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Applications of Chiral Ionic Liquids

Katharina Bica[a] and Peter Gaertner*[a]

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Despite the rapid growth in chiral ionic liquid (CIL) research, successful applications remained hidden for some time, but are increasing fast nowadays. The major part of this review deals with the use of CILs as solvents, catalysts or ligands in asymmetric synthesis. Chiral recognition abilities in spectroscopic techniques such as NMR, NIR or fluorescence spectroscopy are discussed as well as the application of CILs for separation in chromatography. In this review, we focus entirely on the applications of CILs; publications dealing with design and synthesis of CILs only are not mentioned.

Introduction

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 ethyl ammonium 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 led to an extraordinary boost in IL research in recent days. Indeed, academic and industrial research is still growing exponentially and exiting developments and applications are permanently published. During the last years, ILs have been established as alternatives to organic solvents and as new reaction media for chemical reactions and separation techniques.[2–4] 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, including chiral species.[5–8]

Since the first example of a chiral ionic liquid was reported in 1997 by Howarth et al. who prepared the cation-chiral CIL *N*,*N*-bis[(2*S*)-2-methylbutyl]imidazolium bromide, 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 (Figure 1).[9–11]

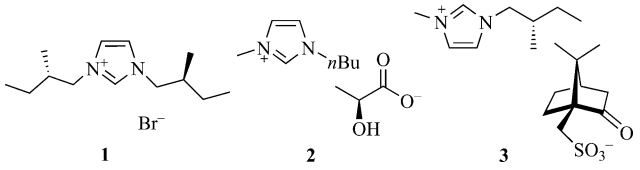


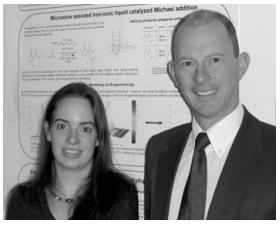
Figure 1. First examples of CILs with (a) chiral cation (left), (b) chiral anion (middle) or (c) both (right).

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 highly enantioselective synthesis with an enantiomeric excess >90% was reported. Nevertheless, even this field is growing rapidly, and applications can be divided into three different groups:

– Chiral ionic liquids in asymmetric synthesis
– Spectroscopic applications of chiral ionic liquids
– Chromatographic applications of chiral ionic liquids

Since the design and synthesis of CILs has been previously reviewed, this review focuses entirely on the application of CILs according to these three topics.

[a] Institute of Applied Synthetic Chemistry, Vienna University of Technology,
Getreidemarkt 9/163, 1060 Vienna, Austria
Fax: +43-1-58801-15499
E-mail: peter.gaertner@tuwien.ac.at



Katharina Bica graduated in Technical Chemistry at the Vienna University of Technology (VUT) in 2005 and received her PhD from the same university in december 2007 under the supervision of Prof. P. Gaertner working on chiral and metal-containing ionic liquids.

Peter Gaertner was born in 1964 in Vienna, Austria. He studied technical chemistry at the Vienna University of Technology (VUT) and received his PhD under the supervision of Prof. Christian Noe in 1991. After a postdoctoral stay as Erwin Schroedinger fellow with Prof. K. C. Nicolaou at Scripps Research Institute in 1996–1997, he returned to VUT and completed his habilitation in 2000 on stereoselective reactions in organic chemistry. In 2001 he became Associate Professor at the Institute of Applied Synthetic Chemistry at VUT and his research has focused on stereoselective synthesis either on solid support or using ionic liquids.

1. Chiral Ionic Liquids in Asymmetric Synthesis

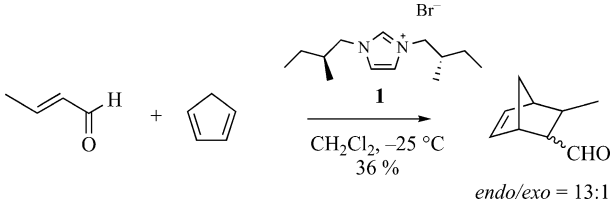
Chiral solvents have already been used as sole inducer of chirality in asymmetric synthesis. In 1975, Seebach et al. performed an electrochemical stereoselective reduction of ketones in the presence of chiral amino ethers as solvents and obtained a modest enantioselectivity of 23% *ee*.[12] However, enantioselectivity remained modest in most cases when chiral solvents were applied, 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. Since a polymer-like behaviour of ILs and a high degree of organization has been reported, a significant transfer of chirality can be expected.[13–15] The comparable simple synthesis and the possibility for recyclation combined with these specific properties suggest that CILs could improve the application of chiral solvents in asymmetric synthesis.

1.1. Diels–Alder Reaction

ILs have been successfully used as solvent and as Lewis acid catalyst for Diels–Alder reactions and, in general, an enhancement in reaction rate and selectivity was observed.[16] It could be shown that an explicit hydrogen bond between the cation and the carbonyl group of the dienophile is responsible for the improvement.[17] Therefore, it is 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. In principle, the CILs are used as solvents with or without co-solvent, however, there are also three publications applying the CILs as chiral inducer in catalytic amounts.

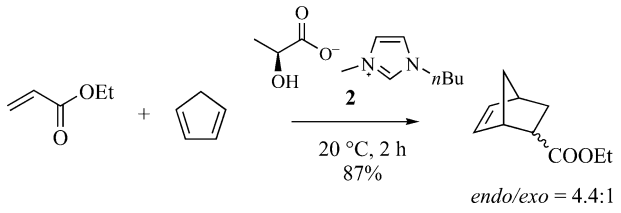
Chiral Ionic Liquids as Solvents

In contrast to many papers published later, the first example of a CIL in literature was immediately applied in asymmetric synthesis: The Diels–Alder reaction of crotonaldehyde or methacrolein with cyclopentadiene in the presence of chiral and achiral dialkylimidazolium salts and dichloromethane as co-solvent was investigated (Scheme 1).[9] 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*-bis[(2*S*)-2-methylbutane]imidazolium bromide **1** did not significantly differ from the one obtained with the non-chiral IL diethylimidazolium bromide and only very low enantiomeric excess, <5%, was achieved with this CIL.



Scheme 1.

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 (Scheme 2).[10] The neutral non-chiral ILs 1-butyl-3-methylimidazolium trifluoromethansulfonate [bmim-OTf], 1-butyl-3-methylimidazolium hexafluorophosphate [bmim-PF_6] and 1-butyl-3-methylimidazolium tetrafluoroborate [bmim-BF_4] but also the anion-chiral CIL bmim-(*S*)-lactate **2** were applied. The reaction rate of the Diels–Alder reaction between ethyl acrylate and cyclopentadiene in the CIL bmim-(*S*)-lactate was considerable higher than in the non-chiral ILs, and 87% yield could be achieved after only 2 hours. A moderate diastereoselectivity of 4.4:1 was found, but again, no enantioselectivity was observed using bmim-(*S*)-lactate **2** as reaction media.



Scheme 2.

The effect of the anion on the diastereoselectivity on the same Diels–Alder reaction between ethyl acrylate and cyclopentadiene was investigated by Nobuoka et al. who used the anion-chiral CIL 1-butyl-3-methylimidazolium (1*S*)-camphor-10-sulfonate **4** [bmim-(1*S*)-CSA] in bmim-BF_4 (15:100 mol/mol) (Figure 2) as solvent.[18] 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-dimethylcamphorsulfonate [bm_2im-(1*S*)-CSA] **5** that lacks the acidic C^2 proton gave a dramatically reduced diastereoselectivity of 3.0:1.

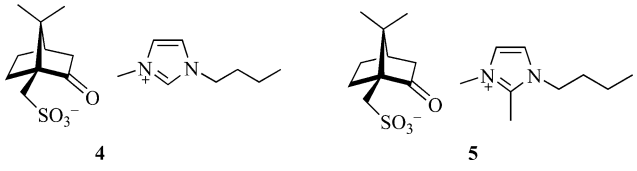
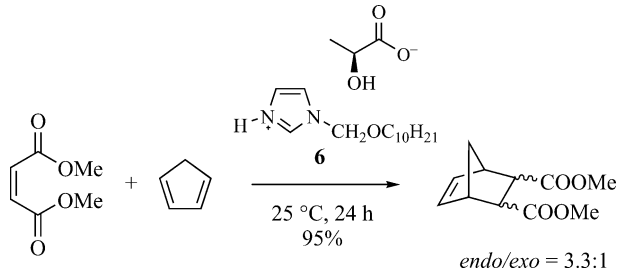


Figure 2. CILs derived from (1*S*)-camphorsulfonic acid.

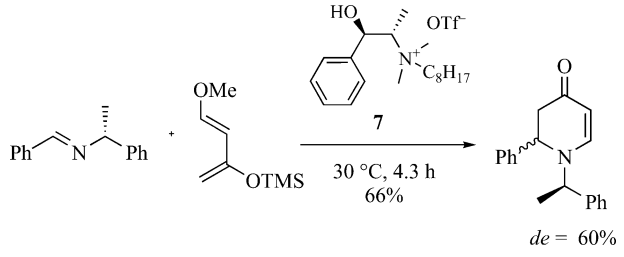
Protic imidazolium ILs have been tested as solvent and reaction media in the Diels–Alder reaction of dimethylmaleate and methyl acrylate (Scheme 3).[19] High conversion of 95% and *endo*/*exo* selectivities of 3.7:1 with protic 1-alkylimidazolium and 1-alkoxyimidazolium lactates **6** were obtained. However, the differences in yield and diastereoselectivity between the racemic (*rac*)-lactates and the enantiopure (*S*)-lactates were negligible.

The asymmetric aza-Diels–Alder reaction of chiral imines with Danishefsky's diene in chiral ephedrinium-derived ILs was investigated by Pégot et al. (Scheme 4).[20] The corresponding cycloadduct was obtained with diastereoselectivities up to 60% *de* in good yield without any use of co-



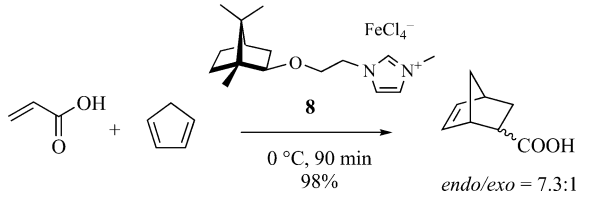
Scheme 3.

solvent or Lewis-acidic catalyst. The use of CIL **7** resulted in a "matched" case of double stereoinduction and in a significant enhancement of diastereoselectivity compared to 32% *de* that was obtained when no CIL but a catalytic amount of $ZnCl_2$ was added.



Scheme 4.

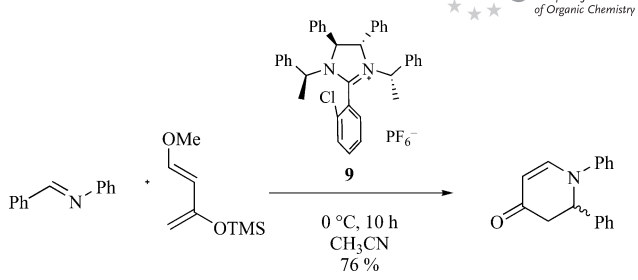
Our group used camphor-derived CILs as solvent for the Diels–Alder reaction of acrylic acid and cyclopentadiene (Scheme 5).[21] Best results could be obtained with the iron-containing camphene-derived CIL **8** with yields of 98% and a diastereoselectivity of 7.3:1. The CIL could be successfully recycled four times with constant yield, however, diastereoselectivity decreased after the third run. Similarly to other examples with acrylic acid derivatives, no enantioselectivity was observed.



Scheme 5.

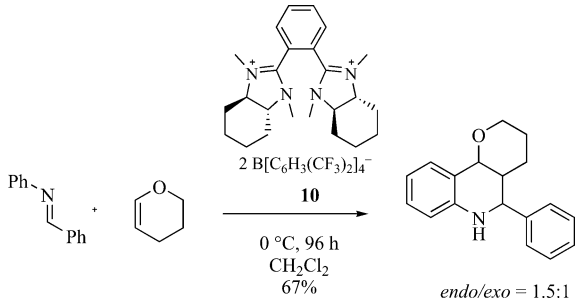
Chiral Ionic Liquds as Catalysts

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 (Scheme 6).[22] In contrast to previous papers, the CIL was used in catalytic amounts only: Generally, 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.



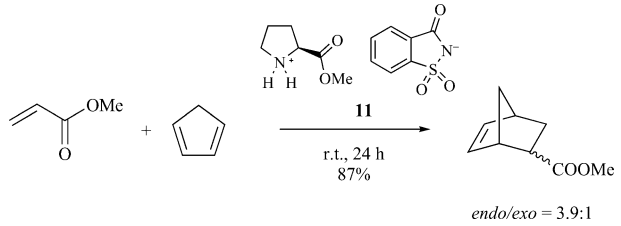
Scheme 6.

The inverse electron demand aza-Diels–Alder reaction of *N*-benzylideneaniline and dihydropyrane could not be catalyzed by monoimidazolinium salt **9**. However, when the bisimidazolinium salt **10** 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 (Scheme 7).[22]



Scheme 7.

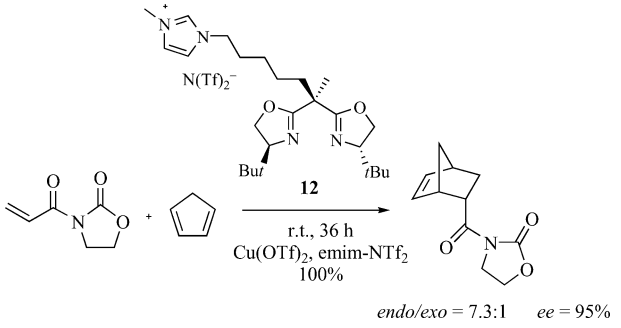
Easily prepared amino acid based CILs with chiral ammonium cation and environmentally benign anions like nitrate or saccharinate were applied as catalysts in the cycloaddition of methyl acrylate and cyclopentadiene (Scheme 8).[23] Excellent yields in the range of 89–99% were obtained with catalytic or stoichiometric amounts of all amino acid CILs (30 or 100 mol-%, resp.) without further addition of co-solvent. The use of 1 equiv. of saccharinate **11** showed better diastereoselectivities (*endo*/*exo* around 3:1 to 4:1) than the corresponding nitrates and is in the same range than values obtained with 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.



Scheme 8.

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 cop-

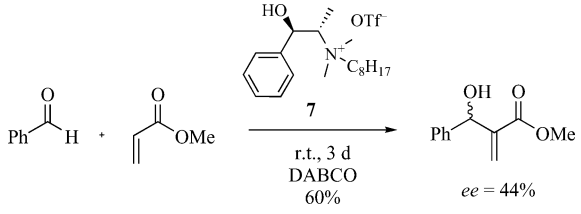
per(II)-catalysed cycloaddition of *N*-acryloyloxazolidinone and cyclopentadiene (Scheme 9).[24] When 10 mol-% of the IL-supported chiral ligand **12** were used with the IL 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide [emim-N(Tf)$_2$] as solvent, a significant enhancement in rate and 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)$_2$.



Scheme 9.

1.2. Asymmetric Baylis–Hillman Addition

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 methyl acrylate (Scheme 10).[25] 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 equiv. of chiral ephedrinium IL **7**. The excess of CIL led 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% *ee* only but resulted in a higher yield of 75%.



Scheme 10.

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 chiral reaction media.[26] 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 3).

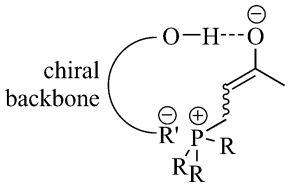
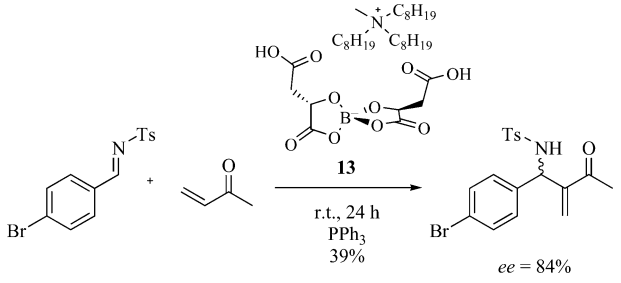


Figure 3. Interaction of anion-chiral CIL with a zwitterionic intermediate.

Thus anion-chiral methyltrioctylammonium ILs **13** which contain a chiral dimalatoborate anion were synthesized in a simple 2-step procedure based on chiral pool (*S*)-malic acid. When tested as solvent in the aza-Baylis–Hillman reaction between methyl vinyl ketone and *N*-(4-bromobenzylidene)-4-toluenesulfonamide using PPh_3 as nucleophilic catalyst, an enantiomeric excess up to 84% could be obtained with a conversion varying between 34 and 39% (Scheme 11). This strategy of efficient chirality transfer via strong intermolecular interactions between solvent molecules and intermediates led to the highest asymmetric induction ever obtained with a chiral solvent as the sole source of chirality.



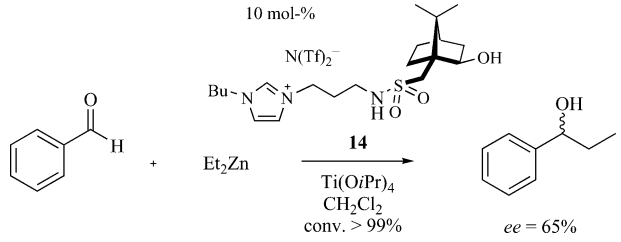
Scheme 11.

1.3. Asymmetric Alkylation of Aldehydes

There are several examples for the successful application of CILs in asymmetric alkylation of aldehyds with diethylzinc. However, it should be noticed that the CILs do not act as innocent solvents in this transformation, since it is well known that azolium salts form N-heterocyclic carbene ligands in presence of bases such as Et_2Zn.[27] Nevertheless, the chiral imidazolium salts used as ligands in the following could be recycled as it is typically for ILs without loss of activity or selectivity, which encouraged us to report these papers in this review.

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 transition metal-promoted addition of organozinc reagents.[28] Various hydrophobic ILs containing chiral

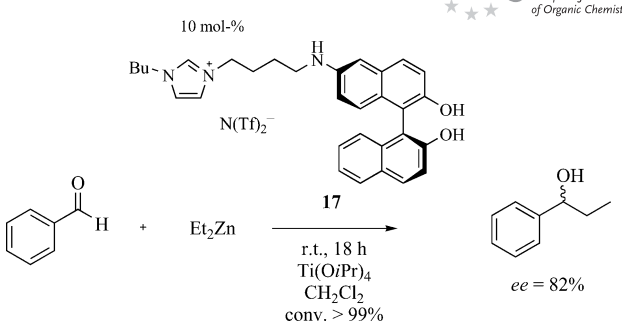
camphorsulfonamide units were used in the titanium-catalyzed asymmetric addition of diethylzinc to benzaldehyde (Scheme 12). However, to carry out the reaction in homogeneous solution, toxic dichloromethane had to be used as solvent. *exo*-Borneol derivative **14** proved to be superior and enantioselectivities of 65% *ee* as well as complete conversion were 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.



Scheme 12.

Modification of these IL-supported camphorsulfonamide derivatives led to trialkoxysilylated camphorsulfonamides that were further immobilized on the surface of mesoporous nanostrucured silica (Figure 4).[29] Highly structured materials with hexagonal symmetry were obtained with both ionic and non-ionic trialkoxysilylated camphorsulfonamide precursors. The catalytic properties of these silica-supported CIL materials were inferior to the results obtained with the soluble task-specific imidazolium salts and enantioselectivities of 3 and 30% *ee*, resp. only were obtained with materials **15** and **16**.

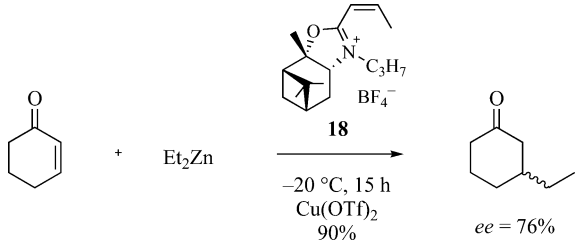
Chiral binaphthyls have proved to be extremely efficient auxiliaries and ligands in asymmetric catalysis; hence easily recoverable BINOL ligands with an ionic imidazolium tag were also developed by Gadenne et al. (Scheme 13).[30] Again, the ionic structure allowed a tuning of solubility of the supported BINOL ligands and combined the advantages of homogeneous catalysis and easy separation and recycling of the chiral ligand **17**. Compared to the camphorsulfonamide CILs higher enantioselectivities up to 82% *ee* could be obtained in the titanium(IV)-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc in the presence of 10 mol-% BINOL-functionalized CIL.



Scheme 13.

1.4. Asymmetric Michael Addition

Malhotra and Wang reported the successful application of terpene-based CILs as catalysts for the enantioselective addition of diethylzinc. Copper-catalyzed enantioselective Michael addition of diethylzinc to various enones has been achieved in the presence of catalytic amounts of α-pinene-derived CILs (Scheme 14).[31] A significant improvement of selectivity from 17 to 74% *ee* was observed when the amount of CIL **18** was increased from 3 to 25 mol-%, however, only a small change in enantiomeric excess was achieved 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% *ee* in the presence of 35 mol-% CIL at –20 °C.



Scheme 14.

The group of Bao investigated the influence of ethyl (*S*)-(–)-lactate and diethyl (*S*)-(+)-tartrate-derived CILs on asymmetric Michael addition of diethyl malonate to chalcone (Scheme 15).[32] Excellent yields in the range of 90 to 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 **19** proved to be superior, however, only modest enantiomeric excess of 25% was ob-

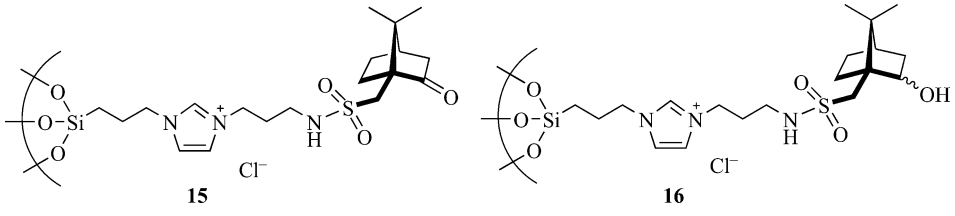
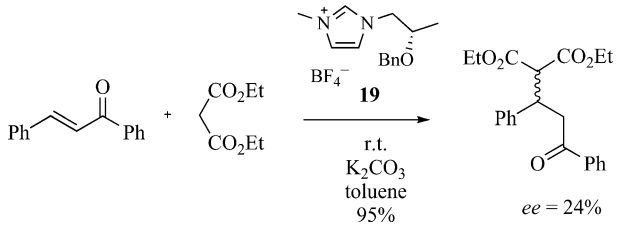


Figure 4. Solid-supported camphorsulfonamide CILs.

served, whereas the tartrate derivative only gave an enantiomeric excess of 10%. Again, the possible formation of N-heterocyclic carbene (NHC)-ligands under basic conditions as present in this reaction should be mentioned.



Scheme 15.

The same reaction was performed in chiral hydroxyl-functionalized CILs prepared from (*S*)-alaninol (**20**), (*S*)-valinol (**21**) and (*S*)-leucinol (**22**) as solvent by Ou and Huang (Figure 5).[33] Instead of toluene, the more polar acetonitrile was used as co-solvent; however, enantioselectivities are in the same range with up to 15% *ee* and moderate to good yields varying from 52 to 86% were obtained.

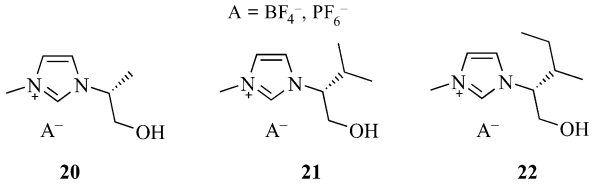
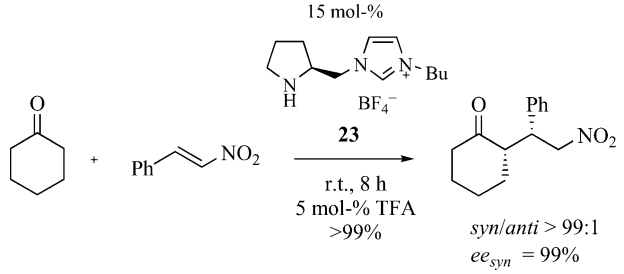


Figure 5. Amino acid-derived CILs for asymmetric Michael addition.

1.5. Organocatalysis

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. 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.[34] It is therefore obvious that CILs might be an interesting alternative to overcome these limitations and many successful examples of CILs in organocatalysis have been reported in the last two years. It is noteworthy, that in all reported cases the CIL is used in substoichiometric amounts and not as chiral reaction media and solvent.

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.[35] This novel catalytic system **23** could efficiently catalyze the Michael addition of a broad range of ketones and aldehydes and of nitroolefines as Michael acceptors with high yields (up to 100%), excellent enantioselectivity (up to 99% *ee*) and diastereoselectivity (*syn*/*anti* up to 99:1) (Scheme 16). The tuneable solubility of the CIL allowed a simple recycling 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.



Scheme 16.

Another successful example for IL-supported organocatalysis was published only one month later by Miao and Chan who used IL-anchored proline **24** as efficient and recyclable catalysts for direct asymmetric aldol reaction (Figure 6; left).[36] 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 (**24**), only low selectivity and conversion was observed in the asymmetric aldol reaction of acetone and 4-cyanobenzaldehyde (Scheme 17, Table 1, entry 1).

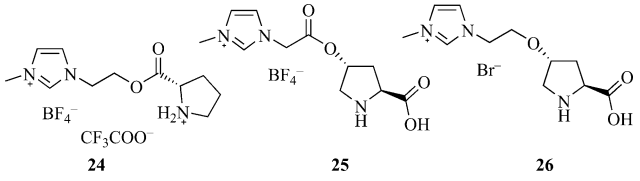
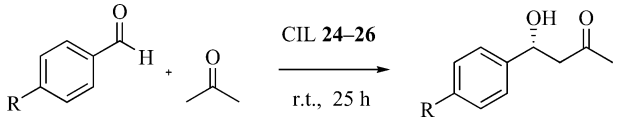


Figure 6. (*S*)-Proline-derived CILs for asymmetric aldol reaction.



Scheme 17.

Table 1. Direct organocatalytic aldol reaction catalyzed by CILs **24**–**27**.

Entry[a]	CIL/catalyst	Amount	Yield	% *ee*
1	**24**	30 mol-%	10	11
2	**25**	30 mol-%	68	85
3[b]	**25**	30 mol-%	64	82
4[c]	**25**	30 mol-%	60	87
5[d]	**26**	30 mol-%	94	82
6	(*S*)-proline	10 mol-%	68	71

[a] Entry 1: R = CN; entries 2–6: R = NO_2. [b] Third recyclation of CIL **25**. [c] DMSO added as co-solvent. [d] 10 mol-% of CIL **26** in bmim-BF_4.

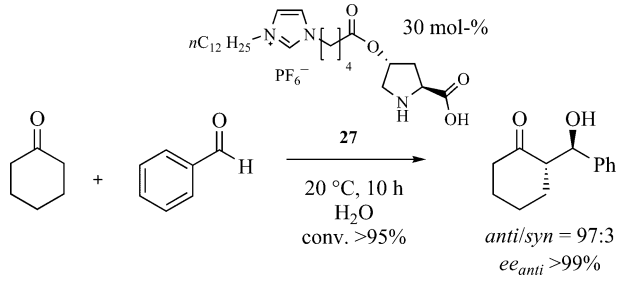
However, when IL-supported (2*S*,4*R*)-4-hydroxyproline **25** which retained the free carboxyl group was applied,

much better yield of 64% and enantiomeric excess of 85% could be obtained (Table 1, entry 2 & 3). The addition of DMSO as co-solvent slightly improved enantioselectivity but decreased yield (entry 4).

Superior catalytic activity of this IL-supported proline derivative **25** compared to (*S*)-proline in neat ketone systems was observed, thus reducing the need for DMSO or DMF as solvent (Table 1, entry 6). Recycling studies revealed that this catalyst can be easily recycled and reused with the same efficiency for four cycles, however, toxic dichloromethane was used to precipitate the catalyst and regain the IL-supported proline (Table 1, entry 3).

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 (Figure 6, right).[38] Direct asymmetric aldol reactions of acetone with various aromatic aldehyds were carried out with 10 mol-% of the (*S*)-proline unit **26** in bmim-BF_4 and led to satisfactory yields and enantioselectivities (Table 1, entry 5). 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.

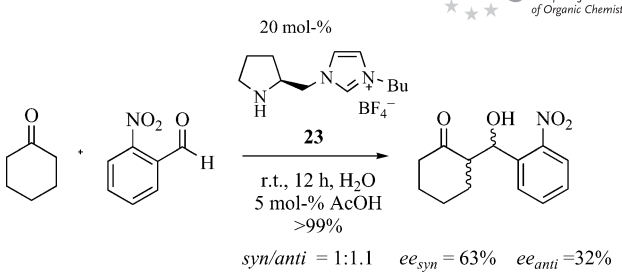
Recently, the group of Zlotin presented a modification of chiral salt **25** with increased chain length to obtain amphiphilic (*S*)-proline-derived organocatalysts (Scheme 18).[37] Chiral salt **27** was able to catalyze the direct asymmetric aldol reaction between cycloalkanones and aromatic aldehydes in the presence of water and retained its activity and selectivity over five reaction cycles.



Scheme 18.

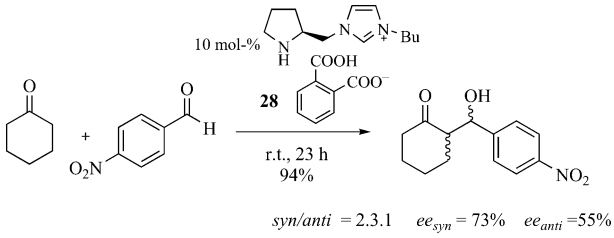
Pyrrolidine-containing CILs were less efficient in the direct asymmetric aldol reaction than the proline-derived systems.[39] Although these functionalized CILs **23** could efficiently catalyze the aldol reaction of 4-nitrobenzaldehyde and acetone in the presence of acidic additives such as acetic acid and water, only poor enantioselectivities of 10% *ee* were observed. However, enantioselectivities of up to 63% *ee* and complete conversion were observed in the aldol reaction of cyclic ketones, although almost equal amounts of *syn* and *anti* product were formed (Scheme 19).

Zhang et al. also presented a combinatorial approach to a series of functionalized CILs, including doubly chiral and bis-functional CILs.[40] Among those, pyrrolidine systems comparable to CIL **23** but with different chiral and achiral anions were tested as chiral organocatalysts for the direct



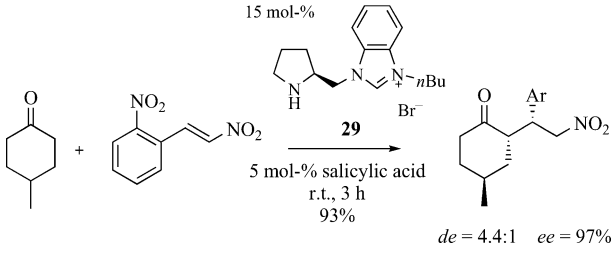
Scheme 19.

aldol reaction of 4-nitrobenzaldehyde and cyclohexanone. Interestingly, best results were obtained with CIL **28** bearing an achiral monophthalate anion, suggesting a non-covalent bifunctional catalysis present (Scheme 20).



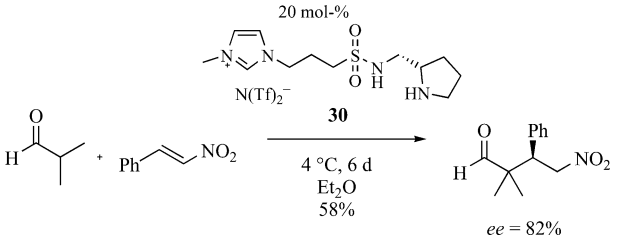
Scheme 20.

Comparable CILs with a benzimidazolium unit attached to (*S*)-pyrrolidine were successfully applied for the desymmetrization of prochiral ketones via Michael addition to nitroolefines (Scheme 21).[41] In the presence of 15 mol-% of chiral benzimidazolium salt **29** that was identified as optimal catalyst and 5 mol-% of salicylic acid, the desired Michael adducts bearing three chiral centres were obtained with good to excellent yield (61 to 99%), good diastereoselectivity (4.0:1 to >10.0:1) and excellent enantioselectivities of 93 to 99% *ee*. Again, the CIL could be simply recycled via ether precipitation and was reused four times with constant stereoselectivity but a distinct loss of catalytic activity in the third and fourth run.



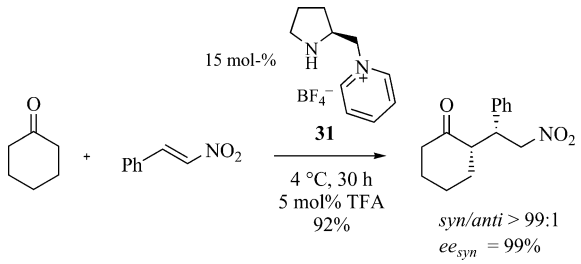
Scheme 21.

A pyrrolidine-based CIL that includes a weakly acidic N–H proton was published by Headley et al., who tethered a chiral pyrrolidine derivative via a sulfonamide functionality on an imidazolium support.[42] CIL **30** was capable of catalyzing the Michael addition of aldehydes 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 (Scheme 22).



Scheme 22.

The group of Headley reported a modification of Luos organocatalytic CIL **23**, in which the imidazolium cation is replaced by a pyridinium moity (Scheme 23).[43] This series of pyrrolidine-based pyridinium CILs was also tested in the asymmetric Michael addition of various ketones and nitrostyrenes, indicating superior catalyic properties of chloride and tetrafluoroborate salt **31** in comparison to the corresponding hexafluorophosphate ore $N(Tf)_2^-$ salts. Similarly to CIL **23**, excellent yields (74 up to 99%), diastereoselectivities (95:5 up to >99:1) and enantioselectivities (up to 99% *ee*) were obtained in the presence 15 mol-% catalyst and 5 mol-% of trifluoroacetic acid as additive.

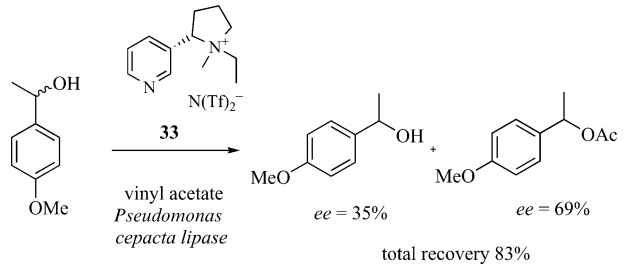


Scheme 23.

Recently, Zhou and co-workers reported a CIL based on camphorsulfonic acid readily as promoter for the (*S*)-proline-catalyzed aldol reaction.[44] When the (*S*)-proline-catalyzed reaction of acetone with 4-nitrobenzaldehyde was conducted in the presence of 10 mol-% 3-(2-hydroxypropyl)-1-methylimidazolium (1*R*)-camphor-10-sulfonate **32**, an increase in reaction rate and yield was observed. In contrast, a large excess (200 mol-%) of the CIL proved best for the accelaration of the (*S*)-proline-catalyzed reaction of cyclohexanone with 4-nitrobenzaldehyde.

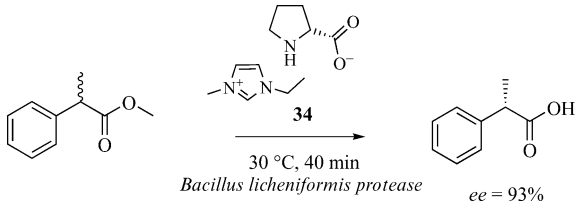
1.6. Biotransformation

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* (Scheme 24).[45] The nicotine-derived CIL **33** was used as reaction media without co-solvent, and medium enantioselectivities were obtained.



Scheme 24.

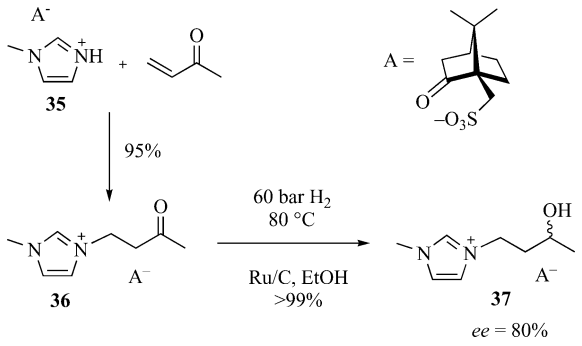
The group of Zhao et al. studied the enzymatic hydrolysis of phenylalanine methyl ester in aqueous solutions of CILs carrying anions of chiral α-amino acids (Scheme 25).[46] The protease activity was stabilized and moderate to high enzyme enantioselectivities could be observed. Interestingly, higher enantioselectivities and yields of (*S*)-phenylalanine were observed in CILs based on (*R*)-amino acids (**34**) compared to those derived from the (*S*)-isomers.



Scheme 25.

1.7. Enantioselective Hydrogenation

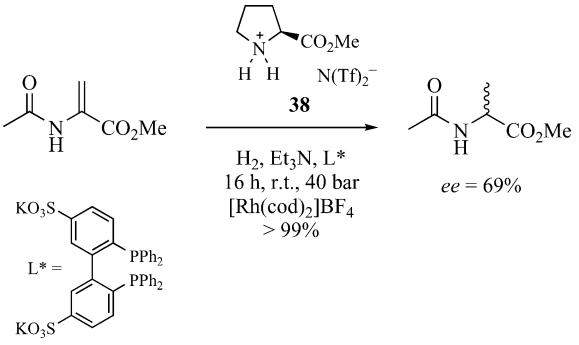
The maybe most surprising example of chirality transfer was published by Wasserscheid et al. who could induce high selectivity by simple ion-pairing effects.[47] *N*-Methylimidazolium (*R*)-camphorsulfonate **35** was reacted in a Michael-type reaction with methyl vinyl ketone (Scheme 26). Hydrogenation of the obtained *N*-(3′-oxobutyl)-*N*-methylimidazolium (*R*)-camphorsulfonate **36** under heterogeneous conditions using ruthenium on charcoal in ethanol at 60 °C and 60 bar gave the corresponding hydroxybutyl derivative **37** in quantitative yield and enantioselectivities up to 80% *ee*. A strong correlation between enantioselectivity and increasing concentration of the imidazolium salt was ob-



Scheme 26.

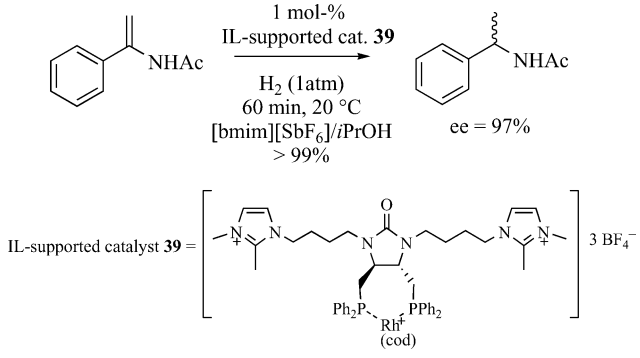
served, indicating the importance of ion-pair interaction. Given the simplicity and the large field of substrates that can be attached to the imidazolium salts, it is obvious that this methodology of chirality transfer bears an enormous potential for asymmetric transformations especially in industrial scale.

A second example of asymmetric hydrogenation was reported by the group of Leitner, who performed the homogeneous rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate and of dimethyl itaconate with tropos biphenylphosphane ligands in readily available amino acid-based CILs (Scheme 27).[48] In the presence of the protic (*S*)-proline-derived CIL **38** the flexible biphenyl unit that does not possess permanent chiral information could induce enantioselectivities of up to 69% *ee* with complete conversion. A remarkable increase of diastereoselectivity was observed when 20 equiv. of triethylamine were added. After extraction of the product with $scCO_2$, the catalyst could be successfully recycled, although a small decrease of conversion and enantioselectivity was observed in the third run.



Scheme 27.

The properties of ILs as alternative support material were applied in 2003 by the group of Lee et al., who prepared chiral 1,4-biphosphane ligands immobilized with two imidazolium units (Scheme 28).[49] Although the rhodium complexed bis-imidazolium salt **39** might not strictly qualify as IL, the structural similarity encouraged us to report this example of ionic liquid-supported ligands in this review. This ionic liquid-grafted biphosphane ligand complexed with rhodium was successfully applied in the asymmetric reduction of *N*-acetylphenylethenamine. High conversion (>99%) and excellent selectivity of 97% *ee* was observed under biphasic conditions (bmim-SbF_6/*i*PrOH), that also allowed recycling of the catalytic system. However, the catalytic efficiency significantly decreased after the second run.

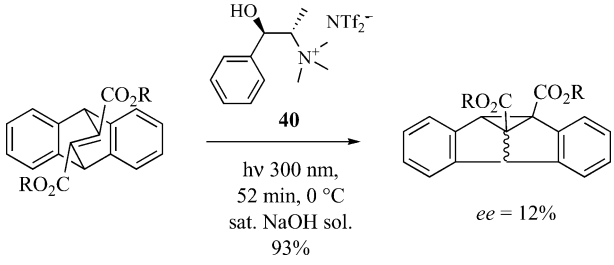


Scheme 28.

1.8. Others

Enantioselective Photodimerization

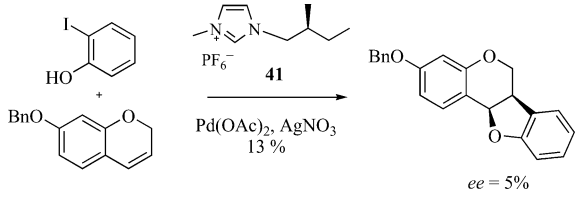
The group of Armstrong evaluated four different CILs derived from commercially available optically resolved materials as chiral inducing solvents for the enantioselective photoisomerization of dibenzobicyclo[2.2.2]octatriene (Scheme 29).[50] Enantiomeric excesses up to 12% were obtained with CIL **40**, indicating an ion pairing interaction of the CIL cations 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.



Scheme 29.

Heck Reaction

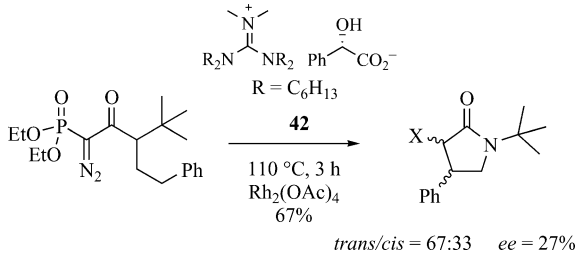
The palladium-catalyzed Heck oxyarylation of 3-(benzyloxy)pterocarpan using the CIL (*S*)-1-methyl-3-(2-methylbutyl)imidazolium hexafluorophosphate (**41**) as solvent was investigated by Kurtan et al. (Scheme 30).[51] However, asymmetric induction of the non-functionalized alkyl chain is low although the imidazolium salt was involved via carbene formation. The reaction resulted in an enantiomeric excess of 5% and 13% yield when $Pd(OAc)_2$ was used. Better yield of 28% but a slightly lower *ee* of 4% was achieved with $PdCl_2$ as catalyst. When an achiral phosphane ligand was added, conversion was improved up to 45% but enantioselectivity was completely lost.



Scheme 30.

C–H Insertion

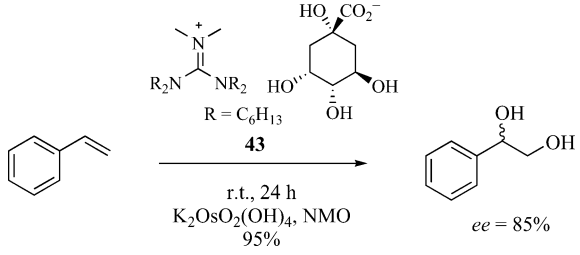
Interesting examples of anion-chiral ILs were reported by Branco et al. who combined a guanidinium cation with anions of readily available natural chiral acids.[52] Thus chiral mandelates, lactates, salts of quinic acid, camphorsulfonates and hydroxyprolinates were obtained and used as chiral inducing agents in two different reactions. The rhodium(II)-catalyzed carbenoid asymmetric C–H insertion of α-phosphono-α-diazoacetamids was performed using the guanidinium (*R*)-mandelate CIL **42** 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 (Scheme 31).



Scheme 31.

Asymmetric Dihydroxylation

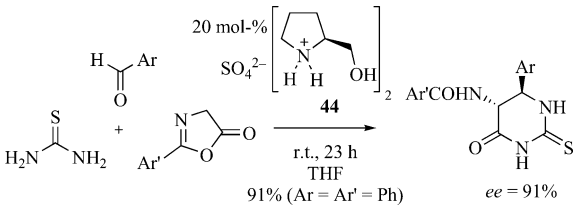
The second reaction investigated with guanidinium CILs was a Sharpless-type osmium-catalyzed asymmetric dihydroxylation of styrene and of 1-hexene to obtain chiral vicinal diols (Scheme 32).[52] A remarkably high enantiomeric excess of 85 and 72%, resp. with excellent yields of 95 and 92% could be achieved when the chiral quinic acid guanidinium salt **43** 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.



Scheme 32.

Biginelli Reaction

Recently, the amino acid-obtained CILs (*S*)-prolinium sulfate, (*S*)-alaninium hexafluoroposphate and (*S*)-threoninium nitrate have been successfully applied for the stereoselective synthesis of polyfunctionalized perhydropyrimidines (Scheme 33).[53] The three-component domino reaction of urea or thiourea derivatives, active methylene components and aromatic aldehydes took place in the presence of catalytic amounts of the CIL (*S*)-prolinium sulfate (20 mol-%) **44** and THF as solvent. The proline-derived CIL proved to be most suitable, and considerably lower yields, diastereo- and enantioselectivities were obtained with the corresponding alanine or threonine-derived CILs. A huge variety of functionalized perhydropyrimidines were obtained as single diastereomers in moderate to high yield (44 up to 92%) and surprisingly high enantioselectivity of 78 up to 95% *ee* (Scheme 31).



Scheme 33.

2. Spectroscopic Applications

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.[54]

In order to investigate interionic diastereomeric interactions between the enantiopure CIL and a racemic substrate, the authors performed ^{19}F NMR spectroscopy of a mixture of racemic Mosher's acid sodium salt and the ephedrine-based CIL **40** in a common NMR solvent (Table 2, entry 1). Depending on the ratio of CIL 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. 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.

The group of Gaumont repeated the experiment with chiral thiazolinium salts and obtained a splitting up to 30 Hz applying the *N*-benzylthiazolinium derivative **45** (entry 2).[55] 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.

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 the (*S*)-valine-derived CILs **46** (entry 3).[56] 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, Mosher's acid potassium salt was used as racemic substrate in the presence of crown ether 18C6 in a polar aprotic solvent CD_2Cl_2. It is important to notice the increase of chiral recognition of a racemic anion and a chiral cation in the use of potassium counterion and

crownether as additive: In fact, a doubling of signal splitting was observed in both ^1H and ^{19}F NMR spectroscopy. These improved interactions are explained by the tightness of the anion pair in the presence of a bulky counter cation like potassium that is trapped by the crown ether 18C6, compared to Mosher's acid sodium salt that was applied in previous communications.

The presence of a second hydroxy group further improved diastereomeric interaction, as shown by the bidentate imidazolinium salts reported by Jurčík et al.[57] 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 obtained when the borate salt **47** was used (entry 4).

In case of isomannide-derived CILs, Mosher's acid silver salt was mixed with the bis(ammonium) iodide salt **52** in CD_3CN to preform Mosher's acid chiral ammonium salt with a $\Delta\delta$ value of 15 Hz.[61] When the solution was mixed with 4 additional equivalents of the chiral bis(ammonium) bis(trifluoromethylsulfonyl)amide salt, the splitting was further enhanced to 23 Hz.

An interesting example of CILs with a spiro skeleton was published by Patil et al. in 2006 and chiral discrimination abilities could be demonstrated in ^1H NMR spec-

Table 2. Diastereomeric interactions of various CILs in ^{19}F and ^1H NMR spectroscopy.

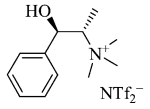
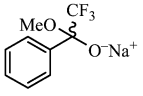
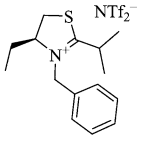
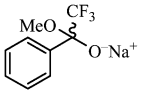
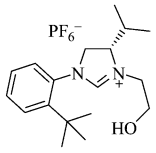
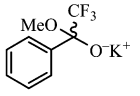
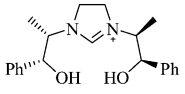
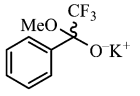
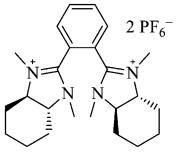
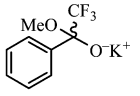
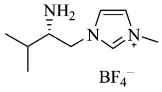
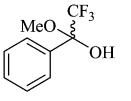
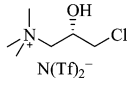
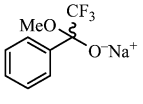
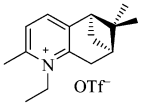
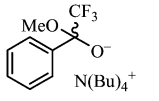
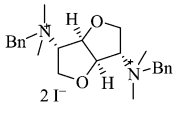
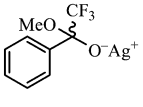
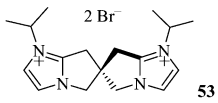
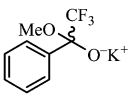
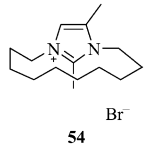
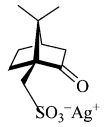
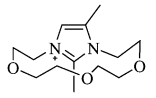
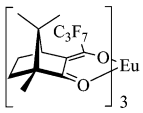
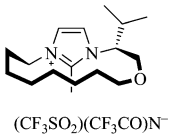
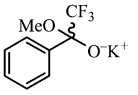
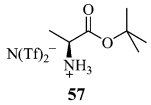
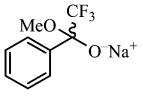
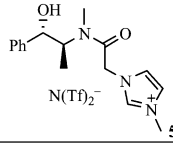
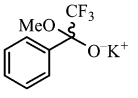
Entry	CIL	Substrate[b]	Conditions[c]	Δδ (^{19}F) [Hz][a]	Δδ (^1H) [Hz][b]	Lit.
1	 **40**		8.2 equiv. CIL CD_2Cl_2	11	–	[54]
2	 **45**		1 equiv. CIL C_6D_6	31	–	[55]
3	 **46**		3.3 equiv. CIL 1 equiv. 18C6 CD_2Cl_2	63	55	[56]
4	 **47**		1 equiv. CIL [D$_6$]acetone	152	24	[57]
5	 **48**		1 equiv. CIL [D$_6$]acetone	53	6	[22]
6	 **49**		3.7 equiv. CIL aqu. CD_2Cl_2	35	–	[58]
7	 **50**		24 equiv. CIL CD_2Cl_2/D_2O	25	–	[59]
8	 **51**		10 equiv. CIL CD_2Cl_2	4		[60]
9	 **52**		1 equiv. CIL CD_3CN	15	–	[61]

Table 2. *(Continued)*.

Entry	CIL	Substrate[b]	Conditions[c]	Δδ (^{19}F) [Hz][a]	Δδ (^{1}H) [Hz][b]	Lit.
10	 **53**		0.5 equiv. CIL 1.5 equiv. 18C6 20% [D$_6$]DMSO in CDCl$_3$	–	6[c]	[62]
11	 **54**		1 equiv. CIL CDCl$_3$	–	7[d]	[63]
12	 **55**		10 equiv. CIL 10 equiv. Et$_3$NCl CDCl$_3$	–	19[d]	[64]
13	 **56**		3 equiv. CIL 1 equiv. 18C6 CDCl$_3$	7	–	[65]
14	 **57**		1 equiv. CIL [D$_6$]DMSO	[e]	–	[66]
15	 **58**		3 equiv. CIL 1 equiv. 18C6 CD$_2$Cl$_2$	37	–	[67]

[a] Shift difference of split CF_3 group at ca. –70 ppm in ^{19}F NMR spectroscopy, if not otherwise stated. [b] Shift difference of split OMe group in ^{1}H NMR spectroscopy, if not otherwise stated. [c] Splitting of the two protons at δ = 4.08 and 4.41 ppm that correspond to the -CH_2 protons next to the spiro centre into two doublets. [d] Shift difference of the imidazolium C5-proton in ^{1}H NMR spectroscopy. [e] Shift difference not reported; small splitting without baseline separation.

troscopy.[62] When the racemic spiro bromide **53** was mixed with 2 equiv. of Mosher's acid potassium salt in the presence of 18-crown-6, a splitting of the signals of the H proximate to the spiro centre into doublets was observed (entry 10). Although optical resolution of the diastereomeric salts with (1*S*)-(+)-camphorsulfonic acid failed, the authors were able to separate the racemic spiro salts via chiral preparative HPLC and thus obtained this CIL in enantiopure form.

Chiral recognition ability between a racemic imidazolium cation and camphorsulfonate was also published by Saigo et al. in 2002 (entry 11).[63] 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 **54** 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 12).[64] 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 **55**. By introduction of a valinol-based cyclophane structure, it was possible to obtain these planar CILs **56** in enantiopure form (entry 13).[65] 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.

Recently, Bwambok et al. described the synthesis and the enantiomeric recognition properties of (*R*)- and (*S*)-alanin *tert*-butyl ester-derived CILs **57**.[66] A small splitting but no baseline separation of the CF_3 group of racemic sodium salt of Mosher's acid was observed in the presence of one equivalent of (*R*)- or (*S*)-CIL **57**, however, no concrete shift difference is given (entry 14).

Previously, we were able to synthesize knew CILs with amido alcohol structure starting from chiral-pool amino alcohols like ephedrine, pseudoephedrine, prolinol or diphenylprolinol.[67] The strongest diastereomeric interactions were observed for the ephedrine-based CIL **58** with a splitting of 37 Hz (entry 14). Interestingly, a maximum splitting was observed for the ephedrine and the pseudoephedrine

derivatives in the presence of 3 equiv. of CIL (Figure 7), whereas increasing splitting with increasing amounts of CIL was observed with the (*S*)-prolinol derivatives.

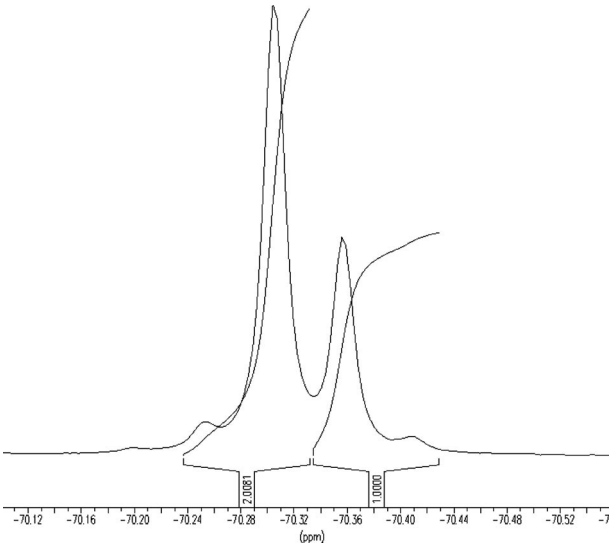


Figure 7. ^{19}F NMR spectrum of an (*S*)-enriched sample of Mosher's acid potassium salt in the presence of CIL **58**.

In comparison to chiral recognition observed in ^{19}F NMR spectroscopy, remarkably few CILs that show chiral recognition in ^{1}H NMR spectroscopy are reported in literature, since a significant splitting of signals is much more difficult to obtain. Indeed, only six papers report a shift difference in ^{1}H NMR, and a maximum splitting of 55 Hz could be obtained with the (*S*)-valine derivative **46** and racemic potassium salt Mosher's acid in the presence of crown ether 18C6.[56]

2.2. Chiral Recognition in NIR

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.[68] The novel CILs (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium bis(trifluoromethylsulfonyl)amide (**59**) could be simply prepared in a one-step anion exchange reaction from commercially available (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium chloride. A variety of pharmaceutical products and amino acids was dissolved in the CIL and diastereomeric interactions were visualized in NIR spectroscopy (Figure 8). Multivariate data analysis gave rise to the enantiomeric composition of samples of the beta-blocker atenolol in high sensitivity (microgram scale) and accuracy (*ee* as low as 0.6%).

2.3. Chiral Recognition in Fluorescence Spectroscopy

The same CIL **59** 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.[68] 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. The method was based on the use of fluorescence technique followed by partial least-squares analysis of the data.

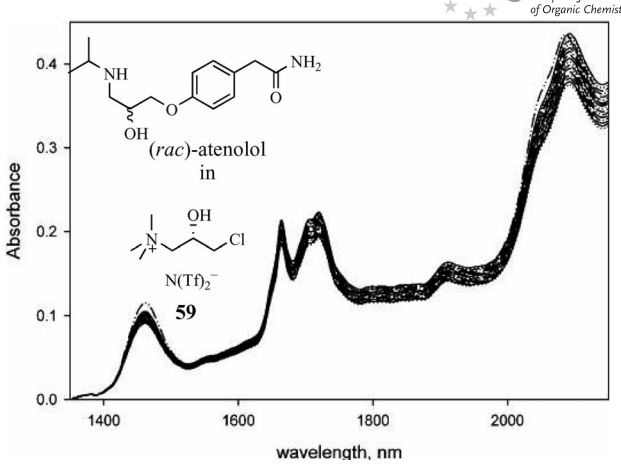


Figure 8. NIR spectra of the pure CIL **59** and 17 solutions of atenolol with different enantiomeric compositions. (Reprinted with permission from ref.[68] Copyright 2008, American Chemical Society).

The chiral recognition ability of alanine *tert*-butyl ester-derived CIL **57** using fluorescence spectroscopy was investigated by Bwambok et al.[66] 2,2,2-Trifluoroanthrylethanol (TFAE), warfarin and naproxen were used as chiral analytes and opposite mean spectra were observed for the (*R*) and (*S*) enantiomers of these analytes when recorded in the presence of CIL **57**, thus demonstrating the chiral recognition ability.

3. Chromatographic Applications

3.1. Chiral Ionic Liquids as Stationary Phases for 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.[69] Extending the realm for chiral separation, there are two principle ways: A chiral selector can be dissolved in a non-chiral IL, or – more elegant – the IL can be chiral itself.[70]

The group of Armstrong published in 2004 the first direct enantiomeric separation of different compounds by using CIL stationary phases in gas chromatography.[71] The *N*,*N*-dimethylephedrinium-based CIL **40** that has been described previously by Wasserscheid et al. 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 9). Since ephedrine is present in nature in both enantiomeric forms and as diastereomeric pseudoephedrine, it was possible to produce CSPs of opposite stereochemistry, which 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 cyclodextrin CSPs. However, after several weeks of use, a loss of separation was observed for certain compounds like the alcohols.

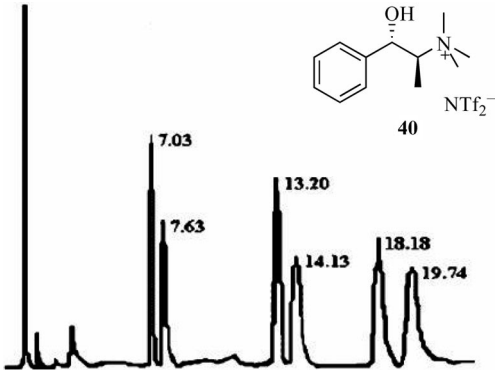


Figure 9. GC chromatogram showing the enantiomeric separation of 2-phenethyl alcohol, 1-phenyl-1-butanol and *trans*-1,2-cyclohexenediol with a fused-silica capillary column coated with (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium bis(trifluoromethylsulfonyl)amide (**40**). (Reprinted with permission from ref.[71] Copyright 2008, American Chemical Society).

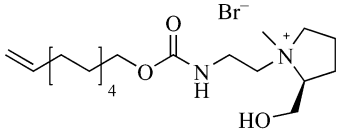
A dehydration induced incomplete racemization process that occurred at temperatures >140 °C was made responsible for the decreasing chiral recognition.

3.2. Enantiomeric Separation in Capillary Electrophoresis

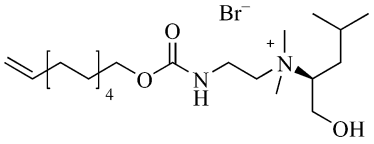
Capillary zone electrophoresis has become a very useful high-performance separation technique for separation of small charged molecules or for the separation of peptides, proteins or fragments of nucleic acids. In the last years, great attention has been paid to the relevance of ILs as new media for capillary electrophoresis with IL-containing background electrolytes.[72]

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.[73] Two amino acid-derived CILs **60** and **61** as well as their polymers were synthesized and used as pseudo-stationary phase in capillary electrophoresis (Figure 10).

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 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 (Figure 11).



60



61

Figure 10. Amino alcohol-derived CILs for capillary electrophoresis.

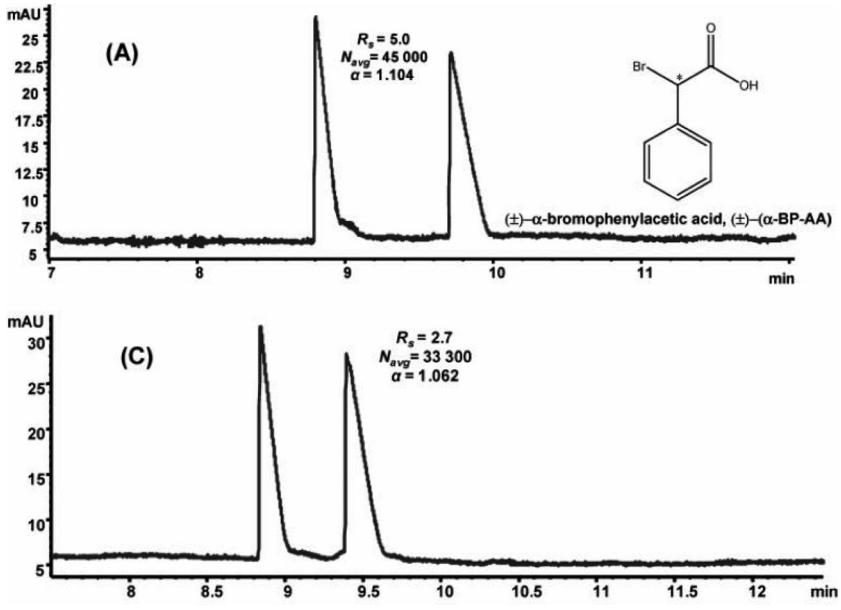
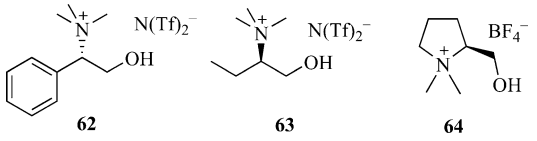


Figure 11. Comparison for enantioseparation of (*rac*)-α-bromophenylacetic acid with CIL **60** and **61**. (Reprinted with permission from ref.[73] Copyright 2008 American Chemical Society).

The evaluation of chiral ethyl- and phenylcholine bis(trifluoromethylsulfonyl)amide as additives for enantiomeric separation of anti-inflammatory 2-arylpropionic acids was investigated by François et al.[74]

These CILs **62** and **63** 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. 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.

Maier et al. used the prolinol-derived CIL (*S*)-2-hydroxymethyl-1,1-dimethylpyrrolidinium tetrafluoroborate (**64**) as additive for dynamic coating of silica capillaries (Figure 12).[75]



62 **63** **64**

Figure 12. CILs applied in capillary electrophoresis.

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 (Figure 12). 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 electrophoresis.

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