, C-8), 14.0 (q, C-7).

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.83; H, 6.79; N, 5.80.

7.3.5 1-[[[(1*S*,2*S*)-(2-Hydroxy-1-methyl-2-phenylethyl)-methylamino]carbonyl]methyl]-3-methylimidazolium chloride 21

Preparation from **20** (4.16 g, 17.2 mmol) according to procedure 7.3.2 gave **21** as colourless glass in >99% yield. An analytical sample was crystallized from anhydrous acetonitrile.



21
$C_{16}H_{22}ClN_3O_2$
323.82 g/mol

$[\alpha]_{589}^{20}$ = +92.61 (EtOH, c = 1.00).

mp 87-91 °C (from acetonitrile).

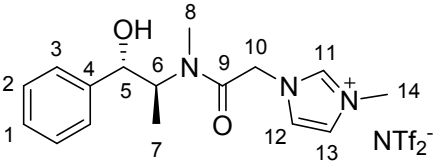
Major rotamere:

^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ_H = 9.37 (s, 1H, H-11), 7.67/7.41 (2s, 2H, H-12/H-13), 7.27 (m, 5H, H-1, H-2, H-3), 5.67/5.34 (2d, J = 16.24 Hz, 2H, H-10), 5.32 (m, 1H, H-5), 4.53 (m, 2H, H-6 and OH), 3.68 (s, 3H, H-14), 3.01 (s, 3H, H-8), 0.74 (d, J = 6.46 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, d_6-DMSO, TMS): δ_C = 166.2 (s, C-9), 141.3 (s, C-4), 137.8 (d, C-11), 128.2 (d, C-2), 127.6 (d, C-1), 127.0 (d, C-3), 124.4/122.1 (2d, C-12/C-13), 74.2 (d, C-5), 58.0 (d, C-6), 51.4 (t, C-10), 35.9 (C-4), 27.3 (q, C-8), 14.2 (q, C-7).

7.3.6 1-[[[(1*S*,2*S*)-(2-Hydroxy-1-methyl-2-phenylethyl)-methylamino]carbonyl]methyl]-3-methylimidazolium bis(trifluoromethansulfonyl) imide 22

Preparation from **121** (3.59 g, 11.0 mmol) according to procedure 7.3.3 gave **22** as colourless crystals in 98% yield.



22
$C_{18}H_{22}F_6N_4O_6S_2$
568.51 g/mol

$[\alpha]_{589}^{20}$ = + 65.62 (EtOH, c = 1.02).

mp 99-102 °C.

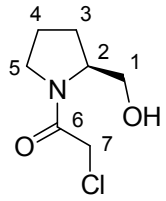
Major rotamere:

^{1}H-NMR (200 MHz, d_6-DMSO): δ_H = 9.08 (s, 1H, H-11), 7.67/7.58 (2s, 2H, H-12/H-13), 7.34 (m, 5H, H-1, H-2, H-3), 5.56/5.28 (2d, J = 16.43 Hz, 2H, H-10a,b), 5.27 (m, 1H, H-5), 4.57 (m, 1H, H-6), 3.90 (s, 3H, H-14), 2.87 (s, 3H, H-8), 0.96 (d, J = 6.65 Hz, 3H, H-7).

^{13}C-NMR (50 MHz, d_6-DMSO): δ_C = 165.7 (s, C-9), 143.0 (s, C-4), 138.1 (d, C-2), 128.2 (d, C-2), 127.7 (d, C-1), 127.2 (d, C-3), 124.0/122.9 (2d, C-12/C-13), 119.6 (q, J = 322.60 Hz, CF_3-), 73.5 (d, C-5), 57.2 (d, C-6), 50.4 (t, C-10), 35.8 (q, C-14), 27.0 (q, C-8), 15.0 (q, C-7).

7.3.7 2-Chloro-1-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethanone 24

Preparation from **23** (3.87 g, 38.3 mmol) according to procedure 7.3.1 gave **24** as colourless liquid in 77% yield.



24
$C_7H_{12}ClNO_2$
177.63 g/mol

R_f = 0.41 (CH_2Cl_2:MeOH 30:1).

$[\alpha]_{589}^{20}$ = -57.85 (EtOH, c = 0.12).

Major rotamere:

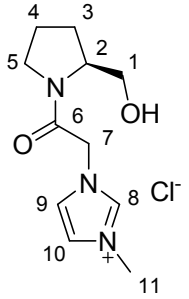
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.50 (m, 2H, H-1a and OH), 4.03 (s, 2H, H-7), 3.66-3.40 (m, 4H, H-5, H-2, H-1b), 2.08-1.60 (m, 4H, H-3, H-4)

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 166.8 (s, C-6), 65.2 (t, C-1), 61.3 (d, C-2), 47.7 (t, C-5), 42.3 (t, C-7), 27.7 (t, C-3), 24.2 (t, C-4).

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.51; H, 6.91; N, 7.36.

7.3.8 1-[[[(2*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]carbonyl]methyl]-3-methylimidazolium chloride 25

Preparation from **24** (1.5 g, 8.4 mmol) according to procedure 7.3.2 gave **25** as colourless glass in 97% yield.



25

$C_{11}H_{18}ClN_3O_2$

259.73 g/mol

$[\alpha]_{589}^{20}$ = -46.51 (EtOH, c = 0.103).

Major rotamere:

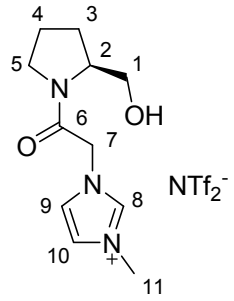
^{1}H-NMR (200 MHz, CD_3OD): δ_H = 9.01 (m, 1H, H-8), 7.64 (m, 2H, H-9,10), 5.80-5.23 (m, 2H, H-7), 4.78 (br s, 1H, OH), 4.35-4.05 (m, 1H, H-1a), 3.99 (s, 3H, H-11), 3.74-3.36 (m, 3 H, H-5, H-2, H-1b), 2.24-1.80 (m, 4H, H-3, H-4).

^{13}C-NMR (50 MHz, CD_3OD): δ_C = 165.7 (s, C-6), 139.4 (d, C-8), 125.3/124.2 (2d, C-9, C-10), 62.7 (t, C-1), 61.3 (d, C-2), 52.0 (t, C-7), 47.8 (t, C-5), 36.6 (q, C-11), 28.0 (t, C-3), 25.0 (t, C-4).

Anal. Calcd. for $C_{11}H_{18}ClN_3O_2 \cdot 1.2\ H_2O$: C, 46.96; H, 7.31; N, 14.93. Found: C, 47.19; H, 7.48; N, 14.43.

7.3.9 1-[[[(2*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]carbonyl]methyl]-3-methylimidazolium bis(trifluoromethansulfonyl)imide 26

Preparation from **25** (2.11 g, 8.15 mmol) according to procedure 7.3.3 gave **26** as colourless oil in >99% yield.



26
$C_{13}H_{18}F_6N_4O_6S_2$
504.42 g/mol

$[\alpha]_{365}^{20}$ = -21.30 (EtOH, c = 0.40).

Major rotamere:

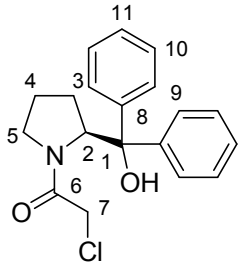
^{1}H-NMR (200 MHz, CD_3OD): δ_H = 8.64 (m, 1H, H-8), 7.24 (m, 2H, H-9, H-10), 4.98 (m, 2H, H-7), 4.41-3.93 (m, 2H, H-1a and OH), 3.84 (s, 3H, H-11), 3.66-3.06 (m, 3H, H-5 and H-1b), 2.17-1.55 (m, 4H, H-3, H-4).

^{13}C-NMR (50 MHz, CD_3OD): δ_C = 164.4 (s, C-6), 137.9 (d, C-8), 124.7/123.0 (2d, C-9, C-10), 120.2 (q, J = 320.95 Hz, CF_3), 65.0 (t, C-1), 62.1 (d, C-2), 51.4 (t, C-7), 47.3 (t, C-5), 36.7 (q, C-11), 27.9 (t, C-3), 24.5 (t, C-4).

Anal. Calcd. for $C_{13}H_{18}F_6N_4O_6S_2$: C, 30.95; H, 3.60; N, 11.11. Found: C, 31.03; H, 3.42; N, 11.00.

7.3.10 2-Chloro-1-[(2*S*)-2-(hydroxydiphenylmethyl)pyrrolidin-1-yl]ethanone 28

Preparation from **27**[153] (3.55 g, 14.0 mmol) according to procedure 7.3.1 gave **28** as colourless oil in 81% yield.



28
$C_{19}H_{20}ClNO_2$
329.82 g/mol

R_f = 0.65 (CH_2Cl_2:MeOH 30:1).

$[\alpha]_{589}^{20}$ = +9.03 (EtOH, c = 1.05).

[153] Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belges* **1988**, *97*, 691.

Major rotamere:

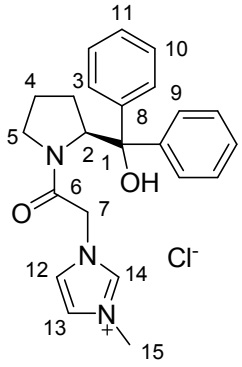
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 7.42-7.10 (m, 12H, H-arom.), 6.14 (s, 1H, OH), 5.10 (dd, J_1 = 8.41 Hz, J_2 = 4.70 Hz, 1H, H-2), 3.90 (s, 2H, H-7), 3.34/2.93 (2m, 2H, H-5), 1.96 (m, 2H, H-3a, H-4a), 1.50 (m, 1H, H-4b), 0.92 (m, 1H, H-3b).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 168.6 (s, C-6), 145.7/142.8 (2s, C-8), 127.8-127.3 (3d, C-9, C-10, C-11), 81.8 (s, C-1), 67.1 (d, C-2), 48.4 (t, C-5), 42.1 (t, C-7), 29.1 (t, C-3), 23.2 (t, C-4).

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.02; H, 6.24; N, 4.09.

7.3.11 1-[[[(2*S*)-2-(Hydroxydiphenylmethyl)pyrrolidin-1-yl]carbonyl]methyl]-3-methylimidazolium chloride 29

Preparation from **28** (2.93 g, 8.9 mmol) according to procedure 7.3.2 gave **29** as colourless glass in 65% yield. Crystallization from anhydrous acetonitrile/ethyl acetate gave colourless crystals.



29
$C_{23}H_{26}ClN_3O_2$
411.92 g/mol

$[\alpha]_{365}^{20}$ = -4.99 (EtOH, c = 1.08)

mp 146-150 °C (from acetonitrile/ethyl acetate).

Major rotamere:

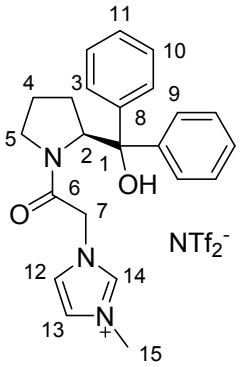
^{1}H-NMR (200 MHz, CD_3OD): δ_H = 8.66 (s, 1H, H-14), 7.60-7.06 (m, 12 H, H-9, H-10, H-11, H-12, H-13), 5.34-4.93 (m, 2H, H-7), 3.86 (s, 3H, H-15), 3.83-3.40 (m, 2H, H-5a and H-2), 3.21 (m, 1H, H-5b), 2.46-1.40 (m, 4H, H-3, H-4).

^{13}C-NMR (50 MHz, CD_3OD): δ_C = 166.8 (s, C-6), 147.0/145.6 (2s, C-8), 139.1 (d, C-14), 129.3-127.9 (3d, C-9, C-10, C-11), 124.8/124.2 (2d, C-12,C-13), 82.6 (s, C-1), 66.3 (d, C-2), 51.6 (t, C-7), 49.1 (t, C-5), 36.5 (q, C-15), 29.8 (t, C-3), 22.6 (t, C-4).

Anal. Calcd. for $C_{23}H_{26}ClN_3O_2 \cdot 0.4\ H_2O$: C, 65.91; H, 6.44; N, 10.03. Found: C, 66.07; H, 6.66; N, 9.94.

7.3.12 1-[[[(2*S*)-2-(hydroxydiphenylmethyl)pyrrolidin-1-yl]carbonyl]methyl]-3-methylimidazolium bis(trifluoromethansulfonyl)imide 30

Preparation from **29** (1.54 g, 3.76 mmol) according to procedure 7.3.3 gave **30** as colourless glass in 99% yield.



30

$C_{25}H_{26}F_6N_4O_6S_2$

656.62 g/mol

$[\alpha]_{365}^{20}$ = +21.42 (EtOH, c = 1.06).

Major rotamere:

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.55 (s, 1H, H-14), 7.45-6.95 (m, 12 H, H-9, H-10, H-11, H-12, H-13), 5.58 (s, 1H, OH), 5.22-4.71 (m, 3H, H-7, H-2), 3.80 (s, 3H, H-15), 3.40/3.10 (2m, 2H, H-5), 3.21 (m, 1H, H-2), 2.43-0.89 (m, 4H, H-3, H-4).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 166.0 (s, C-6), 145.6/142.8 (2s, C-8), 137.1 (d, C-14), 128.4-127.3 (d, C-9, C-10, C-11), 123.94/122.54 (2d, C-12, C-13), 119.4 (q, J = 321.2 Hz, CF_3), 81.5 (s, C-1), 67.5 (d, C-2), 50.6 (t, C-7), 47.3 (t, C-5), 36.5 (q, C-15), 29.8 (t, C-3), 22.6 (t, C-4).

Anal. Calcd. for $C_{25}H_{26}F_6N_4O_6S_2$: C, 45.73; H, 3.99; N, 8.53. Found: C, 45.95; H, 4.07; N, 8.28.

7.3.13 Representative procedure for ^{19}F-NMR-measurements

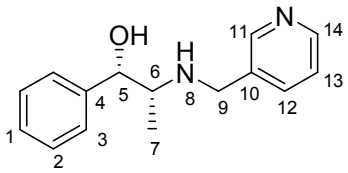
(*rac*)-Potassium methoxy(trifluoromethyl)phenylacetate **31** (12.5 mg; 4.6 mmol) and crown ether 18C6 (12.1 mg, 4.6 mmol) were previously dissolved in 0.5 ml of CD_2Cl_2. Imidazolium salt **18** (80.4 mg, 13.7 mmol) was added and the spectrum was recorded.

^{19}F-NMR (376.5 MHz, CD_2Cl_2): δ_F = -79.5 (s, $(CF_3SO_2)N^-$), -69.8/-69.9 (2s, Mosher's acid CF_3)

7.4 Synthesis of chiral ionic liquids bearing an amino alcohol unit

7.4.1 (1*S*,2*R*)-2-[(Pyridin-3-yl)methylamino]-1-phenylpropan-1-ol 33

Freshly distilled pyridine-3-carboxaldehyde (3.54 g, 33.1 mmol) was added to a mixture of (1*S*, 2*R*)-norephedrine **32** (5.00 g, 33.1 mmol) and activated molecular sieve 3 Å (10 g) in 100 ml of anhydrous methanol and refluxed for 14 hours. Sodium borohydride (1.25 g, 33.1 mmol) was added in small portions and the mixture was stirred at room temperature until TLC indicated complete conversion. The reaction mixture was filtered over silica and hydrolyzed with H_2O_{dest}. Methanol was removed under reduced pressure to give crude product **33**, which was further purified via VFC (200g silica, CH_2Cl_2:MeOH 40:1 + Et_3N) to yield **33** as light yellow oil in 71% yield.



33
$C_{15}H_{18}N_2O$
242.32 g/mol

R_f = 0.29 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = -13.3 (EtOH, c = 1.00).

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.20 (m, 2H, H-11, H-14), 7.38 (d, J = 7.83 Hz, 1H, H-12), 7.06 (m, 6H, H-1, H-2, H-3, H-13), 4.50 (d, 1H, J = 3.91 Hz, H-5), 3.62/3.54 (2d, J = 16. 39 Hz, 2H, H-9a,b), 2.70 (dq, J_1 = 6.36 Hz, J_2 = 4.25 Hz, 1H, H-6), 0.68 (d, 3H, J = 6.46 Hz, H-7).

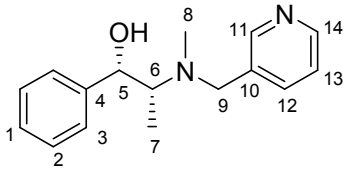
^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 149.2 (d, C-11), 148.2 (d, C-14), 141.5 (s, C-4), 135.7 (d, C-12), 135.4 (s, C-10),128.0 (d, C-2), 127.0 (d, C-1), 126.1 (d, C-3), 123.4 (d, C-13), 73.7 (d, C-5), 57.7 (d, C-6), 48.3 (t, C-9), 14.6 (q, C-7).

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot 0.1\ H_2O$: C, 73.80; H, 7.51; N, 11.48. Found: C, 73.76; H, 7.30; N, 11.45.

7.4.2 (1*S*,2*R*)-2-[Methyl[(pyridin-3-yl)methyl]amino]-1-phenylpropan-1-ol 34

Cmp. **33** (4.30 g, 17.74 mmol) was dissolved in 30 ml of concentrated formic acid and stirred for 30 minutes. Formaldehyde (25 ml, 37% solution in H_2O) was added and the mixture was refluxed overnight. Remaining formaldehyde was removed under reduced pressure, a 4 M NaOH solution in H_2O was added until pH>7 and the reaction mixture was extracted with CH_2Cl_2. The organic layers

were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to yield crude **34**. Crystallization from *n*-hexane/ethyl acetate gave **34** as colourless crystals in 89% yield.



34
$C_{16}H_{20}N_2O$
256.34 g/mol

R_f = 0.24 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = -10.5 (EtOH, c = 1.08).

mp 106-108 °C (from *n*-hexane/ethyl acetate).

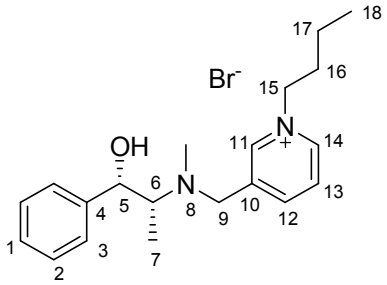
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.43 (dd, J_1 = 4.79 Hz, J_2 = 1.47 Hz, 1H, H-14), 8.35 (d, J = 1.96 Hz, 1H, H-11), 7.43 (d, J = 7.83 Hz, 1H, H-12), 7.32 (m, 5H, H-1, H-2, H-3,), 7.17 (dd, J_1 = 7.83 Hz, J_2 = 4.89 Hz, 1H, H-14), 4.83 (d, 1H, J = 5.48 Hz, H-5), 3.67 (br s, 1H, OH), 3.59 (s, 2H, H-9a,b), 2.92 (m, 1H, H-6), 2.19 (s, 3H, H-8), 1.08 (d, 3H, J = 6.85, H-7).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 149.6 (d, C-11), 148.0 (d, C-14), 143.3(s, C-4), 136.2 (d, C-12), 135.0 (s, C-10), 127.9 (d, C-2), 126.9(d, C-1), 126.2 (d, C-3), 123.2 (d, C-13), 74.4 (d, C-5), 63.6 (d, C-6), 55.9 (t, C-9), 38.1 (q, C-8), 14.6 (q, C-7).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.90; H, 7.86; N, 10.83.

7.4.3 1-Butyl-3-[[methyl-(1*R*,2*S*)-[(2-hydroxy-1-methyl-2-phenyl)ethyl]amino]methyl]pyridinium bromide 35

Cmp. **34** (0.769 g, 3.00 mmol) and freshly distilled *n*-butylbromide (0.615 g, 4.5 mmol) were mixed in a round-bottom flask, sealed, and stirred at 60 °C for 24 hours. Excess *n*-butylbromide was evaporated and the brown oil was washed twice with anhydrous ethyl acetate. Remaining volatile materials were removed under reduced pressure at 60 °C to yield pyridinium bromide **35** as viscous brown oil in quantitative yield.



33
$C_{20}H_{29}BrN_2O$
2393.36 g/mol

$[\alpha]_{589}^{20}$ = -2.2 (EtOH, c = 1.00).

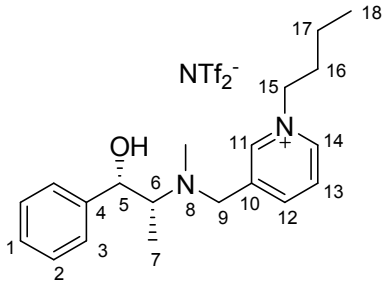
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.28 (d, J = 5.87 Hz, 1H, H-14), 8.86 (s, J = 1.96 Hz, 1H, H-11), 8.07 (d, J = 7.83 Hz, 1H, H-12), 7.89 (dd, J_1 = 7.53 Hz, J_2 = 6.36 Hz, 1H, H-13), 7.34 (m, 5H, H-1, H-2, H-3), 4.98 (d, 1H, J = 5.28 Hz, H-5), 4.75 (t, J = 7.63 Hz, 2H, H-15), 4.26 (br s, 1H, OH), 4.13/3.74 (2d, J = 15.45 Hz/J = 15.26 Hz, 2H, H-9a,b), 2.98 (m, 1H, H-6), 2.26 (s, 3H, H-8), 1.94 (quin, J = 7.73 Hz, 1H, H-16), 1.38 (sext, J = 7.73 Hz, 2H, H-17), 1.16 (d, 3H, J = 6.85 Hz, H-7), 0.98 (t, J = 7.24 Hz, 3H, H-18).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 144.4/144.2 (2d, C-11, C-14), 144.1 (s, C-10), 143.1 (d, C-12), 142.5 (s, C-4), 128.0 (d, C-2), 127.7 (d, C-1), 126.9 (d, C-13), 126.6 (d, C-3), 75.3 (d, C-5), 64.6 (d, C-6), 61.4 (t, C-15), 54.4 (t, C-9), 39.0 (q, C-8), 33.7 (t, C-16), 19.3 (t, C-17), 13.5 (q, C-7), 8.9 (t, C-18).

Anal. Calcd. for $C_{20}H_{29}BrN_2O \cdot 0.1\ H_2O$: C, 59.43; H, 7.53; N, 6.93. Found: C, 59.45; H, 7.24; N, 6.82.

7.4.4 1-Butyl-3-[[methyl-(1*R*,2*S*)-[(2-hydroxy-1-methyl-2-phenyl)ethyl]amino]methyl]pyridinium bis(trifluoromethansulfonyl)imide 36

Cmp. **35** (1.17 g, 2.98 mmol) was dissolved in 3 ml of distilled water and a solution of $Li[N(CF_3SO_2)_2]$ (0.86 g, 3.00 mmol) in 2 ml H_2O_{dest} was added dropwise under stirring. A second phase separated immediately. After 15 minutes, the biphasic system was extracted with CH_2Cl_2. The combined organic layers were washed with small portions of water until no more halide-ions could be detected in the washings (checked by addition of an aqueous solution of $AgNO_3$), dried with Na_2SO_4 and concentrated under reduced pressure. Remaining volatile materials were removed under high-vacuum to yield **36** as brown viscous liquid in 86% yield.



36
$C_{22}H_{29}F_6N_3O_5S_2$
593.60 g/mol

$[\alpha]_{589}^{20}$ = -14.48 (EtOH, c = 1.03).

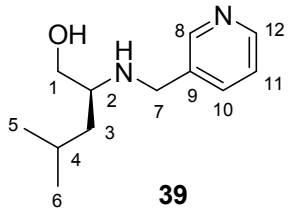
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.49 (d, J = 5.87 Hz, 1H, H-14), 7.90 (m, 2H, H-11, H-13), 7.71 (dd, J_1 = 7.53 Hz, J_2 = 6.36 Hz, 1H, H-13), 7.30 (m, 5H, H-1, H-2, H-3), 4.62 (d, 1H, J = 7.43 Hz, H-5), 4.29 (t, J = 7.63 Hz, 2H, H-15), 3.79/3.77 (2d, J = 15.85 Hz, 2H, H-9a,b), 2.90 (m, 1H, H-6), 2.67 (br s, 1H, OH), 2.15 (s, 3H, H-8), 1.79 (quin, J = 7.83 Hz, 1H, H-16), 1.28 (sext, J = 7.83 Hz, 2H, H-17), 1.17 (d, 3H, J = 6.65, H-7), 0.93 (t, J = 7.34 Hz, 3H, H-18).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 144.7/142.9 (2d, C-11, C-14), 143.8/143.1 (2s, C-10, C-4), 142.3 (d, C-12), 128.3 (d, C-2), 127.7/127.4 (2d, C-1, C-13), 126.7 (d, C-3), 119.5 (q, J = 321.31 Hz, CF_3), 76.0 (d, C-5), 64.3 (d, C-6), 61.9 (t, C-15), 54.7 (t, C-9), 37.6 (q, C-8), 33.2 (t, C-16), 19.1, (t, C-17), 13.2 (q, C-7), 9.4 (t, C-18).

Anal. Calcd. for $C_{22}H_{29}F_6N_3O_5S_2$: C, 44.51; H, 4.92; N, 7.08. Found: C, 44.28; H, 4.75; N, 6.98.

7.4.5 (2*S*)-2-[(Pyridin-3-yl)methylamino]-4-methylpentan-1-ol 39

Preparation from **38** (8.38 g, 71.5 mmol) according to procedure 7.4.1 gave **39** as colourless liquid in 65% yield.



39
$C_{12}H_{20}N_2O$
208.3 g/mol

R_f = 0.17 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = +14.77 (EtOH, c = 1.02).

mp 40-42 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.54 (d, J = 1.96 Hz, 1H, H-8), 8.49 (dd, J_1 = 4.89 Hz, J_2 = 1.57 Hz, 1H, H-12), 7.68 (d, J = 7.83 Hz, 1H, H-10), 7.26 (dd, J_1 = 8.12 Hz, J_2 = 4.40 Hz, 1H, H-11),

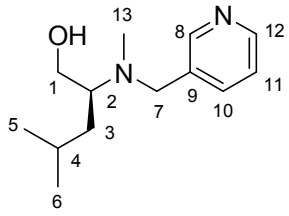
3.85/3.77 (2d, J = 13.30 Hz, 2H, H-7a,b), 3.67/3.31 (2dd, J_1 = 10.86 Hz, J_2 = 3.81 Hz/J_1 = 10.76 Hz, J_2 = 6.30 Hz, 2H, H-1a,b), 2.74 (ddd, J_1 = 13.40 Hz, J_2 = 6.34 Hz, J_3 = 3.91 Hz, 1H, H-2), 2.11 (br s, 2H, OH and NH), 1.62 (m, 1H, H-4), 1.34 (m, 2H, H-3a,b), 0.91/0.88 (2d, 6H, J = 2.93 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 149.2 (d, C-8), 148.1 (d, C-12), 135.8 (d, C-10), 135.7 (s, C-9), 123.3 (d, C-11), 63.1 (t, C-1), 56.3 (d, C-2), 48.1 (t, C-7), 40.8 (t, C-3), 24.7 (d, C-4), 22.8/22.5 (2q, C-5, C-6).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.23; H, 9.59; N, 13.43.

7.4.6 (2*S*)-2-[Methyl[(pyridin-3-yl)methyl]amino]-4-methylpentan-1-ol 40

Preparation from **38** (4.99 g, 24.0 mmol) according to procedure 7.4.2 gave **40** as light yellow oil in 89% yield.



40
$C_{13}H_{22}N_2O$
222.32 g/mol

R_f = 0.33 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = +3.36 (EtOH, c = 1.01).

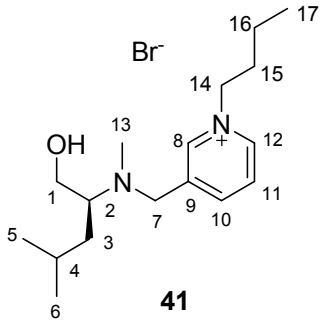
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.50 (m, 2H, H-8, H-12), 7.64 (d, J = 7.83 Hz, 1H, H-10), 7.26 (dd, J_1 = 7.83 Hz, J_2 = 4.30 Hz, 1H, H-11), 3.70/3.50 (2d, J = 13.30 Hz/J = 13.50 Hz, 2H, H-7a,b), 3.41 (m, 3H, H-1a,b and OH), 2.86 (m, 1H, H-2), 2.75 (s, 3H, H-13), 1.45 (m, 2H, H-4), 1.45 (m, 2H, H-3a,b), 1.08 (dq, J_1 = 13.40 Hz, J_2 = 4.56 Hz, 1H, H-4), 0.93/0.60 (2d, 6H, J = 6.65 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 150.0 (d, C-8), 148.5 (d, C-12), 136.3 (d, C-10), 134.6 (s, C-9), 123.3 (d, C-11), 61.7 (d, C-2), 61.1 (t, C-1), 55.1 (t, C-7), 35.5 (q, C-13), 33.8 (t, C-3), 25.1 (d, C-4), 23.5/22.0 (2q, C-5, C-6).

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.08; H, 9.79; N, 12.55.

7.4.7 1-Butyl-3-[[(1*S*)-methyl-(1-hydroxymethyl-3-methyl)propyl-amino]methyl]pyridinium bromide 41

Preparation from **40** (0.67 g, 3 mmol) according to procedure for 7.4.3 gave **41** as yellow oil in 99% yield.



41

$C_{17}H_{31}BrN_2O$

359.34 g/mol

$[\alpha]_{589}^{20}$ = +12.79 (EtOH, c = 0.94).

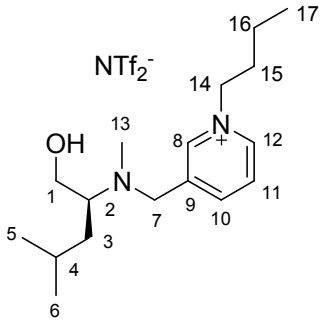
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.38 (s, 1H, H-8), 9.18 (d, J = 5.89 Hz, 1H, H-12), 8.27 (d, J = 8.02 Hz, 1H, H-10), 7.92 (dd, J_1 = 7.63 Hz, J_2 = 6.06 Hz, 1H, H-11), 4.76 (t, J = 7.34 Hz, 3H, H-14), 3.96/3.71 (2d, J = 15.26 Hz, 2H, H-7a,b), 3.39 (m, 3H, H-1a,b and OH), 2.63 (m, 1H, H-2), 2.09 (s, 3H, H-13), 1.84 (quin, J = 7.48 Hz, 2H, H-15), 1.48-1.04 (m, 5 H, H-2, H-3a,b, H-16), 0.75 (t, J = 7.53 Hz, 3H, H-17), 0.90 (m, 1H, H-4), 0.68/0.64 (2d, 6H, J = 6.45 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 144.3 (2d, C-9, C-12), 142.9 (d, C-10), 141.9 (s, C-8), 127.4 (d, C-11), 61.8 (d, C-2), 61.3/61.0 (2t, C-1, C-14), 54.5 (t, C-7), 35.9 (q, C-13), 35.1 (t, C-3), 33.3 (t, C-15), 24.8 (d, C-4), 22.6/22.1 (2q, C-5, C-6), 18.8 (t, C-16), 13.1 (t, C-17).

Anal. Calcd. for $C_{17}H_{31}BrN_2O \cdot 0.3\ H_2O$: C, 55.98; H, 8.73; N, 7.68. Found: C, 55.90; H, 8.47; N, 7.56.

7.4.8 1-Butyl-3-[[(1*S*)-methyl-(1-hydroxymethyl-3-methyl)propyl-amino]methyl]pyridinium bis(trifluoromethansulfonyl)imide 42

Preparation from **41** (0.85 g, 2.36 mmol) according to procedure 7.4.4 gave **42** as light yellow oil in 92% yield.



42
$C_{19}H_{31}F_6N_3O_5S_2$
559.16 g/mol

$[\alpha]_{365}^{20}$ = +7.23 (EtOH, c = 0.97).

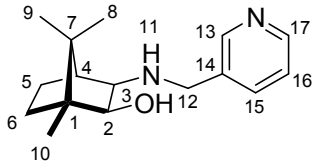
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.80 (s, 1H, H-8), 8.66 (d, J = 6.06 Hz, 1H, H-12), 8.42 (d, J = 8.02 Hz, 1H, H-10), 7.96 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, H-11), 4.57 (t, J = 7.63 Hz, 3H, H-14), 4.03/3.87 (2d, J = 15.26 Hz, 2H, H-7a,b), 3.56 (m, 2H, H-1a,b), 2.83 (m, 2H, H-2 and OH), 2.27 (s, 3H, H-13), 1.97 (quin, J = 7.53 Hz, 2H, H-15), 1.68-1.03 (m, 5 H, H-2, H-3a,b, H-16), 0.96 (t, J = 7.14 Hz, 3H, H-17), 0.90 (m, 1H, H-4), 0.91/0.88 (2d, 6H, J = 4.11 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 145.1 (d, C-9), 143.9 (d, C-12), 142.8 (d, C-10), 142.5 (s, C-8), 128.1 (d, C-11), 119.7 (q, J = 321.3 Hz, CF_3), 62.7 (d, C-2), 62.6 (t, C-1), 61.8 (t, C-14), 54.5 (t, C-7), 36.1 (q, C-13), 34.8 (t, C-3), 33.3 (t, C-15), 25.3 (d, C-4), 23.1/22.2 (2q, C-5, C-6), 19.2 (t, C-16), 13.1 (t, C-17).

Anal. Calcd. for $C_{19}H_{31}F_6N_3O_5S_2$: C, 40.78; H, 5.58; N, 7.51. Found: C, 40.59; H, 5.29; N, 7.26.

7.4.9 (1*S*, 2-*exo*, 3-*exo*)-3-[[(Pyridin-3-yl)methyl]amino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 43

Preparation from **42** (6.49 g, 38.3 mmol) according to procedure 7.4.1 gave **44** as colourless solid 80% yield. Crystallization from *n*-hexan gave colourless crystals.



44
$C_{16}H_{24}N_2O$
260.37 g/mol

R_f = 0.22 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = +13.9 (EtOH, c = 1.00).

mp 44-47 °C (from *n*-hexane).

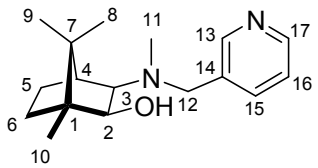
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.54 (m, 2H, H-13, H-17), 7.66 (d, J_1 = 7.83 Hz, 1H, H-15), 7.27 (dd, J_1 = 7.53 Hz, J_2 = 4.99 Hz, 1H, H-16), 4.30 (br s, 1H, OH), 3.86/3.78 (2dd, J_1 = 13.50 Hz, 2H, H-12), 3.43 (d, J = 7.24 Hz, 1H, H-2), 2.79 (d, J = 7.24 Hz, 1H, H-3), 1.79-1.16 (m, 3H, H-4, H-6_{exo}, H-5_{exo}), 1.04 (s, 3H, H-10), 0.99 (m, 2H, H-5_{endo}, H-6_{endo}), 0.94/0.77 (2s, 6H, H-8 and H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 149.4 (d, C-13), 148.6 (d, C-17), 135.6 (d, C-15), 135.0 (s, C-14), 123.4 (d, C-16), 78.6 (d, C-2), 65.6 (d, C-4), 51.8 (t, C-12), 51.4 (d, C-3), 48.7 (s, C-1), 46.5 (s, C-7), 32.7 (q, C-6), 27.0 (t, C-5), 21.8/21.2 (2q, C-8/C-9), 11.2 (q, C-10).

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.67; H, 9.15; N, 10.70.

7.4.10 (1*S*, 2-*exo*, 3-*exo*)-3-[Methyl[(pyridin-3-yl)methyl]amino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 45

Preparation from **44** (2.75 g, 10.6 mmol) according to procedure 7.4.2 gave **45** as light yellow oil in 82% yield.



45
$C_{17}H_{26}N_2O$
274.41 g/mol

R_f = 0.38 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = -3.76 (EtOH, c = 1.14).

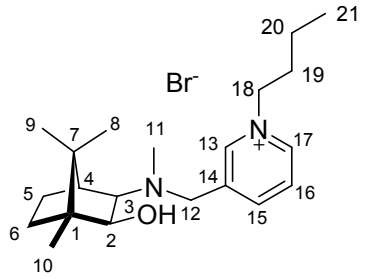
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.44 (m, 2H, H-13, H-17), 7.57 (d, J_1 = 7.83 Hz, 1H, H-15), 7.22 (dd, J_1 = 7.73 Hz, J_2 = 4.79 Hz, 1H, H-16), 4.13 (br s, 1H, OH), 3.43 (m, 3H, H-12a,b, H-2), 2.49 (d, J = 7.04 Hz, 1H, H-3), 2.07 (m, 4H, H-11, H-4), 1.69/1.39 (2m, 2H, H-6_{exo},H-5_{exo}), 1.05 (s, 3H, H-10), 0.96 (m, 2H, H-5_{endo}, H-6_{endo}), 0.92/0.72 (2s, 6H, H-8 and H-9).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 150.4 (d, C-13), 148.9 (d, C-17), 136.5(d, C-15), 133.9 (s, C-14), 123.5 (d, C-16), 79.2 (d, C-2), 73.5 (d, C-3), 59.2 (br t, C-12), 49.4 (d, C-1), 46.9 (s, C-7), 46.7 (d, C-4), 40.5 (br q, C-11), 32.3 (t, C-6), 28.0 (t, C-5), 22.1/21.2 (2q, C-8/C-9), 11.6 (q, C-10).

Anal. Calcd. for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.19; H, 9.58; N, 10.58.

7.4.11 1-Butyl-[[[[(1*S*, 2-*exo*, 3-*exo*)-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl]amino]methyl]pyridinium bromide 46

Preparation from **45** (2.91 g, 10.6 mmol) according to procedure 7.4.3 gave **46** as light brown solid in 99% yield. Crystallization from acetonitrile/ethyl acetate gave colourless crystals.



46

$C_{21}H_{35}BrN_2O$

411.42 g/mol

$[\alpha]_{589}^{20}$ = -1.75 (EtOH, c = 1.03).

mp 146-149 °C (from acetonitrile/ethyl acetate).

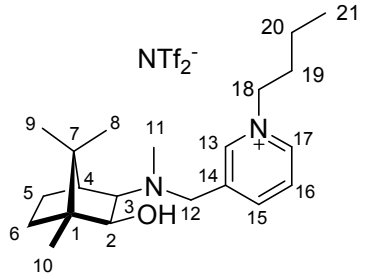
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.54 (s, 1H, H-13), 9.44 (d, J = 6.06 Hz, 1H, H-17), 8.38 (d, J = 7.83 Hz, 1H, H-12), 8.01 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, H-16), 4.92 (t, J = 7.34 Hz, 3H, H-21), 4.07 (d, J = 14.48 Hz, 1H, H-12a), 4.07 (m, 3H, H-12b, H-2 and OH), 2.61 (d, 1H, J = 6.26 Hz, H-3), 2.18 (s, 3H, H-11), 2.15-1.25 (m, 7H, H-4, H-6_{exo},H-5_{exo}, H-19, H-20), 1.13 (s, 3H, H-10), 1.07-0.84 (m, 5H, H-5_{endo}, H-6_{endo}, H-21), 0.92/0.76 (2s, 6H, H-8 and H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 144.5/144.4 (2d, C-13, C-17), 143.2 (d, C-15), 141.2 (s, C-14), 127.7 (d, C-16), 79.4 (d, C-2), 73.3 (s, C-3), 61.2 (t, C-18), 57.7 (t, C-12), 49.1 (d, C-1), 46.6 (s, C-7), 46.3 (d, C-4), 40.7 (q, C-11), 33.3 (t, C-19), 32.2 (t, C-6), 27.2 (t, C-5), 21.4/20.5 (2q, C-8/C-9), 18.9 (t, C-20), 13.2 (q, C-21), 11.6 (q, C-10).

Anal. Calcd. for $C_{21}H_{35}BrN_2O$: C, 61.31; H, 8.57; N, 6.81. Found: C, 61.09; H, 8.81; N, 6.70.

7.4.12 1-Butyl-[[[[(1*S*, 2-*exo*, 3-*exo*)-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl]amino]methyl]pyridinium bis(trifluoromethansulfonyl)imide 47

Cmp. **46** (0.70 g, 1.70 mmol) was dissolved in 2 ml of H_2O_{dest} and 4 ml of acetonitrile and a solution of $Li[N(CF_3SO_2)_2]$ (0.51 g, 1.79 mmol) in 2 ml H_2O_{dest} was added dropwise. The reaction mixture was stirred for 30 minutes at room temperature and acetonitrile was removed under reduced pressure. The biphasic system was extracted with CH_2Cl_2. The combined organic layers were washed with small portions of H_2O_{dest} until no more halide-ions could be detected in the washings (checked by addition of an aqueous solution of $AgNO_3$), dried with Na_2SO_4 and concentrated under reduced pressure. Remaining volatile materials were removed under high-vacuum to yield **47** as light yellow viscous liquid in 93% yield.



47

$C_{23}H_{35}F_6N_3O_5S_2$

611.66 g/mol

$[\alpha]_{589}^{20}$ = +2.06 (EtOH, c = 0.97).

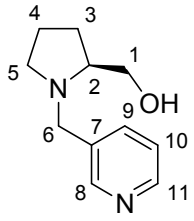
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.74 (s, 1H, H-13), 8.67 (d, J = 6.06 Hz, 1H, H-17), 8.41 (d, J = 8.02 Hz, 1H, H-12), 7.96 (dd, J_1 = 7.92 Hz, J_2 = 6.16 Hz, 1H, H-16), 4.58 (t, J = 7.53 Hz, 3H, H-21), 4.02 (d, J = 14.48 Hz, 1H, H-12a), 3.62 (d, J = 7.04 Hz, 1H, H-2), 3.60 (d, J = 14.67 Hz, 1H, H-12b), 3.20 (br s, 1H, OH), 2.66 (d, 1H, J = 6.84 Hz, H-3), 2.21 (s, 3H, H-11), 2.14-1.15 (m, 7H, H-4, H-6_{exo}, H-5_{exo}, H-19, H-20), 1.16 (s, 3H, H-10), 1.02-0.85 (m, 5H, H-5_{endo}, H-6_{endo}, H-21), 0.96/0.78 (2s, 6H, H-8 and H-9).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 145.2/144.0 (2d, C-13, C-17), 142.9 (d, C-15), 141.8 (s, C-14), 128.1 (d, C-16), 119.5 (q, J = 321.4 Hz, CF_3), 79.9 (d, C-2), 73.7 (s, C-3), 62.2 (t, C-18), 58.0 (t, C-12), 49.5 (d, C-1), 46.9 (s, C-7), 46.6 (d, C-4), 40.7 (q, C-11), 33.2 (t, C-19), 32.3 (t, C-6), 27.5 (t, C-5), 21.7/20.7 (2q, C-8/C-9), 19.1 (t, C-20), 13.1 (q, C-21), 11.3 (q, C-10).

Anal. Calcd. for $C_{23}H_{35}F_6N_3O_5S_2$: C, 45.16; H, 5.77; N, 6.87. Found: C, 45.13; H, 5.54; N, 6.92.

7.4.13 (2*S*)-1-[(Pyridin-3-yl)methyl]pyrrolidin-2-yl]methanol 48

(*S*)-Prolinol **23** (6.56 g, 64.9 mmol) and freshly distilled pyridine-3-carbaldehyde (6.95 g, 64.9 mmol) were dissolved in 100 ml of anhydrous acetonitrile and stirred at room temperature for 12 hours. The solvent was removed under reduced pressure and the crude material was dissolved again in 80 ml of anhydrous methanol. $NaBH_4$ was added in small portions and the mixture was stirred for 2 hours at room temperature until TLC indicated complete conversion. The reaction mixture was carefully hydrolyzed with 50 ml H_2O and methanol was removed under reduced pressure. The aqueous solution was extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over silica (CH_2Cl_2:MeOH 30:1 + Et_3N) to yield **48** as light brown oil in 65% yield.



48
$C_{11}H_{16}N_2O$
192.26 g/mol

R_f = 0.43 (CH_2Cl_2:MeOH 20:1 + Et_3N).

$[\alpha]_{589}^{20}$ = +73.90 (EtOH, c = 1.02).

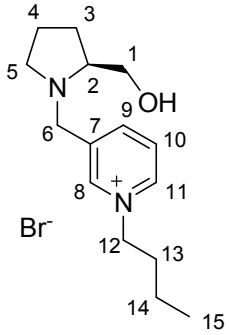
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.50 (d, J = 2.74 Hz 1H, H-8), 8.47 (dd, J_1 = 5.08 Hz, J_2 = 1.96 Hz, 1H, H-11), 7.63 (dt, J_1 = 7.83 Hz, J_2 = 1.76 Hz, J_2 = 1.76 Hz, 1H, H-9), 7.23 (dd, J_1 = 7.83 Hz, J_2 = 4.70 Hz, 1H, H-11), 3.99/3.35 (2d, J = 13.30 Hz, 2H, H-6a,b), 3.65/3.46 (2dd, J_1 = 10.96 Hz, J_2 = 3.72 Hz/ J_1 = 10.96 Hz, J_2 = 2.54 Hz, 2H, H-1a,b), 2.94 (m, 2H, H-5a and OH), 2. 73 (ddd, J_1 = 11.93 Hz, J_2 = 5.77 Hz, J_3 = 2.93 Hz, 1H, H-2), 2.25 (m, 1H, H-5b), 2.06-1.59 (m, 4H, H-3, H-4).

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C = 149.8 (d, C-8), 148.2 (d, C-11), 136.3 (d, C-9), 134.6 (s, C-7), 123.2 (d, C-10), 64.4 (d, C-2), 62.3 (t, C-1), 55.8/54.2 (2t, C-5, C-6), 27.5 (t, C-3), 23.1 (t, C-4).

Anal. Calcd. for $C_{18}H_{16}N_2O \cdot 0.1\ H_2O$: C, 68.08; H, 8.41; N, 14.44. Found: C, 67.94; H, 8.19; N, 14.25.

7.4.14 1-Butyl-3-[[[(2*S*)-2-(hydroxymethyl)pyrrolidine-1-yl]methyl]pyridinium bromide 49

Preparation from **48** (0.577 g, 3 mmol) according to procedure 7.4.3 gave **49** as viscous brown oil in >99% yield.



49
$C_{15}H_{25}BrN_2O$
329.28 g/mol

$[\alpha]_{589}^{20}$ = +23.44 (EtOH, c = 0.76).

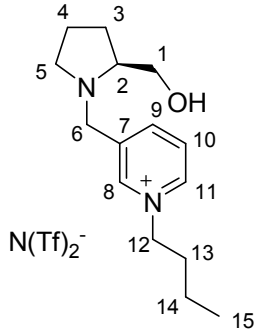
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.64 (s, 1H, H-8), 9.22 (d, J = 5.87 Hz, 1H, H-11), 8.37 (d, J = 7.83 Hz, 1H, H-12), 8.01 (dd, J_1 = 7.83 Hz, J_2 = 6.26 Hz, 1H, H-10), 4.89 (m, 2H, H-12), 4.42/3.71 (2d, J = 14.86 Hz, 2H, H-6a,b), 4.01 (br s, 1H, OH), 3.58 (m, 2H, H-1a,b), 2.85(m, 2H, H-5a, H-2), 2.27 (m, 1H, H-5b), 1.99 (quin, J = 7.73 Hz, 2H, H-13), 1.85-1.48 (m, 4H, H-3, H-4), 1.38 (sext, J = 7.75 Hz, 2H, H-14), 0.91 (t, J = 7.24 Hz, 3H, H-15).

^{13}C-NMR (50 MHz, d_6-DMSO): δ_C = 145.2 (d, C-8), 144.2 (d, C-11), 143.2 (d, C-9), 141.0 (s, C-7), 127.5 (d, C-10), 65.2 (d, C-2), 63.6 (t, C-1), 63.6(t, C-12), 54.6/53.9 (2t, C-5, C-6), 32.7 (t, C-13), 27.4 (t, C-3), 22.6 (t, C-4), 18.7 (t, C-14), 13.3 (q, C-15).

Anal. Calcd. for $C_{15}H_{25}BrN_2O \cdot 0.5\ H_2O$: C, 53.26; H, 7.75; N, 8.28. Found: C, 53.34; H, 7.35; N, 7.89.

7.4.15 1-Butyl-3-[[[(2*S*)-2-(hydroxymethyl)pyrrolidine-1-yl]methyl]pyridinium bis(trifluoromethansulfonyl)imide 50

Preparation from **49** (2.22 g, 6.76 mmol) according to procedure 7.4.4 gave **50** as dark brown oil in 99% yield.



50
$C_{17}H_{25}F_6N_3O_5S_2$
529.52 g/mol

$[\alpha]_{589}^{20}$ = +16.9 (EtOH, c = 1.20).

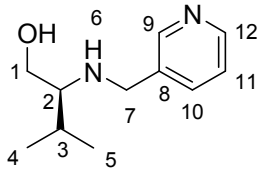
^{1}H-NMR (200 MHz, d_6-DMSO): δ_H = 9.04 (s, 1H, H-8), 8.97 (d, J = 6.06 Hz, 1H, H-11), 8.54 (d, J = 8.02 Hz, 1H, H-12), 8.09 (dd, J_1 = 7.83 Hz, J_2 = 6.06 Hz, 1H, H-10), 4.60 (t, J = 7.43 Hz, 2H, H-12), 4.28/3.67 (2d, J = 14.48 Hz/J = 14.67 Hz, 2H, H-6a,b), 3.42 (br s, 2H, H-1a,b), 2.86/2.73 (2m, 2H, H-5a, H-2), 2.27 (m, 1H, H-5b), 1.91 (quin, J = 7.43 Hz, 2H, H-13), 1.75-1.42 (m, 4H, H-3, H-4), 1.31 (sext, J = 7.75 Hz, 2H, H-14), 0.92 (t, J = 7.34 Hz, 3H, H-15).

^{13}C-NMR (50 MHz, d_6-DMSO): δ_C = 145.1 (d, C-8), 144.0 (d, C-11), 143.1 (d, C-9), 141.1 (s, C-7), 127.5 (d, C-10), 119.3 (q, J = 321.9 Hz, CF_3), 65.2 (d, C-2), 63.8 (t, C-1), 60.6 (t, C-12), 54.8/54.0 (2t, C-5, C-6), 32.8 (t, C-13), 27.4 (t, C-3), 22.6 (t, C-4), 18.8 (t, C-14), 13.2 (q, C-15).

Anal. Calcd. for $C_{17}H_{25}F_6N_3O_5S_2 \cdot 0.9\ H_2O$: C, 37.42; H, 4.95; N, 7.70. Found: C, 37.32; H, 4.48; N, 7.67.

7.4.16 (2*S*)-2-[(Pyridin-3-yl)methylamino]-3-methylbutan-1-ol 53

Preparation from (*S*)-valinol (4.82 g, 46.7 mmol) according to procedure for 7.4.1 gave **53** as yellow oil in 63% yield.



53
$C_{11}H_{18}N_2O$
194.27 g/mol

R_f = 0.28 (CH_2Cl_2:MeOH 30:1 + Et_3N).

$[\alpha]_{589}^{20}$ = -6.48 (EtOH, c = 1.45).

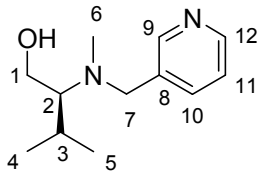
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.54 (d, J = 1.88 Hz, 1H, H-9), 8.49 (dd, J_1 = 4.83 Hz, J_2 = 1.61 Hz, 1H, H-12), 7.68 (d, J = 7.79 Hz, 1H, H-10), 7.25 (dd, J_1 = 7.99 Hz, J_2 = 4.10 Hz, 1H, H-11), 3.85/3.76 (2d, J = 13.30 Hz, 2H, H-7a,b), 3.65/3.39 (2dd, J_1 = 10.75 Hz, J_2 = 4.16 Hz/ J_1 = 10.75 Hz, J_2 = 6.98 Hz, 2H, H-1a,b), 2.74 (ddd, J_1 = 6.50 Hz, J_2 = 6.31 Hz, J_3 = 3.96 Hz, 1H, H-2), 2.15 (br s, 2H, OH and NH), 1.86 (m, 1H, H-3), 0.96/0.91 (2d, 6H, J = 6.85 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 149.2 (d, C-9), 148.1 (d, C-12), 136.1 (s, C-8), 135.8 (d, C-10), 123.3 (d, C-11), 63.8 (d, C-2), 60.5 (t, C-1), 48.7 (t, C-7), 28.5 (d, C-3), 19.2/18.2 (2q, C-5, C-6).

Anal. Calcd. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.81; H, 9.52; N, 14.18.

7.4.17 (2*S*)-2-[Methyl[(pyridin-3-yl)methyl]amino]-3-methylbutan-1-ol 54

Preparation from **53** (0.707 g, 3.64 mmol) according to procedure for 7.4.2 gave **54** as light yellow oil in 97% yield.



54
$C_{12}H_{20}N_2O$
208.30 g/mol

R_f = 0.33 (CH_2Cl_2:MeOH 30:1 + Et_3N).

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

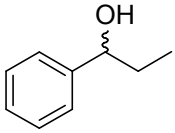
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.51 (s, 2H, H-9, H-11), 7.63 (ddd, J_1 = 7.82 Hz, J_2 = 1.85 Hz, J_3 = 1.85 Hz, 1H, H-10), 7.27 (dd, J_1 = 7.99 Hz, J_2 = 4.16 Hz, 1H, H-11), 3.88/3.74 (2d, J = 13.50 Hz, 2H, H-7a,b), 3.66 (dd, J_1 = 10.66 Hz, J_2 = 4.99 Hz, 1H, H-1a), 3.34 (m, 1H, H-1b), 2.52 (ddd, J_1 = 9.98 Hz, J_2 = 8.61, J_3 = 4.70 Hz, 1H, H-2), 2.27 (s, 3H, H-6), 2.15 (br s, 2H, OH and NH), 1.93 (m, 1H, H-3), 1.68 (br s, 1H, OH), 1.09/0.89 (2d, 6H, J = 6.65 Hz, H-5, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 149.8 (d, C-9), 148.3 (d, C-12), 136.2 (d, C-10), 135.2 (s, C-8), 123.4 (d, C-11), 70.7 (d, C-2), 59.4 (t, C-1), 58.9 (t, C-7), 35.9 (q, C-6), 27.8 (d, C-3), 22.1/19.8 (2q, C-5, C-6).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 68.93; H, 9.83; N, 13.11.

7.4.18 General procedure for the enantioselective alkylation of aldehyds

The chiral ligand (0.2 mmol) was dissolved in 4 ml of anhydrous toluene under a dry argon atmosphere and cooled to 0 °C. A solution of diethylzinc (1.0 M in hexane, 4.4 mmol) was added slowly at 0 °C. After the reaction was stirred for 30 minutes, freshly distilled benzaldehyde **51** (0.21 g, 2 mmol) was added dropwise via microsyringe at 0 °C, and the reaction was stirred for 48 hours at room temperature. The mixture was carefully hydrolyzed with 1 M HCl and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with a small amount of brine, dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (30 g silica, light petrol:diethyl ether 5:1) to yield 1-phenyl-1-propanol **52** as colourless liquid.



52

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 7.30 (s, 5H), 4.52 (t, J = 6.65 Hz, 1H), 2.36 (br s, 1H, OH), 1.76 (m, 1H), 0.88 (t, J = 7.34 Hz, 3 H).

HPLC: Chiralcel OD-H; *n*-hexane/*i*-propanol = 98:2; 0.7 ml/min; 254 nm

t_{R1} = 11.68 min (*R*)

t_{R2} = 12.66 min (*S*)

Analytical data were in similar to those reported in literature.[154]

[154] Thienthong, N.; Perlmutter P. *J. Organomet. Chem.* **2005**, *690*, 2027.

7.5 Iron-catalyzed Kumada-Corriu cross-coupling

7.5.1 Preparation of butylmethylimidazolium-tetrachloroferrate (bmim-$FeCl_4$) 55

Butylmethylimidazolium chloride **12**[151] (5.00 g, 28.6 mmol) and $FeCl_3 \cdot 6\ H_2O$ (7.74 g, 28.6 mmol) were mixed in a round bottom flask and stirred for 5 minutes. Immediately an endothermic reaction took place and provided bmim-$FeCl_4$ **55** as a lower layer. The upper aqueous layer was carefully removed and the remaining ionic liquid was dried under stirring for 2 d at 80 °C and 0.1 Torr to yield 8.96 g (93%) of bmim-$FeCl_4$ **55** as dark brown oil which was characterised via Raman spectroscopy

Analytical data were in accordance with literature values.[70]

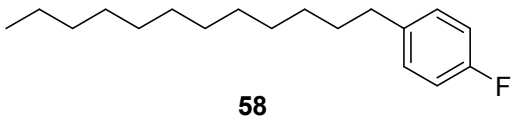
7.5.2 Representing procedure for the bmim-$FeCl_4$ catalyzed cross-coupling

Bmim-$FeCl_4$ **55** (0.1 mmol), halide (2.00 mmol) and an exact amount of hexadecane (~0.2 mmol) as internal standard were mixed in a round bottom flask and diluted with 0.5 ml of diethyl ether. A solution of Grignard reagent in diethyl ether (1.5 ml, 3.00 mmol) was added dropwise under stirring at 0 °C. Immediately a colour change to black could be observed. Stirring was continued for 10 minutes at room temperature and the reaction mixture was hydrolyzed carefully with diluted hydrochloric acid. The aqueous layer was extracted with diethyl ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed at 40 °C/900 mbar. GC-MS analysis was done directly from the reaction as well as from the crude product and proved to be identical.

Purification of the crude mixture by flash column chromatography (100 g silica, light petrol) gave the coupling products as colourless liquids.

7.5.3 1-Fluoro-4-dodecylbenzene 58

Preparation from halide **56** and Grignard reagent **57** according to procedure 7.5.2 gave **58** as colourless liquid in 86% yield.



58
$C_{18}H_{29}F$
264.42 g/mol

R_f = 0.8 (light petrol).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ(ppm) = 7.14 (dd, J_{HH} = 8.51 Hz, $^4J_{HF}$ = 5.58 Hz, 2H, H-2), 6.97 (dd, J_{HH} = 8.70 Hz, $^3J_{HF}$ = 8.70 Hz, 2H, H-3), 2.59 (t, J = 7.73 Hz, 2H, -CH_2Ph), 1.61 (quin, J = 7.14 Hz, 2H, -$\underline{CH_2}CH_2$Ph) 1.29 (m, 18H, -CH_2-), 0.91 (t, J = 6.75 Hz, 3 H, CH_3-).

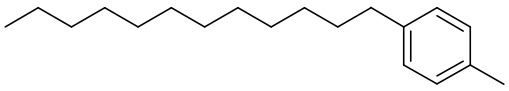
^{13}C-NMR ($CDCl_3$, 50 MHz) δ (ppm) = 161.13(s, $^1J_{CF}$ = 243.0 Hz, C-4), 138.46 (s, $^4J_{CF}$ = 3.18 Hz, C-1), 129.61 (d, $^3J_{CF}$ = 7.7 Hz, C-2), 114.87 (d, $^2J_{CF}$ = 21.2 Hz, C-3), 35.14 (t, -CH_2Ph), 31.95 (t), 31.65 (t), 31.63 (t), 29.7 (m), 29.6 (t), 29.5 (t), 29.4 (t), 29.2 (t), 22.7 (t, -CH_2CH_3), 14.11 (q, -CH_3).

GC/EI-MS: t_R = 18.0 min; *m/z* = 264.3 (M^+, 14), 122.1 (4), 110.2 (33), 119.1 (100), 96.1(2), 83.1 (4), 71.2 (4), 55.2 (4).

Anal. Calcd. for $C_{18}H_{29}F$: C, 81.76; H, 11.05. Found: C, 81.59; H, 11.32.

7.5.4 1-Dodecyl-4-methylbenzene 62

Preparation from halide **56** and Grignard reagent **61** according to procedure 7.5.2 gave **62** as colourless liquid in 73% yield.



62
$C_{19}H_{32}$
260.46 g/mol

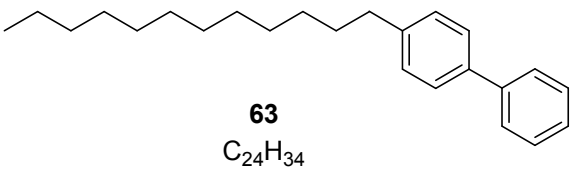
^{1}H-NMR ($CDCl_3$, 200 MHz) δ(ppm) = 7.15 (s, 4H), 2.65 (t, J = 7.83 Hz, 2H), 2.37 (s, 3H), 1.68 (quin, J = 7.34 Hz, 2H), 1.35 (s, 18 H), 0.98 (t, J = 6.55 Hz, 3H).

Analytical data were similar to those reported in literature.[155]

[155] Cahiez, G.; Habiak, V.; Duplais, C.; M. *Angew. Chem.; Int. Ed.* **2007**, *46*, 4364.

7.5.5 1-Dodecyl-4-phenylbenzene 64

Preparation from halide **56** and Grignard reagent **63** according to procedure 7.5.2 gave **64** as white solid in 60% yield.

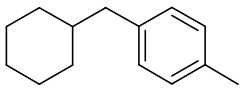


63
$C_{24}H_{34}$
322.53 g/mol

^{1}H-NMR ($CDCl_3$, 200 MHz) δ(ppm) = 7.66-7.28 (m, 9H), 2.70 (t, J = 7.73 Hz, 2H), 1.71 (quin, J = 6.94 Hz, 2H), 1.33 (s, 18 H), 0.95 (t, J = 6.06 Hz, 3H).
Analytical data were in accordance with literature values.[156]

7.5.6 1-(Cyclohexylmethyl)-4-methylbenzene 66

Preparation from halide **65** and Grignard reagent **61** according to procedure 7.5.2 gave **66** as colourless liquid in 64% yield.



66
$C_{14}H_{20}$
188.31 g/mol

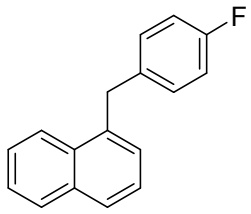
GC/EI-MS: t_R = 14.05 min; *m/z* = 189.3 (M^++1, 4), 188.2 (M^+, 37), 117.1 (5), 115.1 (7), 107.2 (12), 106.2 (100), 103.0 (12), 91.1 (33), 83.1 (23), 79.3 (13), 77.1 (18), 55.2 (45).
Analytical data were in accordance with literature values.[157]

[156] Kanekiyo, T.; Akimoto, Y.; Kubota, M. E.P. Patent 350863, 1990.

[157] Blackwell, J.; Hickinbottom, W. J. *J. Chem. Soc.* **1963**, 373.

7.5.7 1-(4-Fluorobenzyl)naphtalene 68

Preparation from halide **67** and Grignard reagent **57** according to procedure 7.5.2 gave **68** as colourless liquid in 60% yield.

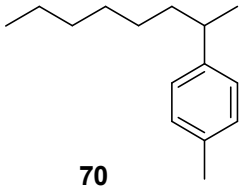


68
$C_{17}H_{13}F$
236.28 g/mol

GC/EI-MS: t_R = 19.31 min; *m/z* = 237.2 (M^++1, 17), 236.2 (M^+, 100), 235.2 (60), 233.1 (30), 221.2 (20), 220.1 (26), 215.1 (23), 207.0 (8), 141.2 (15), 115.1 (16), 109.1 (11), 106.5 (9).
Analytical data were in accordance with literature values.[158]

7.5.8 1-Methyl-4-(octan-2-yl)benzene 70

Preparation from (*rac*)-2-bromooctane[159] **69** and Grignard reagent **61** according to procedure 7.5.2 gave **70** as colourless liquid in 84% yield.



70
$C_{15}H_{24}$
204.35 g/mol

GC/EI-MS: t_R = 13.44 min; *m/z* = 205.3 (M^++1, 7), 204.2 (M^+, 38), 119.3 (100), 117.0 (40), 115.1 (18), 105.1 (34), 104.2 (11), 103.1 (11), 91.0 (38), 77.0 (18), 65.0 (10), 55.2 (4).
Analytical data were in accordance with literature values.[160]

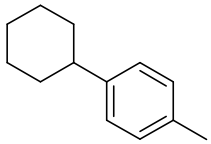
[158] Bratulescu, G.; Le Bigot, Y.; Delmas, M. *Synth. Commun.* **2001**, *31*, 3309.

[159] Alnajjar, M.S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *197*, 416.

[160] Nitta, Y.; Arakawa, Y.; Ueyama, N. *Chem. Pharm. Bull.* **1986**, *34*, 2710.

7.5.9 1-Cyclohexyl-4-methylbenzene 72

Preparation from halide **71** and Grignard reagent **61** according to procedure 7.5.2 gave **72** as colourless liquid in 89% yield.



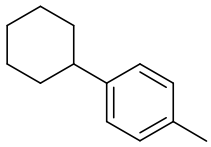
72
$C_{13}H_{18}$
174.28 g/mol

GC/EI-MS: t_R = 12.77 min; *m/z* = 175.3 (M^++1, 11), 172.2 (M^+, 82), 159.2 (18), 145.1 (11), 132.2 (20), 131.1 (100), 129.2 (14), 118.2 (73), 117.2 (51), 116.2 (17), 115.1 (33), 106.2 (13), 105.1 (72), 91.1 (55).

Analytical data were in accordance with literature values.[161]

7.5.10 4-(4-Fluorophenyl)-1-methylpiperidine 80

Preparation from halide **79** and Grignard reagent **57** according to procedure 7.5.2 gave **80** as colourless liquid in 79% yield.



80
$C_{12}H_{16}FN$
193.26 g/mol

GC/EI-MS: t_R = 14.05 min; *m/z* = 194.3 (M^++1, 6), 193.2 (M^+, 56), 192.1 (72), 133.1 (8), 122.1 (13), 121.1 (11), 109.1 (17), 97.2 (36), 96.1 (23), 83.2 (14), 71.2 (29), 70.1 (100), 58.2 (16), 57.2 (39), 56.2 (6).

Analytical data were in accordance with literature values.[162]

[161] Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104.

[162] Allen & Hanburys Ltd. NL Patent 6510107, 1966.

7.5.11 Recycling of bmim-$FeCl_4$ in the iron-catalyzed cross-coupling

Bmim-$FeCl_4$ **55** (0.1 mmol), dodecyl bromide **56** (500 mg, 2.00 mmol) and an exact amount of hexadecane (~0.2 mmol) as internal standard were mixed in a round bottom flask and diluted with 0.5 ml of diethyl ether. A solution of 4-fluorophenylmagnesium bromide **57** in diethyl ether (1.5 ml, 3.00 mmol) was added dropwise under stirring at 0 °C. Immediately a colour change to black could be observed. Stirring was continued for 10 minutes at room temperature and the reaction was left to settle down. The upper ethereal layer was carefully decanted and the remaining bmim-$FeCl_4$/$MgBr_2$-layer was washed twice with 0.5 ml of diethyl ether each. The combined organic layers were concentrated without hydrolysis and subjected directly to flash column chromatography.

Fresh dodecyl bromide **56** (500 mg, 2.00 mmol) and an exact amount of hexadecane (~0.2 mmol) were added again to the orange bmim-$FeCl_4$/ $MgBr_2$-slurry and diluted with 0.5 ml of diethyl ether. Subsequent addition of 4-fluorophenylmagnesium bromide **57** (1.5 ml, 3.00 mmol) at 0 °C gave a colour change to black again and the reaction procedure was repeated like described above.

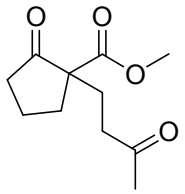
7.6 Ionic liquid-catalyzed Michael Addition

7.6.1 General procedure for the microwave assisted Michael addition

β-Oxo ester (5 mmol) and bmim-$FeCl_4$ **55** (16.8 mg, 0.05 mmol) were mixed in a microwave vial and sealed with a Teflon septum. Freshly distilled enone (7 mmol) was added to the violet solution. Irradiation in a CEM Explorer at 125 °C at 50 W for the time given in Table 24 gave a yellow solution which was directly subjected to flash chromatography (50 g silica, light petrol:ethyl acetate) to afford the alkylated β-oxo ester as colourless liquid.

7.6.2 Methyl-2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate 83

Preparation from β-oxo ester **81** and enone **82** according to procedure 7.6.1 gave **83** as colourless liquid in 94% yield.



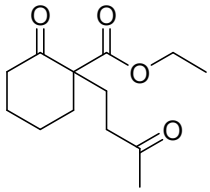
83
$C_{11}H_{16}O_4$
212.24 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 3.69 (s, 3H), 2.68 (ddd, J_1 = 17.85 Hz, J_2 = 9.44 Hz, J_3 = 6.02 Hz, 1H) 2.55-2.25 (m, 4H), 2.21-1.78 (m, 5H), 2.12 (s, 3H).
Analytical data were in accordance with literature values.[163]

7.6.3 Ethyl-2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate 85

Preparation from β-oxo ester **84** and enone **82** according to procedure 7.6.1 gave **85** as colourless liquid in 83% yield.

[163] Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642.

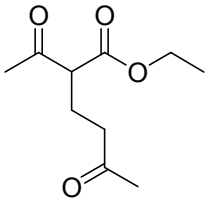


85
$C_{13}H_{20}O_4$
240.30 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.19 (q, J = 7.11 Hz, 2H), 2.68-2.25 (m, 5H), 2.12 (s, 3H), 2.17-1.35 (m, 7H), 1.26 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[131]

7.6.4 Ethyl-2-acetyl-5-oxohexenoate 87

Preparation from β-oxo ester **86** and enone **82** according to procedure 7.6.1 as colourless liquid in 71% yield.

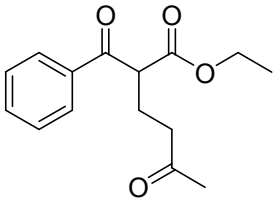


87
$C_{10}H_{16}O_4$
200.23 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.14 (q, J = 7.11 Hz, 2H), 3.43 (t, J = 7.14 Hz, 1H), 2.44 (t, J = 7.04 Hz, 2H), 2.99 (s, 3H), 2.12 (s, 3H), 2.02 (m, 2H), 1.21 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[131]

7.6.5 Ethyl-2-benzoyl-5-oxohexenoate 89

Preparation from β-oxo ester **88** and enone **82** according to procedure 7.6.1 gave **89** as colourless liquid in 79% yield.

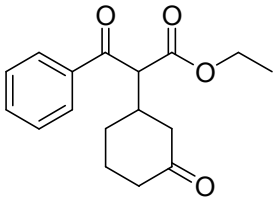


89
$C_{15}H_{18}O_4$
262.30 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 8.01 (m, 2H), 7.48 (m, 3H), 4.43 (dd, J_1 = 7.53 Hz, J_2 = 6.55 Hz, 1H), 4.14 (q, J = 7.11 Hz, 2H), 2.58 (m, 2 H), 2.24 (m, 2H), 2.13 (s, 3H), 1.16 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[164]

7.6.6 Ethyl-3-oxo-2-(3-oxocyclohexyl)-3-phenylpropanoate 91

Preparation from β-oxo ester **88** and enone **90** according to procedure 7.6.1 gave **91** as colourless liquid in 88% yield. A mixture of 2 diastereomers was obtained.



91
$C_{17}H_{20}O_4$
288.34 g/mol

Major diastereomere:

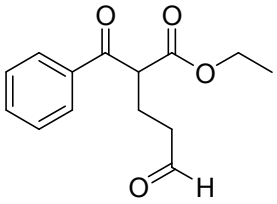
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 7.99 (m, 2H), 7.51 (m, 3H), 4.27 (dd, J_1 = 8.71 Hz, J_2 = 4.99 Hz, 1H), 4.13 (m, 2H), 3.05-1.32 (m, 9H), 1.17 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[165]

[164] Noeel, R.; Vanucci-Bacque, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *J. Org. Chem.* **2005**, *70*, 9044.

[165] Soriente, A.; Arienzo, R.; De Rosa, M.; Spinella, A.; Scettri, A.; Palombi, L. *Green. Chem.* **1999**, *1*, 157.

7.6.7 Ethyl-2-benzoyl-5-oxo-pentanoate 93

Preparation from β-oxo ester **88** and enone **92** according to procedure 7.6.1 gave **93** as colourless liquid in 52% yield.



93
$C_{14}H_{16}O_4$
248.27 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 9.30 (br s, 1H), 7.98 (m, 2H), 7.45 (m, 3H), 4.27 (t, J = 6.94 Hz, 1H), 4.13 (q, J = 7.11 Hz, 2H), 2.50 (m, 2H), 2.28 (m, 2H), 1.17 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[164]

7.6.8 Recycling of bmim-$FeCl_4$ 55 in the iron-catalyzed Michael addition

To a mixture of β-oxo ester **81** (710.8 mg, 5 mmol) and bmim-$FeCl_4$ **55** (16.8 mg, 0.05 mmol) in a round bottom flask was added methyl vinyl ketone **82** (490.6 mg, 7 mmol). The mixture was stirred overnight at 100 °C. Distillation at reduced pressure at gave product **83** as colourless liquid. The remaining black slurry was directly subjected to the next run without further purification.

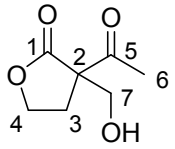
7.7 Ionic liquid catalyzed hydroxymethylation

7.7.1 General procedure for the iron-catalyzed hydroxymethylation of β-oxo esters

β-Keto ester (5 mmol) and bmim-$FeCl_4$ **55** (16.8 mg, 0.05 mmol) were mixed and a 37% aqueous formaldehyde solution (0.45 ml, 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 (30 g silica, light petrol:ethyl acetate) to yield the hydroxymethylated β-oxo ester as colourless liquid.

7.7.2 3-Acetyl-dihydro-3-(hydroxymethyl)furan-2(3H)-one 98

Preparation from **97** according to procedure 7.7.1 gave **98** as colourless liquid in 87% yield.



98
$C_7H_{10}O_4$
158.15 g/mol

R_f = 0.33 (light petrol:ethyl acetate 1:1).

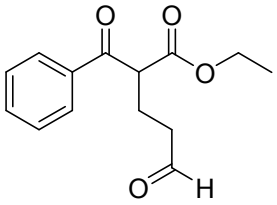
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.37 (m, 1H, H-4a), 4.25 (dd, J_1 = 16.14 Hz, J_2 = 8.51 Hz, 1H, H-4b), 4.04/3.97 (2d, J = 11.15 Hz, 2d, H-7a,b), 3.10 (br s, 1H, OH), 2.72 (ddd, J_1 = 13.2 Hz, J_2 = 7.43 Hz, J_2 = 4.21 Hz, 1H, H-3a), 2.38 (m, 1H, H-3b), 2.33 (s, 3H, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 202.4 (s, C-5), 175.2 (s, C-1), 66.7 (t, C-4), 64.3 (t, C-7), 63.1 (s, C-2), 27.9 (t, C-3), 26.5 (q, C-6).

Anal. Calcd. for $C_7H_{10}O_4 \cdot 0.2\ H_2O$: C, 51.98; H, 6.48. Found: C, 52.00; H, 6.73.

7.7.3 Methyl-1-(hydroxymethyl)-2-oxocyclopentane carboxylate 94

Preparation from **81** according to procedure 7.7.1 gave **94** as colourless liquid in 87% yield.

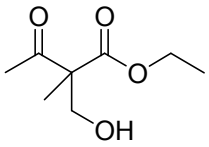


94
$C_{14}H_{16}O_4$
248.27 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 3.74 (s, 2H), 3.62 (s, 3H), 3.09 (br s, 1H, OH), 2.24 (m, 4H), 1.94 (m, 2H).
Analytical data were in accordance with literature values.[149]

7.7.4 Ethyl-2-(hydroxymethyl)-2-methyl-3-oxobutanoate 96

Preparation from **95** according to procedure 7.7.1 gave **96** as colourless liquid in 83% yield.



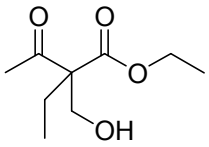
96
$C_8H_{14}O_4$
174.19 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 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).
Analytical data were in accordance with literature values.[166]

[166] Akeboshi, T.; Ohtsuka, Y.; Sugai, T.; Ohta, H. *Tetrahedron* **1998**, 54, 7387.

7.7.5 Ethyl-2-acetyl-2-(hydroxymethyl)butanoate 100

Preparation from **99** according to procedure 7.7.1 gave **100** as colourless liquid in 33% yield.

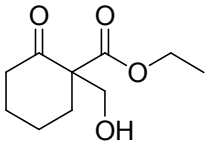


100
$C_9H_{16}O_4$
188.22 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.15 (q, J = 7.11 Hz, 2H), 3.92/3.89 (2d, J = 11.54 Hz/ J = 11.74 Hz, 2H), 2.96 (br s, H, OH), 2.15 (s, 3H), 1.93 (m, 2H), 1.22 (t, J = 7.14 Hz, 3H), 0.80 (t, J = 7.53 Hz, 3H).
Analytical data were in accordance with literature values.[167]

7.7.6 Ethyl 1-(hydroxymethyl)-2-oxocyclohexane carboxylate 101

Preparation from **84** according to procedure 7.7.1 gave **101** as colourless liquid in 73% yield.



101
$C_{10}H_{16}O_4$
200.23 g/mol

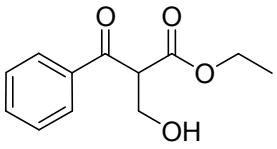
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.18 (q, J = 7.17 Hz, 2H), 3.76/3.63 (2d, J = 11.35 Hz, 2H), 3.00 (br s, 1H, OH), 2.60-2.24 (m, 3H), 1.96 (m, 1H), 1.61-1.48 (m, 4H), 1.21 (t, J = 7.14 Hz, 3H).
Analytical data were in accordance with literature values.[168]

[167] Longeray, R.; Dreux, J. *Bull. Soc. Chim. France* **1964**, *11*, 2849.

[168] Chan, T. H.; Schwerdtfeger, A. E. *J. Org. Chem.* **1991**, *56*, 3294.

7.7.7 Ethyl 2-(hydroxymethyl)-3-oxo-3-phenylpropanoate 102

Preparation from **88** according to procedure 7.7.1 gave **102** as colourless liquid in 70% yield.

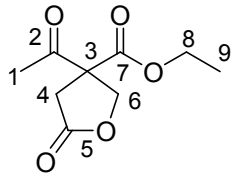


102
$C_{12}H_{14}O_4$
222.24 g/mol

^{1}H-NMR (200 MHz, $CDCl_3$): δ_H =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.[146]

7.7.8 Ethyl-3-acetyl-tetrahydro-5-oxofuran-3-carboxylate 106

Diethyl acetylsuccinate **105** (1.080 g, 5 mmol) and bmim-$FeCl_4$ **55** (168.1 mg, 0.5 mmol) were mixed and a 37% aqueous formaldehyde solution (0.45ml, 6 mmol) was added to the violet solution. The reaction was stirred at 80 °C for 2 hours until TLC indicated complete conversion. Water was evaporated under reduced pressure and the remaining slurry was directly subjected to flash column chromatography (30 g silica, light petrol:ethyl acetate 3:1) to yield ethyl 3-acetyl-tetrahydro-5-oxofuran-3-carboxylate **106** as colourless oil (850.8 mg, 85%).



106
$C_9H_{12}O_5$
200.19 g/mol

R_f = 0.59 (light petrol:ethyl acetate 1:1)
^{1}H-NMR (200 MHz, $CDCl_3$): δ_H = 4.56 (s, 2H, H-6), 4.23 (q, J = 7.11 Hz, 2H, H-8), 3.04/2.93 (2d, J = 18.0 Hz, 2H, H-4a,b), 2.20 (s, 3H, H-1), 1.25 (t, J = 7.14 Hz, 3H, H-9).
^{13}C-NMR (50 MHz, $CDCl_3$): δ_C = 198.8 (s, C-2), 173.1 (s, C-5), 168.8 (s, C-7), 69.7 (t, C-6), 62.9 (t, C-8), 62.3 (s, C-3), 33.5 (t, C-4), 26.0 (q, C-1), 13.7 (q, C-9).

GC/EI-MS: t_R = 14.05 min; *m/z* = 201.1 (M^++1, 1), 158.1 (60), 140.0 (100), 129.0 (16), 124.0 (17), 113.1(40), 112 (56), 98.9 (24, 86,1 (33), 67.9 (27).

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.54; H, 6.04. Found: C, 53.82; H, 5.90.

7.7.9 Recycling of bmim-$FeCl_4$ in the iron-catalyzed hydroxymethylation

β-Keto ester (5 mmol) and bmim-$FeCl_4$ **55** (16.8 mg, 0.05 mmol) were mixed and a 37% aqueous formaldehyde solution (0.45 ml, 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 crude product was isolated by Kugelrohr distillation. Fresh starting materials were added and the reaction was repeated as described above.

8. Literature

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9. Appendix

9.1 List of abbreviations

A	anion
Ac	acetyl
Ar	aromat
arom	aromatic
acac	acetyl acetonate
ATR-IR	attenuated total reflection infrared spectroscopy
bmim-BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
bmim-PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
bmim-$N(Tf)_2$	1-butyl-3-methylimidazolium bis(trifluoromethansulfonyl)imide
bmim-$FeCl_4$	1-butyl-3-methylimidazolium tetrachloroferrate
BINOL	*S*-(-)-1,1'-bi-2-naphthol
Bn	benzyl
br	broad
Bu	butyl
Cbz	benzyloxycarbonyl
CIL	chiral ionic liquid
Cmp	compound
conc	concentrated
CSA	camphor sulfonate
CSP	chiral stationary phase
DABCO	1,4-diazabicyclo[2.2.2]octane
DAIB	(-)-3-*exo*-dimethylaminoisoborneol
d	days
de	diastereomeric excess
dest	destilled
DEPT	distortionless enhancement by polarization transfer
DFT	denisity functional theory
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
emim-$N(Tf)_2$	1-ethyl-3-methylimidazolium bis(trifluoromethansulfonyl)imide
eq	equivalents
Et	ethyl
Et_2O	diethyl ether
EXAFS	extended X-ray absorption fine structure
FTIR	fourier transformed infrared spectroscopy
GC/MS	gas chromatography – mass spectroscopy
GC	gas chromatography

HPLC	high performance liquid chromatography
hr, hrs	hour, hours
HRMS	high resolution mass spectroscopy
IL	ionic liquid
i-Pr	isopropyl
J	coupling constant
M	molar
m.p.	melting point
Me	methyl
Met	metal
min	minutes
NIR	near infrared
NMO	*N*-morpholin *N*-oxide
N	nematic
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance spectroscopy
$N(Tf)_2$	bis(trifluoromethansulfonyl)imide
o.n.	overnight
p	para
p-TsOH	*p*-toluolsulfonic acid
Ph	phenyl
R	rest (general)
rac	racemic
R_f	retention factor
rf	reflux
r.t.	room temperature
s, sec	secondary
SiO_2	silica 60
Sm	smectic
t, tert.	tertiary
Tf	trifluormethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TMEDA	*N*,*N*,*N*,*N*-tetramethylethylendiamine
TMS	tetramethylsilane
TLC	thin layer chromatography
t_R	retention time
triflimide	bis(trifluoromethansulfonyl)imide
UV-VIS	ultraviolet-visible spectroscopy
VFC	vacuum flash chromatography
X	halide

9.2 Crystallographic data

9.2.1 Crystallographic data for (1*S*,2*R*)-2-(Methyl-pyridin-3-yl-methyl-amino)-1-phenyl-propan-1-ol 34.

Table 29: Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for (1S,2R)-2-(Methyl-pyridin-3-yl-methyl-amino)-1-phenyl-propan-1-ol 34. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(1)	89641(12)	57506(12)	13637(10)	20(1)
N(1)	80630(13)	85826(12)	36933(12)	17(1)
N(2)	80526(16)	62281(15)	82495(13)	25(1)
C(1)	62582(15)	63157(14)	15096(13)	16(1)
C(2)	48279(16)	72186(15)	9576(14)	19(1)
C(3)	32748(16)	67487(17)	9482(15)	22(1)
C(4)	31258(17)	53712(17)	14688(16)	23(1)
C(5)	45348(17)	44556(16)	19890(16)	22(1)
C(6)	60906(16)	49256(15)	20072(15)	18(1)
C(7)	79809(15)	68702(15)	16548(14)	16(1)
C(8)	90228(15)	74439(14)	32835(14)	16(1)
C(9)	108166(17)	79100(18)	34609(17)	24(1)
C(10)	80764(19)	100002(16)	29987(17)	24(1)
C(11)	86147(16)	87126(15)	53469(14)	19(1)
C(12)	78639(15)	75545(14)	60121(14)	16(1)
C(13)	86708(17)	71908(17)	75542(15)	21(1)
C(14)	65870(20)	55670(16)	74044(17)	26(1)
C(15)	57004(19)	58354(17)	58608(16)	23(1)
C(16)	63348(16)	68574(15)	51538(14)	19(1)

Table 30: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (1S,2R)-2-(Methyl-pyridin-3-yl-methyl-amino)-1-phenyl-propan-1-ol 34.

	x	y	z	U_{eq}
H(1)	8869	5810	457	30
H(2)	4914	8158	587	22
H(3)	2314	7375	583	26
H(4)	2070	5056	1470	27
H(5)	4437	3507	2333	26
H(6)	7045	4293	2362	22
H(7)	7810	7676	908	19
H(8)	9170	6615	3999	20
H(9A)	11426	8334	4475	36
H(9B)	10724	8631	2679	36
H(9C)	11443	7062	3342	36
H(10A)	9228	10409	3446	36
H(10B)	7283	10656	3190	36
H(10C)	7727	9882	1897	36
H(11A)	8279	9678	5586	23
H(11B)	9873	8650	5836	23
H(13)	9720	7653	8145	25
H(14)	6133	4883	7884	31
H(15)	4675	5329	5294	28
H(16)	5735	7077	4102	22

Hydrogen atoms inserted in idealized positions and refined riding with the atoms to which they were bonded. All H atoms had $U_{iso} = U_{eq}$ x 1.2 (x 1.5 for CH_3) of their carrier atoms.

Table 31: Anisotropic displacement parameters ($Å^2$ x 10^3) for 34.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	23(1)	25(1)	16(1)	1(1)	11(1)	6(1)
N(1)	20(1)	16(1)	16(1)	0(1)	9(1)	-1(1)
N(2)	32(1)	30(1)	18(1)	6(1)	14(1)	14(1)
C(1)	17(1)	18(1)	11(1)	-2(1)	5(1)	-1(1)
C(2)	20(1)	21(1)	14(1)	1(1)	5(1)	2(1)
C(3)	17(1)	27(1)	18(1)	-3(1)	4(1)	3(1)
C(4)	18(1)	28(1)	22(1)	-7(1)	7(1)	-5(1)
C(5)	23(1)	19(1)	24(1)	-4(1)	11(1)	-5(1)
C(6)	19(1)	17(1)	19(1)	-1(1)	7(1)	0(1)
C(7)	19(1)	18(1)	14(1)	1(1)	8(1)	2(1)
C(8)	17(1)	18(1)	16(1)	1(1)	8(1)	-2(1)
C(9)	19(1)	27(1)	28(1)	-1(1)	12(1)	-4(1)
C(10)	32(1)	17(1)	26(1)	3(1)	15(1)	-2(1)
C(11)	21(1)	20(1)	16(1)	-3(1)	8(1)	-5(1)
C(12)	18(1)	19(1)	14(1)	-1(1)	8(1)	1(1)
C(13)	21(1)	27(1)	14(1)	0(1)	7(1)	7(1)
C(14)	39(1)	20(1)	28(1)	6(1)	24(1)	7(1)
C(15)	28(1)	22(1)	25(1)	-1(1)	16(1)	-3(1)
C(16)	21(1)	20(1)	16(1)	-1(1)	9(1)	-2(1)

Table 32: Bond lengths [Å] and angles [deg] for Cmp. 34.

Bond distances		Bond angles	
O(1)-C(7)	1.4284(15)	C(7)-O(1)-H(1)	109.5
O(1)-H(1)	0.84	C(11)-N(1)-C(10)	
N(1)-C(11)	1.4634(16)	111.02(10)	
N(1)-C(10)	1.4683(17)	C(11)-N(1)-C(8)	
N(1)-C(8)	1.4800(16)	111.79(10)	
N(2)-C(14)	1.338(2)	C(10)-N(1)-C(8)	
N(2)-C(13)	1.339(2)	113.93(10)	
C(1)-C(6)	1.3945(18)	C(14)-N(2)-C(13)	
C(1)-C(2)	1.3982(17)	117.66(12)	
C(1)-C(7)	1.5149(16)	C(6)-C(1)-C(2)	
C(2)-C(3)	1.3960(18)	118.79(11)	
C(2)-H(2)	0.95	C(6)-C(1)-C(7)	
C(3)-C(4)	1.389(2)	120.57(11)	
C(3)-H(3)	0.95	C(2)-C(1)-C(7)	
C(4)-C(5)	1.391(2)	120.54(11)	
C(4)-H(4)	0.95	C(3)-C(2)-C(1)	
C(5)-C(6)	1.3951(18)	120.44(13)	
C(5)-H(5)	0.95	C(3)-C(2)-H(2)	119.8
C(6)-H(6)	0.95	C(1)-C(2)-H(2)	119.8
C(7)-C(8)	1.5461(17)	C(4)-C(3)-C(2)	
C(7)-H(7)	1.00	120.39(13)	
C(8)-C(9)	1.5384(17)	C(4)-C(3)-H(3)	119.8
C(8)-H(8)	1.00	C(2)-C(3)-H(3)	119.8
C(9)-H(9A)	0.98	C(3)-C(4)-C(5)	
C(9)-H(9B)	0.98	119.47(12)	
C(9)-H(9C)	0.98	C(3)-C(4)-H(4)	120.3
C(10)-H(10A)	0.98	C(5)-C(4)-H(4)	120.3
C(10)-H(10B)	0.98	C(4)-C(5)-C(6)	
C(10)-H(10C)	0.98	120.24(13)	
C(11)-C(12)	1.5121(17)	C(4)-C(5)-H(5)	119.9
C(11)-H(11A)	0.99	C(6)-C(5)-H(5)	119.9
C(11)-H(11B)	0.99	C(1)-C(6)-C(5)	
C(12)-C(16)	1.3936(17)	120.65(12)	
C(12)-C(13)	1.3964(17)	C(1)-C(6)-H(6)	119.7
C(13)-H(13)	0.95	C(5)-C(6)-H(6)	119.7
C(14)-C(15)	1.386(2)	O(1)-C(7)-C(1)	
C(14)-H(14)	0.95	111.55(11)	
C(15)-C(16)	1.3911(18)	O(1)-C(7)-C(8)	
C(15)-H(15)	0.95	107.22(10)	
C(16)-H(16)	0.95	C(1)-C(7)-C(8)	
		110.85(9)	
		O(1)-C(7)-H(7)	109.1
		C(1)-C(7)-H(7)	109.1
		C(8)-C(7)-H(7)	109.1

N(1)-C(8)-C(9) 114.15(11)	
N(1)-C(8)-C(7) 110.60(10)	
C(9)-C(8)-C(7) 110.79(10)	
N(1)-C(8)-H(8)	107.0
C(9)-C(8)-H(8)	107.0
C(7)-C(8)-H(8)	107.0
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
N(1)-C(10)-H(10A)	109.5
N(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
N(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
N(1)-C(11)-C(12) 112.92(10)	
N(1)-C(11)-H(11A)	109.0
C(12)-C(11)-H(11A)	109.0
N(1)-C(11)-H(11B)	109.0
C(12)-C(11)-H(11B)	109.0
H(11A)-C(11)-H(11B)	107.8
C(16)-C(12)-C(13) 117.55(12)	
C(16)-C(12)-C(11) 122.39(11)	
C(13)-C(12)-C(11) 120.01(11)	
N(2)-C(13)-C(12) 123.85(13)	
N(2)-C(13)-H(13)	118.1
C(12)-C(13)-H(13)	118.1
N(2)-C(14)-C(15) 122.95(13)	
N(2)-C(14)-H(14)	118.5
C(15)-C(14)-H(14)	118.5
C(14)-C(15)-C(16) 119.01(13)	
C(14)-C(15)-H(15)	120.5
C(16)-C(15)-H(15)	120.5
C(15)-C(16)-C(12) 118.95(12)	
C(15)-C(16)-H(16)	120.5
C(12)-C(16)-H(16)	120.5

Torsion angles

C6-C1-C2-C3	1.85(17)
C7-C1-C2-C3	-174.44(11)
C1-C2-C3-C4	-0.84(19)
C2-C3-C4-C5	-0.55(19)
C3-C4-C5-C6	0.9(2)
C2-C1-C6-C5	-1.51(17)
C7-C1-C6-C5	174.78(12)
C4-C5-C6-C1	0.15(19)
C6-C1-C7-O1	37.54(14)
C2-C1-C7-O1	-146.24(11)
C6-C1-C7-C8	-81.87(13)
C2-C1-C7-C8	94.35(13)
C11-N1-C8-C9	-78.43(13)
C10-N1-C8-C9	48.44(14)
C11-N1-C8-C7	155.84(10)
C10-N1-C8-C7	-77.29(13)
O1-C7-C8-N1	-178.23(9)
C1-C7-C8-N1	-56.26(13)
O1-C7-C8-C9	54.17(13)
C1-C7-C8-C9	176.14(11)
C10-N1-C11-C12	152.27(11)
C8-N1-C11-C12	-79.30(13)
N1-C11-C12-C16	-25.19(17)
N1-C11-C12-C13	157.45(12)
C14-N2-C13-C12	0.9(2)
C16-C12-C13-N2	-0.7(2)
C11-C12-C13-N2	176.82(12)
C13-N2-C14-C15	0.1(2)
N2-C14-C15-C16	-1.3(2)
C14-C15-C16-C12	1.5(2)
C13-C12-C16-C15	-0.59(19)
C11-C12-C16-C15	-178.01(12)

9.2.2 Crystallographic data for 1-Methyl-3-[[[dimethyl[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl]ethyl]ammonio] methyl]pyridinium diiodide 37

Table 33: Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1-Methyl-3-[[[dimethyl[(1R,2S)-2-hydroxy-1-methyl-2-phenyl]ethyl]ammonio] methyl]pyridinium diiodide 37. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
I(1)	9187(1)	2756(1)	10267(1)	22(1)
I(2)	1687(1)	5112(1)	6153(1)	19(1)
O(1)	5785(2)	1788(1)	7213(2)	21(1)
N(1)	2366(3)	2210(1)	7156(2)	16(1)
N(2)	206(3)	276(1)	9816(2)	18(1)
C(1)	5369(3)	2970(2)	5135(3)	17(1)
C(2)	4994(3)	3875(2)	4613(3)	20(1)
C(3)	5450(3)	4212(2)	3408(3)	25(1)
C(4)	6255(3)	3650(2)	2702(3)	26(1)
C(5)	6591(3)	2742(2)	3194(3)	24(1)
C(6)	6165(3)	2405(2)	4416(3)	21(1)
C(7)	4915(3)	2619(2)	6496(3)	17(1)
C(8)	2975(3)	2469(2)	5808(3)	16(1)
C(9)	2360(3)	1771(2)	4421(3)	19(1)
C(10)	483(3)	2443(2)	6490(3)	20(1)
C(11)	2620(3)	1191(2)	7529(3)	17(1)
C(12)	2225(3)	871(2)	8920(3)	17(1)
C(13)	581(3)	605(2)	8616(3)	18(1)
C(14)	1435(3)	167(2)	11361(3)	22(1)
C(15)	3101(3)	411(2)	11728(3)	24(1)
C(16)	3510(3)	766(2)	10516(3)	20(1)
C(17)	3287(3)	2765(2)	8689(3)	19(1)
C(18)	-1566(3)	-2(2)	9432(3)	25(1)

Table 34: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for Cmp 37.

	x	y	z	U_{eq}
H(1O)	6690(30)	1980(30)	7980(30)	31
H(2)	4430	4261	5078	24
H(3)	5210	4831	3065	30
H(4)	6573	3885	1887	31
H(5)	7113	2351	2695	29
H(6)	6417	1787	4764	25
H(7)	5247	3096	7374	20
H(8)	2419	3065	5326	19
H(9A)	2421	2039	3449	28
H(9B)	1173	1600	4158	28
H(9C)	3089	1226	4762	28
H(10A)	88	2356	7353	30
H(10B)	-168	2042	5560	30
H(10C)	309	3083	6127	30
H(11A)	1884	849	6528	21
H(11B)	3825	1034	7790	21
H(13)	-302	657	7536	21
H(14)	1150	-77	12191	27
H(15)	3967	337	12811	29
H(16)	4657	937	10764	24
H(17A)	2731	2677	9428	29
H(17B)	3247	3414	8401	29
H(17C)	4483	2564	9237	29
H(18A)	-2365	387	8553	38
H(18B)	-1777	66	10413	38
H(18C)	-1733	-642	9075	38

Hydrogen atoms inserted in idealized positions and refined riding with the atoms to which they were bonded. All H atoms had $U_{iso} = U_{eq}$ x 1.2 (x 1.5 for CH_3) of their carrier atoms.

Table 35: Anisotropic displacement parameters ($Å^2$ x 10^3) forCmp. 37.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I(1)	22(1)	21(1)	20(1)	0(1)	7(1)	0(1)
I(2)	22(1)	16(1)	22(1)	2(1)	11(1)	3(1)
O(1)	18(1)	20(1)	21(1)	5(1)	5(1)	3(1)
N(1)	17(1)	14(1)	16(1)	0(1)	8(1)	0(1)
N(2)	24(1)	15(1)	20(1)	1(1)	13(1)	-1(1)
C(1)	14(1)	17(1)	20(1)	1(1)	7(1)	-1(1)
C(2)	20(1)	17(1)	25(1)	0(1)	11(1)	-2(1)
C(3)	24(1)	23(1)	30(1)	8(1)	13(1)	-1(1)
C(4)	21(1)	34(1)	25(1)	5(1)	13(1)	-3(1)
C(5)	21(1)	30(1)	25(1)	-1(1)	13(1)	0(1)
C(6)	19(1)	20(1)	25(1)	-1(1)	11(1)	0(1)
C(7)	16(1)	16(1)	17(1)	1(1)	6(1)	0(1)
C(8)	15(1)	19(1)	15(1)	1(1)	7(1)	-1(1)
C(9)	19(1)	24(1)	13(1)	-1(1)	7(1)	-3(1)
C(10)	18(1)	20(1)	25(1)	4(1)	11(1)	2(1)
C(11)	23(1)	14(1)	18(1)	1(1)	12(1)	2(1)
C(12)	22(1)	14(1)	16(1)	1(1)	9(1)	1(1)
C(13)	21(1)	16(1)	15(1)	2(1)	7(1)	1(1)
C(14)	31(1)	20(1)	19(1)	3(1)	13(1)	1(1)
C(15)	29(1)	26(1)	15(1)	2(1)	7(1)	

1(1)					
C(16)	22(1)	21(1)	18(1)	-1(1)	8(1)
1(1)					
C(17)	25(1)	17(1)	16(1)	-2(1)	9(1)
1(1)					
C(18)	24(1)	23(1)	32(1)	4(1)	16(1)
0(1)					

Table 36: Bond lengths [Å] and angles [deg] for Cmp. 37.

Bond distances			
		C(17)-H(17C)	0.9800
		C(18)-H(18A)	0.9800
O(1)-C(7)	1.429(3)	C(18)-H(18B)	0.9800
O(1)-H(1O)	0.84000(12)	C(18)-H(18C)	0.9800
N(1)-C(17)	1.503(3)		
N(1)-C(10)	1.512(3)	Bond angles	
N(1)-C(11)	1.522(3)		
N(1)-C(8)	1.560(3)	C(7)-O(1)-H(1O)	102(3)
N(2)-C(13)	1.342(3)	C(17)-N(1)-C(10)	107.56(18)
N(2)-C(14)	1.353(3)	C(17)-N(1)-C(11)	110.74(18)
N(2)-C(18)	1.473(3)	C(10)-N(1)-C(11)	109.72(19)
C(1)-C(2)	1.396(3)	C(17)-N(1)-C(8)	111.29(18)
C(1)-C(6)	1.396(3)	C(10)-N(1)-C(8)	107.28(17)
C(1)-C(7)	1.525(3)	C(11)-N(1)-C(8)	110.15(17)
C(2)-C(3)	1.391(3)	C(13)-N(2)-C(14)	121.2(2)
C(2)-H(2)	0.9500	C(13)-N(2)-C(18)	119.4(2)
C(3)-C(4)	1.392(4)	C(14)-N(2)-C(18)	119.3(2)
C(3)-H(3)	0.9500	C(2)-C(1)-C(6)	119.6(2)
C(4)-C(5)	1.389(4)	C(2)-C(1)-C(7)	119.2(2)
C(4)-H(4)	0.9500	C(6)-C(1)-C(7)	121.2(2)
C(5)-C(6)	1.390(3)	C(3)-C(2)-C(1)	119.8(2)
C(5)-H(5)	0.9500	C(3)-C(2)-H(2)	120.1
C(6)-H(6)	0.9500	C(1)-C(2)-H(2)	120.1
C(7)-C(8)	1.533(3)	C(4)-C(3)-C(2)	120.6(3)
C(7)-H(7)	1.0000	C(4)-C(3)-H(3)	119.7
C(8)-C(9)	1.522(3)	C(2)-C(3)-H(3)	119.7
C(8)-H(8)	1.0000	C(5)-C(4)-C(3)	119.7(2)
C(9)-H(9A)	0.9800	C(5)-C(4)-H(4)	120.2
C(9)-H(9B)	0.9800	C(3)-C(4)-H(4)	120.2
C(9)-H(9C)	0.9800	C(4)-C(5)-C(6)	120.1(3)
C(10)-H(10A)	0.9800	C(4)-C(5)-H(5)	120.0
C(10)-H(10B)	0.9800	C(6)-C(5)-H(5)	120.0
C(10)-H(10C)	0.9800	C(5)-C(6)-C(1)	120.3(3)
C(11)-C(12)	1.505(3)	C(5)-C(6)-H(6)	119.8
C(11)-H(11A)	0.9900	C(1)-C(6)-H(6)	119.8
C(11)-H(11B)	0.9900	O(1)-C(7)-C(1)	112.61(18)
C(12)-C(13)	1.380(3)	O(1)-C(7)-C(8)	109.51(19)
C(12)-C(16)	1.402(3)	C(1)-C(7)-C(8)	109.41(17)
C(13)-H(13)	0.9500	O(1)-C(7)-H(7)	108.4
C(14)-C(15)	1.377(4)	C(1)-C(7)-H(7)	108.4
C(14)-H(14)	0.9500	C(8)-C(7)-H(7)	108.4
C(15)-C(16)	1.382(3)	C(9)-C(8)-C(7)	111.54(19)
C(15)-H(15)	0.9500	C(9)-C(8)-N(1)	111.19(19)
C(16)-H(16)	0.9500	C(7)-C(8)-N(1)	113.00(17)
C(17)-H(17A)	0.9800	C(9)-C(8)-H(8)	106.9
C(17)-H(17B)	0.9800	C(7)-C(8)-H(8)	106.9

N(1)-C(8)-H(8)	106.9
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
N(1)-C(10)-H(10A)	109.5
N(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
N(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-N(1)	115.21(18)
C(12)-C(11)-H(11A)	108.5
N(1)-C(11)-H(11A)	108.5
C(12)-C(11)-H(11B)	108.5
N(1)-C(11)-H(11B)	108.5
H(11A)-C(11)-H(11B)	107.5
C(13)-C(12)-C(16)	118.0(2)
C(13)-C(12)-C(11)	119.9(2)
C(16)-C(12)-C(11)	121.8(2)
N(2)-C(13)-C(12)	121.3(2)
N(2)-C(13)-H(13)	119.3
C(12)-C(13)-H(13)	119.3
N(2)-C(14)-C(15)	119.8(2)
N(2)-C(14)-H(14)	120.1
C(15)-C(14)-H(14)	120.1
C(14)-C(15)-C(16)	119.9(2)
C(14)-C(15)-H(15)	120.1
C(16)-C(15)-H(15)	120.1
C(15)-C(16)-C(12)	119.7(2)
C(15)-C(16)-H(16)	120.2
C(12)-C(16)-H(16)	120.2
N(1)-C(17)-H(17A)	109.5
N(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
N(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
N(2)-C(18)-H(18A)	109.5
N(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
N(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Torsion angles

C6-C1-C2-C3	-1.4(4)
C7-C1-C2-C3	178.0(2)
C1-C2-C3-C4	0.9(4)
C2-C3-C4-C5	0.6(4)
C3-C4-C5-C6	-1.7(4)
C4-C5-C6-C1	1.2(4)
C2-C1-C6-C5	0.3(3)
C7-C1-C6-C5	-179.0(2)
C2-C1-C7-O1	-163.4(2)
C6-C1-C7-O1	16.0(3)
C2-C1-C7-C8	74.6(3)
C6-C1-C7-C8	-106.1(2)
O1-C7-C8-C9	-63.8(2)
C1-C7-C8-C9	60.1(3)
O1-C7-C8-N1	62.3(2)
C1-C7-C8-N1	-173.78(19)
C17-N1-C8-C9	167.10(19)
C10-N1-C8-C9	-75.5(3)
C11-N1-C8-C9	43.9(2)
C17-N1-C8-C7	40.8(3)
C10-N1-C8-C7	158.18(19)
C11-N1-C8-C7	-82.4(2)
C17-N1-C11-C12	51.3(3)
C10-N1-C11-C12	-67.3(2)
C8-N1-C11-C12	174.83(19)
N1-C11-C12-C13	88.5(3)
N1-C11-C12-C16	-96.4(3)
C14-N2-C13-C12	-1.9(4)
C18-N2-C13-C12	-179.8(2)
C16-C12-C13-N2	1.6(4)
C11-C12-C13-N2	176.8(2)
C13-N2-C14-C15	1.1(4)
C18-N2-C14-C15	179.0(2)
N2-C14-C15-C16	0.0(4)
C14-C15-C16-C12	-0.2(4)
C13-C12-C16-C15	-0.5(4)
C11-C12-C16-C15	-175.7(2)

9.3 Curriculum Vitae

PERSONAL DETAILS – Katharina Bica

Permanent Address: Hütteldorferstrasse 131/9, 1140 Vienna - Austria
Date of Birth: September 14th 1980, Vienna, Austria

EDUCATION

Since 2004/11	Ph.D. research; Research Group – Prof. Gaertner; Institute of Applied Synthetic Chemistry; Vienna University of Technology
2007/04-2007/06	Visiting scientist at QUILL Research Centre, The Queen's University of Belfast, Belfast BT9 5AG, UK. – Prof. K. R. Seddon
2004/06	Diploma examination with distinction (MSc equivalent); Diploma thesis: Stereoselective 1,3-dipolare cyloaddition on chiral hydrobenzoin auxiliaries
1999/09 – 2004/06	Studies of Technical Chemistry at the Vienna University of Technology; Specialisation: Organic Chemistry and Technology
1991/09 – 1999/06	Grammar school with A-level with distinction
1987/09 – 1991/06	Elementary school

WORK EXPERIENCE & INTERNSHIP

Since 2004/12	University assistant at the Institute of Applied Synthetic Chemistry Vienna University of Technology
2003/08 – 2003/09	Internship at Sandoz GmbH; Vienna - Austria • Medicinal Chemistry
2002/10 – 2003/04	Scientific co-worker in the research group of Prof. Gaertner
2002/07 – 2002/09	Internship at OMV AG; Vienna – Austria • Petrochemistry
2001/09 – 2001/10	Internship at OMV AG; Vienna – Austria • Mineral oil and fuel analytics

PUBLICATIONS & CONFERENCE CONTRIBUTIONS

Publications

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Gaertner, P.; Bica, K.; Einzinger, Ch. *Monatshefte* **2004**, *135*, 549-555.

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1st European Chemistry Congress; Budapest, Hungary, August 2006.

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