Asymmetric Catalysis

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# Effective Chirality Transfer in Ionic Liquids through Ion-Pairing Effects

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The interest in chiral ionic liquids (CILs) has increased significantly in recent years. The first example of an ionic liquid with a chiral anion was reported in 1999 by Seddon et al. in a study dealing with lactate ionic liquids.[1] Further ionic liquids with chiral anions were prepared later by the groups of Ohno,[2] Machado,[3] and Leitner[4] derived from 19 natural amino acids, (*S*)-10-camphorsulfonate and (*R*)-1,10-binaphthylphosphate, and borate anions based on *l*-(−)-malic acid, respectively. Chiral cations are also accessible from the chiral pool; however, usually multistep syntheses are necessary. First examples included the synthesis of chiral oxazolinium ions from amino acids and the preparation of chiral hydroxyammonium salts derived from the corresponding amino alcohols.[5] A review of the various syntheses leading to chiral ionic liquids was recently published by Baudequin et al.[6] Examples of ionic liquids with chirality in both ions are very rare to date.[3]

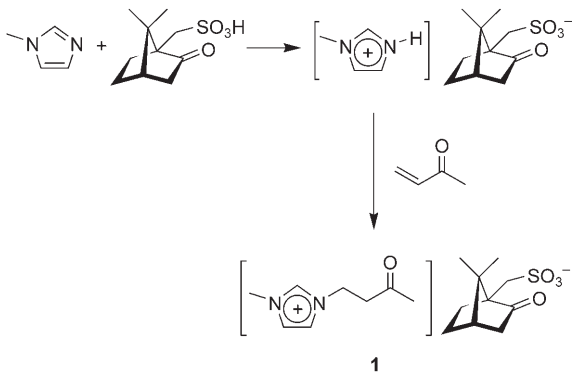
Asymmetric synthesis in which the solvent is the source of chiral information is possible. However, up to now few convincing examples have been reported, and the enantioselectivities achieved in this way have been small to moderate in most cases. In 1975, a chiral amino ether was used as a solvent for the electrochemical reduction of ketones. The reaction proceeded with 23% *ee*.[7] Experiments with chiral lactate ionic liquids gave less than 5% *ee* in Diels–Alder reactions.[1] The first significant chiral induction with ionic liquids, up to 44% *ee*, was obtained for a Baylis–Hillman reaction.[8] The best results so far were obtained by Leitner and co-workers using a chiral-anion-containing ionic liquid for an aza-Baylis–Hillman reaction.[4] For this specific case an ionic transition state was postulated in which the Brønsted acidic, chiral anion is incorporated as a kind of organocatalyst. Selectivities of up to 84% *ee* could be achieved in this way for the reaction of activated alkenes with amines to give highly functionalized chiral allylic amines.

These examples suggested to us that the transfer of chiral information from a chiral ion (for example, of an ionic liquid) to a neutral transition state is not very effective. However, the transfer of chiral information between the ions of an ionic liquid should be much more probable. This initial assumption was also in good accordance with earlier experiments by us and others in which the strong interionic interaction between the cation of an ionic liquid and a racemic Mosher's salt anion was probed using $^{19}$F NMR spectroscopy.[5,9,10] Strong interionic interactions through hydrogen bonds were found in ionic liquids in the solid as well as in the liquid state. This was confirmed by X-ray diffraction, $^{1}$H NMR spectroscopy, conductivity, and microcalorimetry experiments.[11,12] Interionic interactions were also found in the gas phase under steam-distillation-like conditions in atmospheric pressure chemical ionization mass spectrometry experiments.[13] For several ILs discrete neutral aggregates of the general formula $[(DAIm)(X)]_n$ (DAIm = dialkylimidazolium, X = anion, $n \approx 1$–3) were characterized by mass spectroscopy in the gas phase.

Herein we report for the first time an asymmetric synthesis that makes use of solely the strength of ion pairing in an ionic liquid to induce chirality. We demonstrate this new concept with the asymmetric hydrogenation of a ketone using [*N*-(3′-oxobutyl)-*N*-methylimidazolium][(*R*)-camphorsulfonate] (**1**) as the model substrate. Compound **1** was prepared in analogy to one of our previous publications by protonation of methylimidazole with (*R*)-camphorsulfonic acid followed by a Michael-type addition of methyl vinyl ketone in an overall yield of over 95% (Scheme 1).[14]

IL **1** is a viscous liquid at room temperature and consists of a prochiral cation and an enantiomerically pure counterion. The hydrogenation of **1** using molecular hydrogen at 60 °C/60 bar in the presence of a heterogeneous, achiral Ru/C catalyst in ethanolic solution yielded the corresponding hydroxy-functionalized ionic liquid [*N*-(3′-hydroxybutyl)-*N*-methylimidazolium][(*R*)-camphorsulfonate] (**2**, Scheme 2) in quantitative yield after 8 h.

The enantioselectivity of the transformation at the ionic liquid's cation was determined after anion exchange to the bis(trifluoromethanesulfonyl)imidate salt using the method



**1**

***Scheme 1.*** Synthesis of the prochiral ionic liquid **1**.

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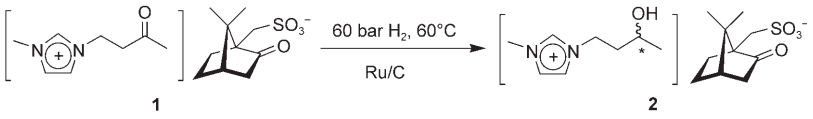


***Scheme 2.*** Hydrogenation of a keto-functionalized ionic liquid.

reported by Mosher et al.[15–18] The newly formed hydroxy group of the cation reacted with the *R* enantiomer of Mosher's acid chloride ((*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetylchloride, (*R*)-MTPACl) to give the corresponding diastereomeric cation shown in Figure 1.

For confirmation of the *ee* value, IL **2** was also analyzed by $^{19}$F NMR spectroscopy after esterification with (*S*)-MTPACl (Figure 2). The $^{19}$F NMR spectra of these esters clearly show a reversal of the signal intensity, confirming the applicability of

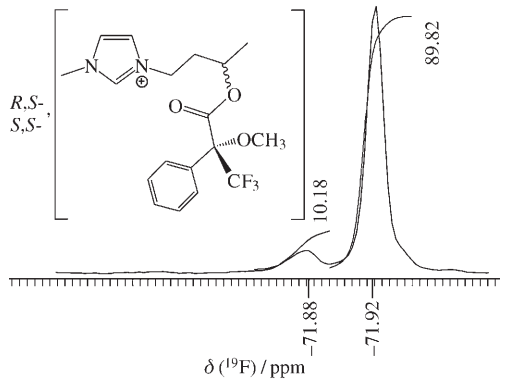


***Figure 1.*** $^{19}$F NMR spectra of **2** after anion exchange and reaction with (*R*)-MTPACl.

the method for our specific case. (Note that esterification with (*S*)-MTPACl results in the diastereomeric *S*,*R* and *R*,*R* esters, while the reaction with (*R*)-MTPACl results in the diastereomeric *S*,*S* and *R*,*S* esters.)[19,20]

The reaction proceeded in up to 80% *ee* to give the hydrogenation product **2** bearing the enantiomeric pure (*R*)-camphorsulfonate anion. The degree of enantioselectivity was found to be dependent on the concentration of the substrate **1** in ethanol during the reaction. Ethanol was used as a diluting solvent for the hydrogenation reaction as the viscosity of the pure ionic liquid **1** was too high for the reaction to be run under solvent-free conditions. The higher the concentration of **1** in ethanol, the higher the *ee* of the hydrogenated cation (see Table 1). This behavior can be explained by taking into account the ion-pair-separating effect of the ethanol solvent. The concentration dependence of the chiral induction is already a strong indication that the chiral induction is based on the ion-pair interactions between the cation and the anion of the ionic liquid. Consequently, the degree of chiral induction can be taken as a probe of the intimacy of the ion-pair interaction in the transition state of the hydrogenation reaction.

In a further set of experiments, we aimed to exclude the possibility that the chiral induction observed in the hydrogenation of **1** resulted from a modification of the surface of the heterogeneous, achiral Ru/C catalyst by the enantiomerically pure anion present in the reaction mixture. Chiral induction by such a surface modification has been described for systems containing cinchona alkaloids as modifiers in enantioselective hydrogenation reactions which reached selectivities of up to 98.8% *ee*.[21] For this purpose, we

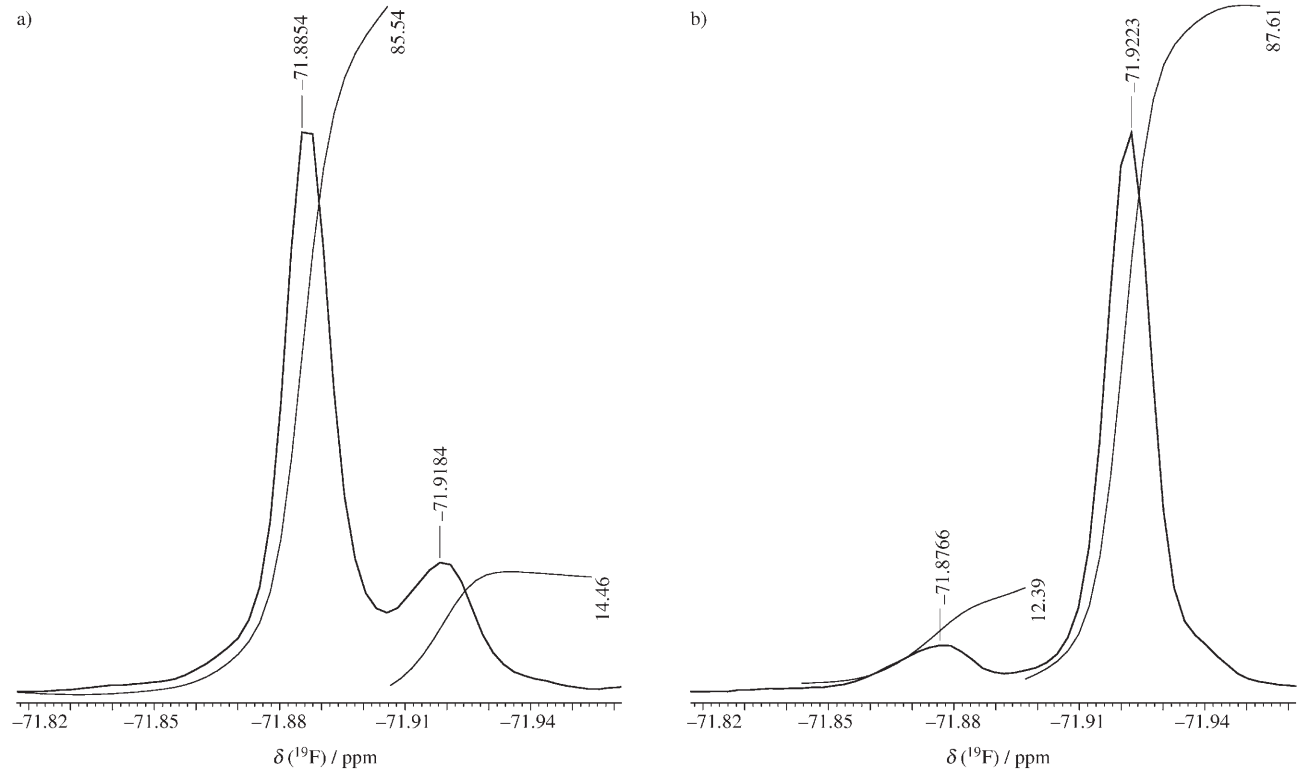


***Figure 2.*** Diastereomeric esters prepared by reaction of **2** with a) (*S*)-MTPACl and b) (*R*)-MTPACl after anion exchange.

  

***Table 1:*** Enantiomeric excess with varying concentrations of ionic liquid **1** in ethanol.[a]

| Entry | Conc. **1** [mmol mol$^{-1}$] (mol $L_{ethanol}^{-1}$) | *ee*[b] |
|---|---|---|
| 1 | 11.6 (0.2) | 32% |
| 2 | 22.8 (0.4) | 63% |
| 3 | 28.3 (0.5) | 80% |

[a] Hydrogenation at 60 °C und 60 bar $H_2$ for 8 h with quantitative yield; no further products were detected by $^1$H and $^{13}$C NMR spectroscopy (see the Supporting Information). [b] Enantiomeric excess was determined by $^{19}$F NMR spectroscopy after esterification with Mosher's acid chloride.

investigated the hydrogenation of the non-ionic substrate acetophenone in the presence of enantiomerically pure sodium (*R*)-camphorsulfonate using the same Ru/C catalyst. In this case, however, the *ee* determined by $^{19}$F NMR spectroscopy for the reaction product was below 5% in all cases, proving that the ionic nature of the prochiral substrate is essential for the strong ion-pairing in ionic liquids and the successful asymmetric hydrogenation.

In conclusion, we could demonstrate the great potential of ion-pairing effects to transfer chiral information from an ion to the transition state of a reaction at its prochiral counterion. Fundamentally different from common methodologies using chiral metal complexes, covalently bound chiral auxiliaries, or chiral solvents, this new concept of chirality transfer just makes use of the fact that every reaction at a prochiral ion must take place in close proximity to its counterion. Our methodology provides a very efficient route to doubly chiral ionic liquids. Moreover, after deprotonation or dealkylation of the chiral cation, neutral chiral molecules can be obtained in a kind of ionic auxiliary chemistry. To realize the full potential of the approach, we are currently investigating the influence of different ion structures, catalysts (chiral (to reveal cooperative effects) or achiral, homogeneous, or heterogeneous), reaction parameters (such as hydrogen pressure and temperature), and added solvents of different polarities. We furthermore expect that our approach can be extended to other reactions of prochiral ions. Apart from aspects of chiral synthesis, our study also reveals some fundamental aspects of ion-pairing effects in ionic liquids. A better understanding of the nature of cation–anion interactions is the key to the rational design of ionic liquids as these interactions determine physicochemical properties as well as interactions with dissolved substances and thus reactivity.

## *Experimental Section*

**1**: (*R*)-camphorsulfonic acid (10 g, 0.043 mol) was added in small portions to a solution of 1-methylimidazole (3.6 g, 0.043 mol) in dichloromethane (150 mL) at room temperature. The mixture was stirred for 2 h at room temperature. After removal of the solvent in vacuo, 1*H*-3-methylimidazolium-(1*R*)-camphorsulfonate was isolated as a white solid. This intermediate (11.3 g, 0.036 mol) was dissolved in ethanol (150 mL), and methyl vinyl ketone (5.93 mL, 0.072 mol) was added. This mixture was heated for 24 h at reflux. The solvent was removed in vacuo, and **1** was obtained as a brownish, highly viscous product.

Hydrogenation of **1**: Ru/C catalyst (5% Ru; 50 wt% with respect to **1**) was added to a solution of **1** in ethanol (100 mL). This mixture was transferred to an autoclave, heated to 60 °C under 60 bar $H_2$, and stirred for 8 h. After filtration of the catalyst and removal of the solvent under vacuum, the product **2** was isolated as a highly viscous brownish liquid.

Determination of the enantiomeric excess of **2**: a) Anion metathesis: The ionic liquid **2** (3 g, 7.76 mmol) was dissolved in water (30 mL) and stirred vigorously while a solution of lithium bis(trifluoromethanesulfonyl)imidate (Li[$NTf_2$], 2.24 g, 7.76 mmol) in water (20 mL) was added. After 30 min the resulting two liquid phases were separated. The aqueous phase was washed with $CH_2Cl_2$, and this organic phase was combined with the ionic-liquid phase. The IL phase was washed with water five times and dried under vacuum. A brown viscous IL was obtained (2.37 g, 5.43 mmol, 70%). b) Esterification: After anion metathesis, the ionic liquid was dissolved in $CH_2Cl_2$. Pyridine (3 equiv) and (*R*)-MTPACl or (*S*)-MTPACl (1.5 equiv) were added at room temperature and under inert atmosphere. The resulting solution was analyzed by $^{19}$F NMR spectroscopy using a JEOL ECX 400 spectrometer.

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