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Asymmetric hydrogenation catalysis via ion-pairing in chiral ionic liquids

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ABSTRACT

The relevant interactions between the organic ions of ionic liquids (ILs) include van der Waals forces, hydrogen bonding and coulombic interactions. In solutions these interactions lead to the formation of aggregates. Depending on the strength of the interactions and the concentration of the IL in the solvent, different aggregates are formed with ion-pairs being the dominant species at low concentrations. A probe for investigating these interactions is the enantioselectivity of a reaction carried out on a prochiral ion in presence of its chiral counter-ion. As asymmetric induction requires structurally well-defined interactions, the induced enantioselectivity can be correlated to ion aggregate formation. The first proof of this concept was provided by the asymmetric hydrogenation of [N-(3′-oxobutyl)-N-methylimidazolium]-[(*R*)-camphorsulfonate] and -[(*S*)-camphorsulfonate] using a heterogeneous Ru on C contact. Depending on the substrate IL concentration an enantioselectivity of up to 94% could be realized. The catalytic results were linked to the probability of the ion pair formation as evidenced by DOSY-NMR measurements and dielectric relaxation spectroscopy. The expansion of this principle to chiral ionic liquids that can be easily decomposed to chiral building blocks of synthetic relevance led us to the development of two approaches: a) the application of an IL substrate consisting of a chiral cation and a keto-functionalized, prochiral carboxylate counter-ion allowing for the synthesis of chiral esters in the sequence of IL hydrogenation and esterification; and b) reversible binding of a prochiral substrate to the cation of an IL with a chiral, enantiopure anion allowing the synthesis of neutral chiral building blocks in a sequence of binding, hydrogenation and splitting. The latter approach was tested for two ILs based on the hydroxyl-functionalized cation cholinium to which a prochiral keto functionalized carboxylic acids was reversibly attached via esterification. The hydrogenation of such prochiral ester cation in the presence of enantiopure anions resulted in ees of up to 63%.

1. Introduction

The properties of ionic liquids are dominated by interionic forces that result from a combination of coulombic, hydrogen-bonding and van der Waals interactions. The nature and strength of those interactions is influenced by the structure and functionalization of the ions. Many theoretical studies have been published dealing with molecular modeling of ion interactions [1–18]. Related experimental investigations have focused on the physico-chemical properties of ionic liquid mixtures [19] or solutions of polar molecules in ionic liquids [20]. Analytical techniques used successfully to probe ionic interactions are mass spectrometric analysis [21,22], NMR-spectroscopy [23–27], fluorescence-spectroscopy [28], FT-IR and Raman spectroscopy [29–31], and a combination of osmotic coefficient, conductivity, volumetric and acoustic properties [32]. In addition, dielectric relaxation spectroscopy (DRS) has received much attention in the last years as it offers a direct measurement of the ion pairing effects and degree of organization within the ionic liquid [33–37]. Another technique that proved to provide interesting information is optical Kerr effect spectroscopy [38].

Besides these analytical methods cation–anion interactions and ionic liquid-transition state interactions can also be studied by using the selectivity of a reaction as the probe. This approach was published by Chiappe et al. who demonstrated in the bromination of alkynes that the structure of the ionic liquid under investigation had a strong influence on the transition state, the reaction order and therefore the rate of syn- and anti-addition products [39]. Similar investigations were carried out to study the ionic liquid's influence on the reaction selectivity of the C- vs. O-alkylation of sodium β-naphthoxide with benzyl halides [40] and for Diels–Alder reactions [41]. Two publications describe the degree of ion-pair interaction in camphorsulfonate ionic liquids and both link this interaction to the endo/exo stereoselectivity of a Diels–Alder reaction [42,43].

The interest in chiral ionic liquids (CILs) has increased significantly in recent years. The first ionic liquid with a chiral anion (lactate) was reported in 1999 by Seddon's group [44]. Further ionic liquids with chiral anions were prepared later by the groups of Ohno (19 natural amino acids) [45], Machado ((*S*)-10-camphorsulfonate and (*R*)-1,10-binaphtylphosphate) [46], and Leitner (L-(-)-malic acid) [47]. Chiral cations are rarer, as their synthesis from substances of the chiral pool usually requires multi-step

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syntheses [48,49]. Common starting materials are aminoacids and aminoalkohols [50], alkaloids, terpenes, hydroxyacids or carbohydrates. More chiral cations are accessible via alkylation of imidazole or imidazoline with chiral alkylation agents [51]. Bulky anions based on a binaphtyl backbone bearing axial chirality have been synthesized by the groups of Leitner [52] and Giernoth [53]. Ionic liquids with chirality in both ions are very rare to date. Machado's Group published the first "doubly chiral" ionic liquid in 2005 [54].

Chiral ionic liquids have found applications in chiral analytics and asymmetric chemical reactions. In chiral analytics they are used as additives to the mobile phases, as stationary phases in chiral chromatography [55–64] or as chiral NMR shift reagents [65–69]. Another main field of research is influencing asymmetric reactions by CILs. There are two main approaches for utilizing CILs in asymmetric reactions. The first applies the CIL as part of the catalyst, the second as reaction solvent.

Incorporating CILs as part of the catalytic system was realized in several different ways and demonstrated for many reactions. Some of the most relevant examples deal with the application of a CIL as ligand in the asymmetric Diels–Alder reaction [70] and as proline-based organocatalysts in asymmetric Michael-addition [71] and aldol reactions [72–75]. Francio et al. used a rhodium complex with a tropoisomeric ligand in the presence of a CIL for homogeneously catalyzed hydrogenation reactions and realized in this way good enantioselectivities [52]. Furthermore, they were able to show that a CIL can lead to a selective poisoning of one of the possible enantiomers of a catalyst complex. This can enable asymmetric catalysis despite the use of a racemic mixture of the applied chiral ligand [76].

Asymmetric induction by the solvent throughout a chemical reaction is possible but the enantioselectivities achieved in this way are usually small to moderate [77]. It was shown that the strong interionic interactions in ionic liquids hinder the transfer of chirality to uncharged molecules and transition states, which are common in most organic reactions [78]. However, it has been also found that the chiral anion of a CIL does strongly interact with an appropriate counter-ion and that the degree of such interaction is solvent and concentration dependent [65,79]. These ion-pair interactions could be verified by ^{19}F-NMR-spectroscopy using a racemic mixture of methoxy-α-trifluoromethylphenylacetate (deprotonated Mosher's acid) sodium salt as substrate in an enantiomeric pure ephedrinium bis(trifluoromethylsulfonyl)imide ionic liquid. Consequently, the first results of solvent induced chirality transfer with high enantioselectivities were obtained by Leitner et al. for the aza-Baylis–Hillman reaction [47] and by Schulz et al. for the hydrogenation of the prochiral keto-functionalized cation of (*R*)-camphorsulfonate ionic liquids [80]. For the aza-Baylis–Hillman reaction an ionic transition state was postulated in which the Brønsted acidic, chiral anion is incorporated as a kind of organocatalyst.

Chirality transfer in ionic liquids via ion-pairing effects is a very young field of research. But the basic principle of chiral recognition was reported first in 1931, when it was found that diastereoselective interactions between a configurationally labile charged metal complex and a chiral counter-ion can induce stereoselectivity at the metal center (Pfeiffer effect) [85]. In the field of homogeneous metal catalyzed reactions many recent publications picked up on this effect and utilized it remarkably successfully [86–91]. Asymmetric counter-ion directed catalysis (ACDC) evolved as a new term for this concept. In the last years a number of papers have been published in high-ranked journals that make successful use of these chiral recognition effects in organocatalysis, [92] Brønsted acid catalysis, [93] and phase transfer catalysis [94]. Chiral recognition has been also proven by 1D and 2D-NMR studies with chiral ions and racemic counter ions [95].

As stated before, chirality transfer between the ions of an IL has been demonstrated for the hydrogenation of prochiral cations in the presence of their enantiomeric pure counter-ion camphorsulfonate. As an asymmetric induction requires structurally well-defined interactions, it is expected that the induced enantioselectivity should correlate with the probability of ion pairing. First evidence for this hypothesis was found in the heterogeneously catalyzed (Ru/C), asymmetric hydrogenation of [N-(3′-oxobutyl)-N-methylimidazolium]-[(*R*)-camphorsulfonate] in ethanol (Scheme 1) [80].

The induced enantioselectivity showed a strong dependence on the IL concentration in the applied organic solvent with a maximum at medium concentrations of up to 94% ee. This behavior was linked to the degree of ion pair formation. The latter was determined by DOSY-NMR measurements and dielectric relaxation spectroscopy. These analytical techniques provided indeed evidence that the highest degree of ion pairing and the highest enantioselectivity correlate well for different IL-solvent combinations. Further experiments varying the structure of the IL cation showed that the cation's H-bonding ability has a strong influence on ion-pairing and thus also on the effectiveness of asymmetric induction [80–84].

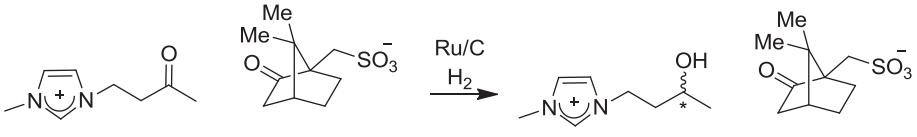
In all previous studies dealing with the asymmetric hydrogenation of prochiral IL cations in the presence of an enantiopure counter-ion, imidazolium-based ionic liquids were applied as substrates and thus doubly chiral imidazolium salts were obtained. As neutral chiral building blocks are of much higher synthetic relevance than chiral salts we were interested to convert these newly formed chiral ions into neutral substances. However, in the case of imidazolium salts, such a transformation would require high temperatures and/or reaction with strong nucleophiles. These experimental conditions would result in many side reactions and very likely in racemization of the chiral group of the ion.

In this contribution we report on our on-going attempts to use asymmetric induction via ion-pair interactions for the preparation of neutral, enantiomeric enriched organic molecules that form interesting building blocks for organic synthesis. Still we are interested in gaining more insight into the nature of ion pairing in ionic liquid solutions and the degree of asymmetric induction that can be realized in this way.

2. Synthesis of chiral esters through asymmetric hydrogenation of prochiral carboxylate salts

Our first synthetic approach towards this goal was the hydrogenation of [(*1R,2S*)-dimethylephedrinium] salts carrying a prochiral keto-functionalized carboxylate counter-ion (Scheme 3 and 4). In this "reverse" approach to our previous studies, the cation is derived from the chiral pool and has shown successful application in chiral recognition [65]. The hydrogenation product, a chiral carboxylate with enantiomeric excess can be easily converted to a neutral molecule by an esterification reaction. Also the isolation of the chiral ester should be straight forward by extraction with organic solvents from the remaining salt.

We tested this concept using the same heterogeneous catalyst as used in our previous work and applying DOSY-NMR spectroscopy to gain further understanding for the influence of ion-pairing in this type of asymmetric reaction (see Section 2.1.1). In a separate set of experiments, the homogeneous Wilkinson catalyst was applied in the same hydrogenation reaction in combination with racemic and enantiopure BINAP ligands. In this way we aimed to probe whether ion pairing



Scheme 1. Enantioselective hydrogenation of a keto-functionalized imidazolium camphorsulfonate ionic liquid.

within the CIL is also influencing the selectivity of the homogenously catalyzed hydrogenation reaction (see Chapter 2.1.2). As the first step, however, we had to synthesize the substrate salt for these studies.

2.1. Synthesis of CILs with optical pure cation and prochiral anion

As prochiral anions the keto-functionalized carboxylates phenylglyoxylate and levulinate were chosen. The corresponding ionic liquids were synthesized using an anion-exchange resin yielding the CILs [(*1R,2S*)-dimethylephedrinium][phenylglyoxylate] IL1 and -[levulinate] IL2 in quantitative yield (Scheme 2).

2.1.1. Heterogeneously catalyzed hydrogenation of ILs based on keto-functionalized carboxylic acids

Hydrogenations were carried out in batch autoclaves using the same achiral ruthenium on charcoal catalyst as used in the previous work (40 bar H_2, 10 wt.% Ru/C (5% Ru), T = 60 °C, t = 5d) [80]. After hydrogenation the anions were further converted to the methyl ester by reaction with methanol in presence of the acidic cation exchange resin H-Amberlite. The obtained esters were analyzed via chiral gas chromatography. The overall reaction for IL2 is depicted in Scheme 3.

The enantioselectivity obtained in the hydrogenations of IL1 and IL2 are shown in Table 1, the reactions were carried out in methanolic solutions at different concentrations.

The overall enantioselectivities are much lower than in the case of the hydrogenation of keto-functionalized imidazolium camphorsulfonates. This probably reflects the differences in the structure of the ions, especially of the cation, compared to the imidazole based ILs. A successful asymmetric induction requires structurally defined ion-pairs with a close contact of the chiral center and the prochiral keto-functionality. The overall values are therefore difficult to compare. However, the observed small ee demonstrates a certain generality of the concept.

For IL1 the ee induced is almost constant, with a minor maximum at a concentration of 0.2 mol/L. Note that the enantioselectivity found for the hydrogenation of ([N-(5′-oxohexyl)-N-methylimidazolium][(*S*)-mandelate], in which the comparable (*S*)-mandelate acts as the source of the chirality, also showed little concentration dependence [83]. Although the cations are difficult to compare it can be assumed, that those very similar anions might have a tendency for ion-pairing by hydrogen bonding and π-stacking over a relatively broad concentration range.

For IL2 a slightly stronger dependency of ee on concentration is found, with a maximum at 0.2 mol/L. In order to correlate the observed enantioselectivities to ion-pairing, DOSY-NMR spectroscopy measurements have been carried out. In accordance with the existing literature a bpp-led (bipolar pulsed pairs longitudinal echo current delay) sequence was used for the measurements [81]. DOSY-NMR is a very versatile and powerful method to investigate transport properties of diffusing ions in solution. It allows for the independent calculation of the self-diffusion coefficients of the cation and anion of an ionic liquid [81,96–101]. By a combination of conductivity measurements and the determination of the self-diffusion coefficients of anions and cations, the degree of dissociation α_{diss} of ionic liquid ions can calculated from the modified Stokes–Einstein Eq. (1) [96].

$$\sigma_D = \alpha_{diss}\frac{Ne^2}{kT}(D_- + D_+), \tag{1}$$

with σ_D = conductivity, N = cations per volume, e = electric charge and D_-/D_+ = self-diffusion coefficients of the anion and cation.

The degree of dissociation represents the degree of order in the system and gives an insight into the aggregation behavior of the ions of an IL. Measurements for similar IL/solvent systems have shown, that the minima of the degree of dissociation and the probability of ion pairing correlate well [81,84].

Unfortunately, IL1 has no ^{1}H-NMR signals that can be analyzed by this method as the method requires separated signals of cation and anion whereas in this case the protons on the cation overlap with the aromatic protons of the anion. The results for IL2 are shown in Fig. 1.

Indeed, the minimum of the degree of dissociation and the maximum of the induced *ee* are found in good agreement. This indicates asymmetric induction via ion-pairing. Unfortunately the formation of ion-pairs does not lead to a high degree of asymmetric induction for this specific system compared to the imidazolium-based ILs. But still the small induction shows that the concept of asymmetric induction via ion-pairing is also applicable for the synthesis of enantiomeric enriched esters.

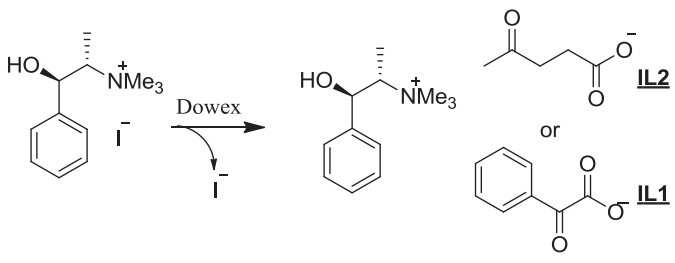
2.1.2. Homogeneously catalyzed hydrogenation of keto-functionalized carboxylate ionic liquids

With the influence of ion-pairing on the heterogeneously catalyzed asymmetric hydrogenation clearly proven, we were interested to investigate whether inter-ionic induction would also influence the homogeneously catalyzed hydrogenation of prochiral ionic liquids. Whereas chiral poisoning could be excluded by test reactions with non-ionic substrates in the case of heterogeneous catalysts, [80] chiral poisoning of homogeneous catalysts can be excluded by using a chiral cation together with a neutral catalyst complex. Note that poisoning by a chiral counter-ion or metal complexation would require the use of a chiral anion together with the cationic transition metal complex. IL1 is a suitable substrate for homogeneously catalyzed hydrogenation and also carries its chiral center at the cation. As a catalyst, the standard Wilkinson complex $Rh(PPh_3)_3Cl$ was used as a pure compound and with an added PPh_3 ligand in an IL/catalyst/ligand ratio of 250:1:4. To avoid additional influences by the temperature dependency of the IL aggregation behavior, hydrogenations were carried out under the same reaction conditions as previously used in the heterogeneous hydrogenation. THF was used as solvent.

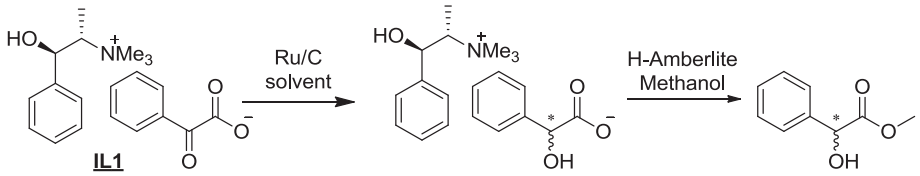
In addition, the influence of a chiral counter-ion on the hydrogenation was investigated. Chiral ligands were applied to test the possibility for chiral enhancement. For this purpose the corresponding complexes with racemic and enantiopure (*S*)-BINAP-ligand were also tested. All homogeneously catalyzed hydrogenations of the phenylglyoxylate anion were carried out under the same conditions ($p(H_2)$ = 40 bar, T = 60 °C, reaction time = 5d).

The reaction mixture was worked up analogously to the heterogeneously catalyzed reaction by converting the chiral anion into the corresponding methyl ester. The latter was analyzed by chiral GC. Note that the reaction rate was very slow – independent of the ligand used – with a degree of conversion below 10% after five days of reaction time. The results are shown in Table 2.

The hydrogenation using the standard Wilkinson catalyst yielded no *ee*, independent on the addition of more PPh_3 ligand. Therefore, the influence of the chiral cation on the catalyst complex seems not strong enough to influence the enantioselectivity of the catalyst. This also shows that the chiral cation does not interact strongly with the catalyst complex in a manner that leads to a chiral poisoning effect.



Scheme 2. Synthesis of ILs 1 and 2 based on the chiral cation [(*1R,2S*)-dimethylephedrinium] and prochiral carboxylate ions.

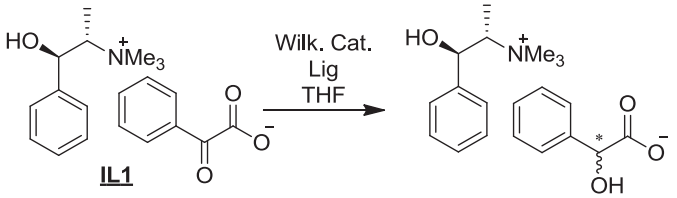


Scheme 3. Heterogeneously catalyzed hydrogenation of IL1 followed by an esterification yielding a neutral product.

A small degree of enantioselectivity was found, however, with a racemic mixture of the BINAP ligand for the hydrogenation of IL1. ^{31}P-NMR spectroscopy showed that the catalyst is not altered by addition of the IL, as neither the chemical shift of the ligand changed nor was a diastereomeric splitting observed. As the catalyst is not charged the induction is not a variant of asymmetric counter-ion directed catalysis, but is attributed to ion pairing within the IL. The results of the hydrogenation using enantiopure BINAP gives further indication that the chiral cation can lead to chiral enhancement in combination with a chiral ligand. This shows the strong influence of ion–ion interactions within solutions of ionic liquids and can be used for asymmetric synthesis. Obviously, further understanding of concentration effects and structural optimization of the salt/ligand combination e.g. using a Noyori-type catalyst are required to obtain ee-values of preparative interest.

2.2. Synthesis of neutral chiral building blocks by reversible attachment of a prochiral substrate to a CIL

In another attempt to utilize the asymmetric induction between the ions of a CIL for asymmetric synthesis we adapted a method used in peptide chemistry [103]. Here, the substrate is bound reversibly to a support, the reaction proceeds while the substrate is bound to the support, and finally the product is liberated from the support. In our case the support is an ionic liquid composed of a hydroxyl-functionalized cation and a chiral enantiopure counter-ion. The hydroxyl functional group enables the reversible binding of carboxylic acids to the cation. In order to test the influence of the anion's structure on the chiral induction, two different enantiopure anions were tested. As the first candidate [cholinium][(S)-camphorsulfonate] IL3 was synthesized and applied. This IL candidate was selected due to the fact that in our previous work [80–84] the best ee values were obtained with [S-camphorsulfonate] salts. As the second candidate, a hydrophobic chiral anion was selected as the hydrophobic nature of the salt leads to advantages in the workup procedure. Consequently, [cholinium][((R)-1,1′-Binaphtyl-2,2′-sulfonimid] ([cholinium][BINBAM]) IL4, based on a bulky anion with axial chirality, was synthesized and applied. Both salt syntheses were achieved in a straightforward manner by neutralizing [cholinium][OH] with the respective chiral acid. [Cholinium][OH] is commercially available and cheap, but has to be cleaned from the remaining amine before use. (S)-camphorsulfonic acid is derived from the chiral pool and therefore inexpensive. [BINBAM]- is not commercial and was synthesized in cooperation with the Giernoth group, following the previously published procedure [53]. Scheme 5 shows the synthesis of IL3 and IL4.



Scheme 4. Homogeneously catalyzed hydrogenation of [(*1R,2S*)-dimethylephedrinium][phenylglyoxylate] (IL1).

Completion of the reaction was checked by NMR-spectroscopy and the reaction in all cases gave quantitative yields after drying the product salt under high vacuum.

As prochiral substrates for the creation of the new chiral center by this method we selected again keto-functionalized carboxylic acids. These can be bound to the cholinium ion by esterification and liberated after the hydrogenation reaction by ester cleavage. For an easier separation of the carboxylic acid out of the IL medium after reaction, the acid can again be converted to the ester by using an acidic cation exchange resin and methanol as solvent and substrate. The overall product of the reaction sequence (Scheme 6) is a chiral acid or methyl ester, respectively. The enantiomeric excess of these neutral products can be analyzed via chiral GC.

The first step of the reaction sequence of Scheme 6 is the esterification of the carboxylic acid and the cholinium ion of the IL. The esterification is an acid or base catalyzed equilibrium reaction, in which the water has to be removed from the system to achieve high conversions. The usual esterification protocol [104] involves refluxing the acid and the alcohol in toluene in presence of an acid catalyst. Water is removed by either a drying agent or a water-separator. By applying this method to the esterification of the cholinium cation with the prochiral substrates phenylglyoxylic acid (S1) and levulinic acid (S2) only moderate degrees of conversion were obtained. We assume that this observation is linked to the highly hydrophilic nature of IL3.

Higher yields could be achieved by using Steglich conditions [102]. This method of esterification is very elegant as the main reagent dicyclohexylcarbodiimide enhances the reaction by activation of the acid and also binds the by-product water and therefore pushes the equilibrium in favor of the ester product. In order to suppress possible side reactions, a small amount of dimethylaminopyridine was added (DMAP) (Scheme 7).

In contrast to the esterification of IL3, conversion of the IL4 with the prochiral acids phenylglyoxylic acid (S1) and levulinic acid (S2) in toluene led directly to high yields in the desired esters, probably due to the strongly hydrophobic nature of IL4. Details on the synthetic procedures are given in the Section 4, the degrees of esterification for all substrates-IL reactions are shown in Table 3.

The second reaction step is the asymmetric hydrogenation of the so-formed ester. Tetrahydrofurane (THF) was applied as the solvent for the hydrogenation of the acids bound to IL3. For the hydrogenation of the acids bound to IL4 only DMF was viable, due to the poor solubility of the IL in all the other solvents suitable for hydrogenation. In order to calculate the correct concentration of IL for the hydrogenations the average molecular weight was calculated taken into account for the achieved degree of esterification. All the samples were hydrogenated under the

Table 1
Asymmetric hydrogenation of the [(*1R,2S*)-dimethylephedrinium]-based ionic liquids IL1 and IL2 in methanolic solution.

Concentration [mol/L]	ee in anion after hydrogenation of IL1 [%]	ee in anion after hydrogenation of IL2 [%]
0.1	9	4
0.2	14	14
0.3	12	9
0.5	11	n. d.

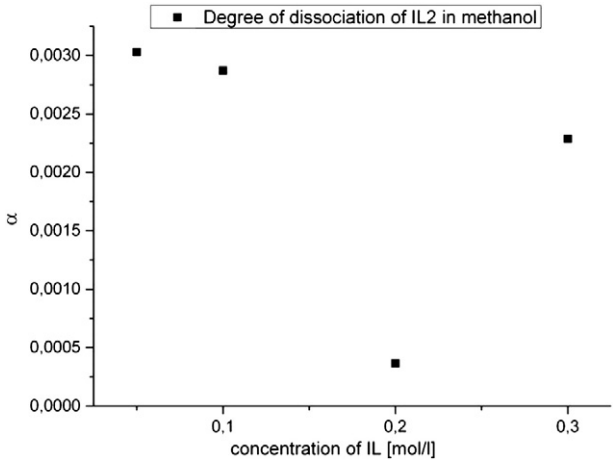


Fig. 1. Degree of dissociation of IL2 at different concentrations in methanol.

same reaction conditions ($p(H_2) = 40$ bar, T = 60 °C, 10 wt.% Ru/C (5% Ru), RT = 5d) using 20 mL batch autoclaves.

After the hydrogenation the chiral acids were liberated from the IL by acidic ester cleavage followed by extraction and chiral gas chromatography. The results are shown in Table 3.

A challenge within the reaction system is the incomplete esterification and its negative influence on the chirality transfer from the IL anion to the prochiral center of the reaction. Consequently, for low degrees of esterification no ee was found for both substrates bound to IL3. With higher degrees of esterification, ee induced during the hydrogenation of the prochiral center was clearly visible. Remarkably, for almost quantitative esterification (Entry 5, Table 3) the ee during hydrogenation was highest and reached 63%. The very clear dependence of the induced ee on the degree of esterification is a very strong indication that the chirality transfer does indeed proceed via ion pairing effects. It is evident that the here presented concepts need further elaboration to explore the scope of substrates and optimal concentration ranges. However, we present here the first successful example of the synthesis of a chiral ester using reversible binding to a chiral ionic liquid.

3. Conclusion

We have explored two basic methods to apply ion pair interactions within chiral ionic liquids for the asymmetric synthesis of neutral compounds. The first applied ion pair interactions between a chiral cation and a prochiral keto-functionalized anion in heterogeneously and homogeneously catalyzed hydrogenation. In the heterogeneous version of the reaction the obtained ees were low but could be linked to inter-ionic interactions by DOSY-NMR measurements. For the homogenous version of the reaction we found chiral enhancement when racemic or enantiopure chiral ligands were applied together with the prochiral ionic liquid.

As a second method we attached prochiral, keto-functionalized carboxylic acids to a hydroxyl functionalized cation of a chiral ionic liquid. During hydrogenation of the resulting salt, chiral induction was indeed observed in all cases where the prochiral substrate was attached to a high degree to the ionic liquid. An enantiomeric excess of up to 63% could be realized for the hydrogenation of IL4 in DMF (c = 0.05 mol/L). After the hydrogenation reaction the enriched acid was liberated from the IL by ester cleavage or esterification. In principle, this method enables the use of the CIL as a chiral auxiliary, as the latter may be re-used in a next reaction cycle.

Table 2
Homogeneous hydrogenation of IL1 and phenylglyoxylic acid using PPh_3, racemic and enantiopure S-BINAP.

	PPh_3	rac-BINAP	S-BINAP
	ee in cation after hydrogenation [%]		
Phenylglyoxylic acid	0	0	7
IL1	0	14	34

4. Experimental section

All the syntheses were carried out under argon unless otherwise specified. Solvents for the hydrogenation reactions were of spectroscopic grade. Methylimidazole was distilled und kept under argon at −18 °C prior to use. [Cholinium][OH] solution (Aldrich, 46 wt.%) was diluted to double of its volume with water, filtered over activated charcoal. Afterwards its concentration was determined by titration. All other chemicals were purchased at Aldrich and used as received. Ruthenium on charcoal (5% Ru) was purchased from Fluka.

The conductivity of solutions was determined using a conductivity cell (LTA 1, WTW, cell constant K = 1, platinized platinum electrode). NMR experiments were carried out using a Jeol ECX 400 MHz spectrometer with a 2-channel (HF, LF)-probe. Spectra were referenced to the solvent. The procedure of DOSY-NMR followed published procedures using a bpp-led sequence [81,100,101,105,106] All GC chromatograms were recorded using a Varian 3900 equipped with a Varian CD 8410 auto-sampler and a flame-ionization detector. As a chiral column, a Varian CP Chirasil-Dex was used (25 m × 0.32 mm).

4.1. [(1R,2S)-N,N-dimethylephedrinium][phenylglyoxylate] (IL1)

A 0.1 molar solution of [(1*R*,2*S*)-N,N-dimethylephedrinium][iodide] was eluted slowly over a Dowex 1 × 8-column, which was presaturated with [phenylglyoxylate]. The eluent was intermittently tested to be iodide free by $Ag[NO_3]$. Afterwards, the column was rinsed with water and the combined solutions were dried using a rotary evaporator and HV. The product was obtained as a white solid in near quantitative yield.

^{1}H−NMR (DMSO−d6, 400 MHz, ppm) : δ = 1.08 (d, 3H, ^{3}J = 6.6 Hz), 3.22 (s, 9H), 3.65 (q, 1H, ^{3}J = 6.5 Hz), 5.56 (s, 1H), 6.82 (s, 1H), 7.23−7.80 (m, 5H).

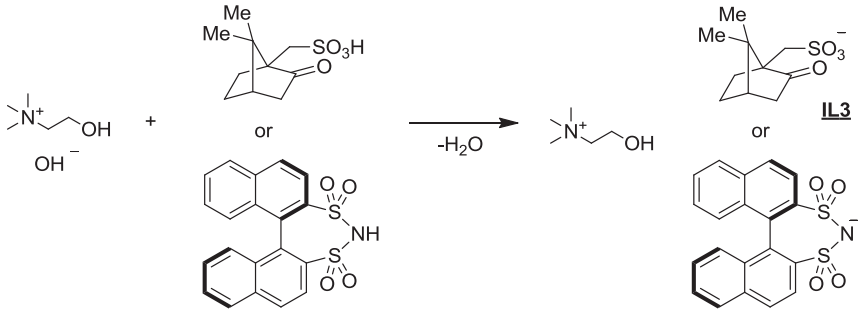
^{13}C−NMR (DMSO−d6, 100, 4 MHz, ppm) : δ = 6.44, 52.06, 69.51, 74.70, 125.58, 128.12, 128.78, 129.18, 129.62, 132.16, 135.05, 140.45, 172.76, 182.52.

4.2. [(1R,2S)-N,N-dimethylephedrinium][levulinate] (IL2)

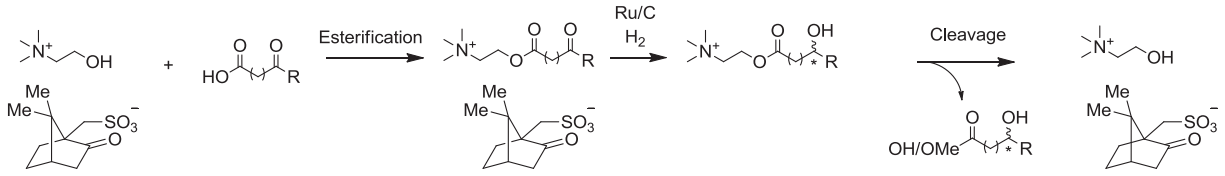
A 0.1 molar solution of [(1*R*,2*S*)-N,N-dimethylephedrinium][iodide] was eluted slowly over a Dowex 1 × 8-column, which was presaturated with [levulinate]. The eluent was intermittently tested to be iodide free by $Ag[NO_3]$. Afterwards, the column was rinsed with water and the combined solutions were dried using a rotary evaporator and HV. The product was obtained as a white solid in near quantitative yield.

^{1}H−NMR (DMSO−d6, 400 MHz, ppm) : δ = 1.08 (d, 3H, ^{3}J = 6.6 Hz), 2.00 (s, 3H), 2.08 (t, 2H, ^{3}J = 7.2 Hz), 2.42 (t, 2H, ^{3}J = 7.1 Hz), 3.22 (s, 9H), 3.57 (q, 1H, ^{3}J = 6.9 Hz), 5.63 (s, 1H), 6.82 (s, 1H), 7.10−7.46 (m, 5H).

^{13}C−NMR (DMSO−d6, 100, 4 MHz, ppm) : δ = 7.25, 32.02, 51.05, 67.80, 74, 45, 126.31, 126.44, 127.47, 128.48, 129.0, 136.6, 143.77, 175.35, 203.17.



Scheme 5. Synthesis of the chiral cholinium salts ILs IL3 and IL4.



Scheme 6. Asymmetric hydrogenation of a keto-functionalized carboxylic acid reversibly attached to a chiral carrier IL (IL3).

4.3. Column preparation

A Dowex 1 × 8 column (Cl-form, capacity = 1.2 mmol/mL) was washed with 2 M NaOH until no chloride could be detected when adding a silver nitrate solution. After washing to neutral pH with water, the column was charged with 0.1 M solution of the acid corresponding to the desired anion. The column was washed to neutrality again.

4.4. [Cholinium][(S)-camphorsulfonate] (IL3)

To one equivalent of the pretreated [cholinium][OH] solution, one equivalent of (*S*)-camphorsulfonic acid was added. After stirring for 1 h, the solvent was removed under reduced pressure (rotary evaporator and HV). The product was obtained as a white solid in quantitative yield.

^{1}H−NMR (DMSO−d6, 400 MHz, ppm) : d = 0.70 (s, 3H),
1.01 (s, 3H), 1.20−1.28 (m, 2H), 1.74−1.91 (m, 3H),
2.20 (m, 1H), 2.33 (d, 1H, ^{3}J = 14.8 Hz), 2.65 (m, 1H),
2.83 (d, 1H, ^{3}J = 14.8 Hz), 3.07 (s, 9H),
3, 37 (t, 2H, ^{3} J = 5.2 Hz) 3, 80 (m, 2H), 5.30 (brs, 1H)

^{13}C−NMR (DMSO−d6, 100.4 MHz, ppm) : δ = 19.37, 19.94,
23.91, 26.20, 42.32,
46.71, 47.13, 53.13, 55.24, 58.29, 66.93.

4.5. [Cholinium][(R)-1,1′-binaphtyl-2,2′-sulfonimid] (IL4)

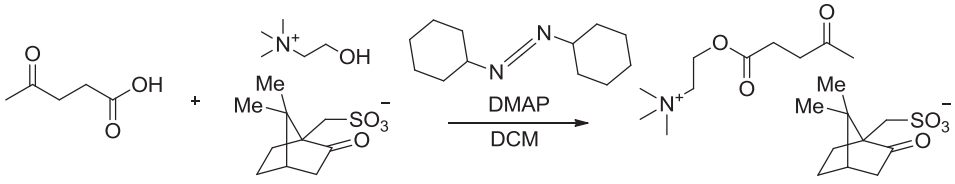
To one equivalent of the pretreated [cholinium][OH] solution, one volume equivalent of DMF and afterwards one equivalent of [H][((*R*)-1,1′-Binaphtyl-2,2′-sulfonimid] was added. After stirring for 1 h, the solvent was removed using a rotary evaporator and HV. The product was obtained as a brown–white solid in near quantitative yield.

^{1}H−NMR (DMSO−d6, 400 MHz, ppm) : δ = 3.03 (s, 9H),
3.34 (m, 2H), 3.78 (s, 2H), 6.97 (d, 2H, ^{3}J = 8.8 Hz),
7.28 (m, 2H), 7.54 (m, 2H), 7.90−8.14 (m, 6H)

^{13}C−NMR (DMSO−d6, 100.4 MHz, ppm) : δ = 25.66,
53.68, 55.68, 67.46, 123.22, 127.29, 127.62,
127.96, 132.10, 132.98, 134.44, 140.86.

4.6. Acidic esterification in toluene

One equivalent of IL and one equivalent of the acid was dissolved in toluene. After addition of a 0.05 equivalent of H_2SO_4 and 10 wt.% of anhydrous Mg[SO_4] the reaction mixture was refluxed at 130 °C for 24 h. The mixture was then filtered. For IL3 as substrate the solvent was removed in HV at 75 °C, afterwards the mixture was dissolved in water and extracted with ether. The aqueous phase was dried under reduced pressure yielding the product as yellow oil. For IL4 as substrate the organic phase was washed with water and afterwards dried in HV yielding the product as a brown solid.



Scheme 7. Esterification of IL3 and levulinic acid using Steglich reagents.

Table 3
Asymmetric hydrogenation of carboxylic acids bound to a chiral carrier ILs.

Entry	Ionic liquid	Substrate	Degree of esterification [%]	Solvent	Concentration [mol/L]	ee in product after hydrogenation [%]
1	IL3	S1	56	THF	0.1	37
2	IL3	S1	33	THF	0.1	0
3	IL3	S2	74	THF	0.1	30
4	IL3	S2	40	THF	0.1	0
5	IL4	S2	97	DMF	0.05	63

4.7. Esterification using Steglich reagents

One equivalent of the acid was dissolved in dichloromethane and 1.05 equivalents of dicyclohexylcarbodiimide were added. After stirring for 10 min one equivalent of the IL and 0.05 equivalents of N,N-dimethylaminopyridine were added. The reaction mixture was stirred for 16 h. Afterwards it was heated to 60° for one hour. The so formed white precipitate was filtered of. For IL3 the organic phase was extracted three times with water. Drying the aqueous phase under reduced pressure yielded the product as yellow oil. For IL4 the organic phase was washed with water. Drying the aqueous phase yielded the product as a brown solid.

The highest degrees of esterification for all substrates are shown in Table 4.

4.8. Heterogeneously catalyzed hydrogenation reactions

The ionic liquid was dissolved in the respective solvent and ruthenium on activated charcoal was added (5% Ru/C, 10 wt.% with respect to the substrate IL). The mixture was hydrogenated in a batch autoclave at 60 °C, 40 bar hydrogen pressure for 5 days. After filtration of the catalyst and removal of the solvent the product was obtained.

4.9. Homogeneously catalyzed hydrogenation reactions

The ionic liquid was dissolved in THF. Afterwards the catalyst $Rh(TPP_3)_3(Cl)$ and – if applied – an additional ligand was added (in case of ligand use the molar ratio was IL/Cat./Ligand of 250/1/4). The hydrogenation reactions were carried out at a hydrogen pressure of 40 bar at 60 °C over 5 days. Afterwards, the solvent was removed under reduced pressure.

4.10. Analysis by chiral GC of IL1 and IL2

After the hydrogenation the reaction mixture was dried in HV. A sample was taken and dissolved in methanol. After the addition of an excess of H-Amberlite, the solution was stirred for 15 min. The mixture was filtered and the filtrate was afterwards analyzed in the chiral gas chromatography.

Table 4
Results of the esterification of the cholinium ionic liquids IL3 and IL4 with phenylglyoxylic acid (S1) and levulinic acid (S2) using different esterifaction methods.

Ionic liquid	Substrate	Method of esterification	Degree of esterification [%]
IL3	S1	Acidic	33
		Steglich	56
IL3	S2	Acidic	40
		Steglich	74
IL3	S1	Acidic	95
		Steglich	90
IL4	S2	Acidic	97
		Steglich	95

4.11. Analysis by chiral GC of IL3 and IL4

After hydrogenation, the reaction mixture was dried in HV. A sample was taken and dissolved in water. After the addition of sulfuric acid and stirring for 30 min, the liberated acid was extracted three times with diethyl ether. Afterwards, methanol and H-Amberlite were added to the combined organic phases in order to yield the corresponding methyl ester. The organic phase was afterwards analyzed using chiral gas chromatography.

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