Journal of Molecular Catalysis A: Chemical 357 (2012) 117–124

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Potential of ionic liquids as co-modifiers in asymmetric hydrogenation on platinum

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ARTICLE INFO

Article history:
Received 15 December 2011
Received in revised form 27 January 2012
Accepted 30 January 2012
Available online 8 February 2012

Keywords:
Enantioselective hydrogenation
α-Ketoester
Ionic liquids
Cinchona alkaloids

ABSTRACT

The enantioselective hydrogenation of methyl benzoylformate on Pt/Al_2O_3 has been studied in the presence of various ionic liquids (ILs) and three structurally related chiral modifiers: cinchonidine (CD), *O*-phenyl-cinchonidine (PhOCD), and *O*-naphthyl-cinchonidine (NaphOCD). Addition of ca. 1% IL to a polar organic solvent – particularly alcohols – improved the enantioselectivity by up to 12% (to 92–93%) in the presence of CD. On the other hand, ILs diminished the reaction rate sometimes dramatically, by two orders of magnitude, and the poisoning effect was even stronger in cyclohexene hydrogenation under identical conditions. Comparative studies revealed that only ILs possessing a heteroaromatic cation interact strongly with Pt or the *O*-aryl function of PhOCD and NaphOCD. A tentative explanation is the strong π-bonding interaction of ILs with the Pt surface (leading to site blocking and deactivation) and with the *O*-aryl function of the modifier not involved in the adsorption onto Pt (resulting in a shift in enantioselectivity).

1. Introduction

There has been a rapid development in catalysis in the past decade using ionic liquids (ILs) as solvents or catalysts of various transformations [1–6]. The properties of ILs can be tuned in a broad range by varying the cations and anions. Application of ILs in enantioselective hydrogenations with chiral complexes is a thoroughly investigated, successful approach [7–9]. In heterogeneous catalytic hydrogenations on metal surfaces the use of ILs has yet been limited to the saturation of C=C and C=O bonds in simple molecules [10,11] and to chemoselective transformations. The latter reactions include the partial hydrogenation of various α,β-unsaturated carbonyl compounds [12–17], halonitro-compounds [18,19], alkynes [20,21], cyclooctadiene [22], and propionitrile [23].

Despite of the excellent results achieved in various fields of heterogeneous and homogeneous catalysis, application of ILs has also some disadvantages. ILs are still expensive for large scale applications; they are characterized by relatively high viscosity and low substrate diffusion rates leading to mass transport limitations. An attractive strategy to overcome some of these difficulties is the application of a thin supported IL layer on a solid surface [24]. This method allows heterogenization of soluble metal complexes in continuous flow fixed-bed reactors [25] and also biphasic hydrogenation reactions [26]. A less common approach is the simple addition of an IL in small amounts to the polar solvent of the reaction [27,28].

The potential of ILs to influence the enantioselection is the topic of the present study. The test reaction is the hydrogenation of methyl benzoylformate (**1**, Scheme 1) on the commonly used Pt/Al_2O_3 reference catalyst modified by cinchonidine (CD) and its *O*-phenyl and *O*-naphthyl derivatives PhOCD and NaphOCD, respectively (Scheme 1). A fundamental question addressed here is the nature of interactions between the IL, the Pt surface, and the reaction components. To clarify this point we studied the transformation (i) in a weakly polar organic solvent and added various ILs as a layer supported on the catalyst (catalyst modifier), (ii) in a polar solvent mixture containing the IL in small amounts (reaction modifier), and (iii) applied the IL as the solvent itself.

The enantioselective hydrogenation of α-ketoesters has been intensively studied in the past decades, mainly using the simplest substrate, pyruvate esters [29,30]. Only after recognizing the importance of side reactions involving the α-H atom of pyruvate esters [31–35] has the interest been shifted to the more stable benzoylformates as suitable model substrates. The general characteristics of this reaction have already been clarified. Under optimized conditions, in an acetic acid–toluene mixture at 273 K, 98% ee was obtained by Bartók's group [36] but the best ees in the absence of acid and at room temperature were significantly lower, in the range 84–88% [37,38].

The present study shows that ILs possessing a heteroaromatic ring (Fig. 1) may strongly interact with the chiral modifier and the metal surface, and thus can influence the reaction rate and enantioselection.

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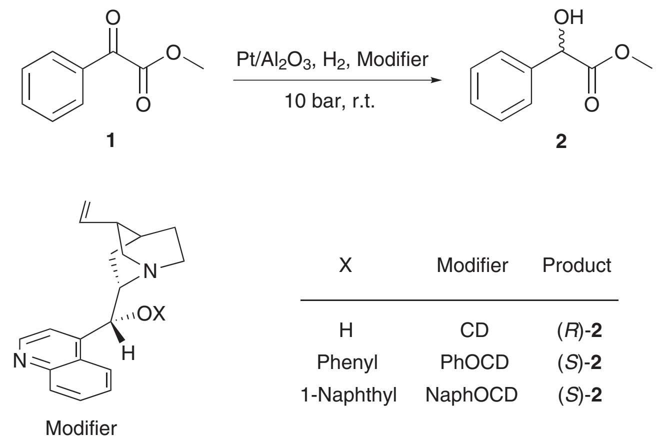
doi:10.1016/j.molcata.2012.01.029



X	Modifier	Product
H	CD	(*R*)-**2**
Phenyl	PhOCD	(*S*)-**2**
1-Naphthyl	NaphOCD	(*S*)-**2**

Scheme 1. Test reaction and the structures of the chiral modifiers.

2. Experimental

2.1. Materials

Methyl benzoylformate (**1**, 99%, Acros), toluene (99.7%, Fluka), 3-pentanone (98%, Fluka), acetic acid (AcOH, 99.8%, Fluka), acetonitrile (99.5%, Sigma–Aldrich), 1,2-dichlorobenzene (99%, Acros), tetrahydrofuran (THF, 99.5%, Sigma–Aldrich), 2-propanol (99.8%, Sigma–Aldrich), 2-butanol (99%, Acros), triethylamine (99.5%, Sigma–Aldrich), piperidine (99%, Sigma–Aldrich), pyridine (98%, J.T. Baker), morpholine (99%, Fluka), and cinchonidine (CD, 96%, Aldrich) were used as received. Synthesis of *O*-phenyl-cinchonidine (PhOCD) and *O*-(1-naphthyl)-cinchonidine (NaphOCD) was described elsewhere [39]. The ILs were used as received (Fig. 1): [BMIm][BF$_4$] (99%, ABCR), [BMIm][PF$_6$] (98%, Acros), [BMIm][FEP] (99%, Merck), [BMIm][NTf$_2$] (99%, ABCR), [BMPy][BF$_4$] (for synthesis, Merck), [BMPy][PF$_6$] (99%, ABCR), [BMPr][OTf] (for synthesis, Merck), [BMPr][FEP] (for synthesis, Merck), [MMPp][NTf$_2$] (98%, Merck), [MMMo][NTf$_2$] (98%, Merck). The 5 wt.% Pt/Al$_2$O$_3$ (E 4759) was purchased from BASF (Engelhard).

For the synthesis of catalysts modified with a supported IL layer, 50 mg freshly activated 5% Pt/Al$_2$O$_3$ was put in a Schlenk tube together with a magnetic stir bar. The appropriate amount of IL (15 mg for a 30% loading) was introduced as a solution in about 1 ml of acetone. The mixture was gently stirred and acetone removed slowly in a flow of N$_2$ overnight. The catalyst was finally dried in vacuum for several hours and stored under N$_2$ atmosphere.

2.2. Catalytic hydrogenations

As a standard reaction procedure, hydrogenation of **1** was carried out in a magnetically stirred stainless steel autoclave with 50 ml glass inlet and PTFE cover. The pressure (usually 10 bar) was controlled by a computerized constant-volume, constant-pressure equipment (Büchi BPC 9901). Prior to the reaction, the 5 wt.% Pt/Al$_2$O$_3$ was pretreated in flowing N$_2$ at 400 °C (673 K) for 30 min, then in hydrogen at the same temperature for 60 min. After cooling to room temperature in hydrogen, the activated catalyst was flushed overnight by nitrogen. This step is necessary to slowly reoxidize the surface of Pt particles by the oxygen impurity in the nitrogen flow and thus avoid the uncontrolled interaction of residual surface hydrogen with oxygen in open air. After pretreatment, 10 mg of 5 wt.% Pt/Al$_2$O$_3$ was introduced in the homogeneous reaction mixture containing 250 mg (1.5 mmol) of **1**, 30 mg of IL (if any), 1 or 2 mg of modifier and 3 ml of solvent. After stirring at 750 rpm for 60 min under nitrogen atmosphere

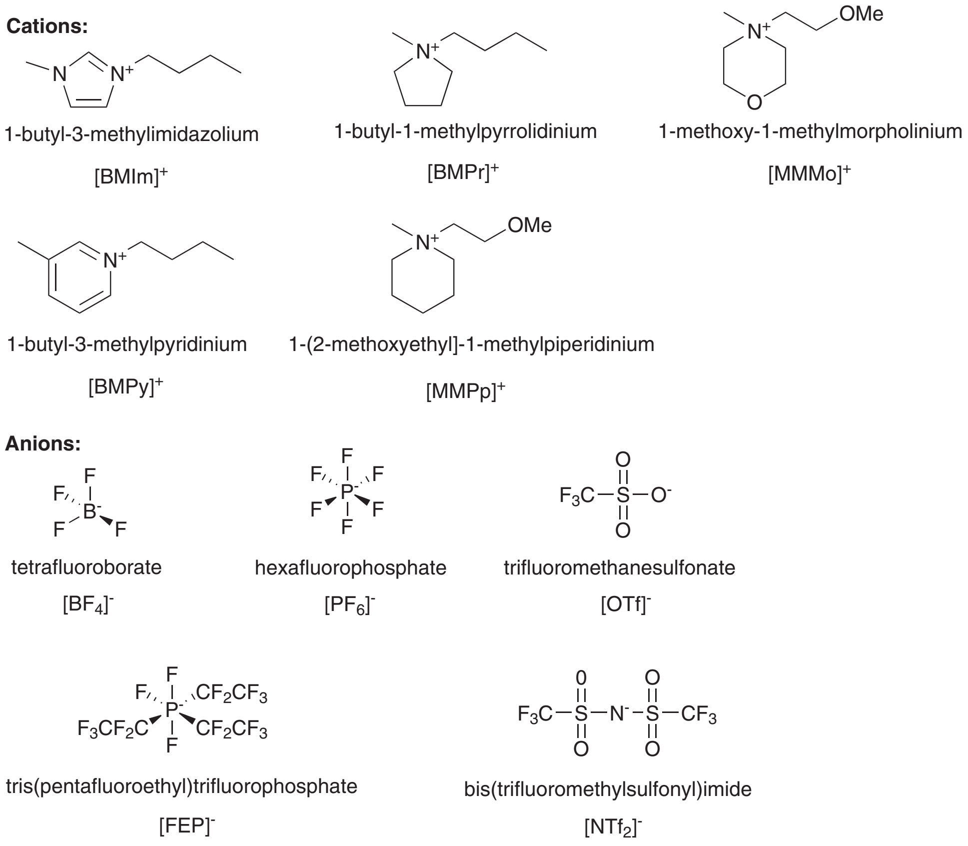


Fig. 1. Cations and anions of ILs used in this study.

Table 1
Effect of organic solvents and ILs on the hydrogenation of **1** to (*R*)-**2** on CD-modified Pt/Al_2O_3. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 1 mg CD, 3 ml solvent (organic or IL); 10 bar, room temperature.

Solvents	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})
Toluene	60	35	88	210
Acetic acid	15	54	78	1300
3-Pentanone	15	69	92	1700
Tetrahydrofuran	15	75	87	1800
Ethyl acetate	15	43	90	1100
1,2-dichlorobenzene	60	63	90	380
2-Propanol	15	39	76	910
2-Butanol	15	82	84	2000
Acetonitrile	180	56	9	110
Et_3N	120	95	4	300
Piperidine	120	91	0	270
Pyridine	180	94	0	190
Morpholine	120	14	0	43
[BMPr][FEP]	1440	100	71	–
[MMMo][NTf_2]	1440	100	87	–
[MMMo][NTf_2]	30	9	83	110
[MMPp][NTf_2]	30	12	86	140
[BMIm][BF_4]	780	6	46	3
[BMIm][PF_6]	720	9	64	5

(pre-equilibration to improve the reproducibility), the reaction started at room temperature by stirring after the introduction of hydrogen. The Pt/Al_2O_3 modified with an IL layer was used directly, without a second reductive treatment at 400 °C.

The conversions and enantiomeric excesses (ee) were determined by using a Thermo Finnigan trace gas chromatograph with a CP-Chirasil-DEX CB (25 m × 0.25 mm × 0.25 μm) capillary column. The reaction rates are characterized by the turn-over frequencies (TOFs). TOFs are related to the total amount of Pt present in the reaction mixture (mol substrate converted by 1 mol Pt in 1 h). The estimated error of TOFs was about ±10% and that of ee was about ±1–2%. The reactions were repeated several times to reduce the standard deviation. The sometimes poor reproducibility could be improved by deactivating the glassware with trimethylsilyl chloride. The glassware was pretreated by immersing it into aqua regia for 15 min. After washing with water and drying, it was treated with a 10 vol.% toluenic solution of trimethylsilyl chloride for 30 min. After careful washing with toluene, methanol and acetone, the glassware was dried in vacuum.

Hydrogenation of cyclohexene was carried out according to the standard procedure but at 3 bar, using 1.5 mmol of cyclohexene, 30 mg of IL and 3 ml of solvent.

3. Results and discussion

3.1. Solvent effect in the hydrogenation of methyl benzoylformate (1)

At first we investigated some commonly used ILs as solvents and compared their properties to those of organic solvents (Table 1). The reaction rates are characterized by the average TOF calculated from the conversion and the total amount of Pt present in the reactor. Although the effect of organic solvents on the reaction rate and enantioselectivity is very strong, no general correlation with the typical solvent properties (E_T^N, α, or β [40,41]) could be established. In the hydrogenation of benzoylformates [36] and other α-ketoesters the highest ees are commonly achieved in the presence of the good H-bond donor acetic acid ($\alpha = 1.12$). Under the conditions applied here, some basic (H-bond acceptor) solvents, such as 3-pentanone ($\beta = 0.45$) and ethyl acetate ($\beta = 0.45$), allowed significantly higher ees up to 92%. On the other hand, the ee was 90% also in the very weakly basic and non-acidic solvent dichlorobenzene ($\beta = 0.03$, $\alpha = 0$), while strongly basic solvents, such as Et_3N ($\beta = 0.71$) (almost) ceased the enantioselection. The poor ee of 9% in acetonitrile may be due to competing hydrogenation of the solvent to ethylamines [42]. The detrimental effect of basic impurities of the catalyst on the enantioselective hydrogenation of **1** was reported at first by Orito et al. [43] and the very low ees in amine type organic solvents in the hydrogenation of ethyl pyruvate by Blaser et al. [44], but the phenomena could not be interpreted.

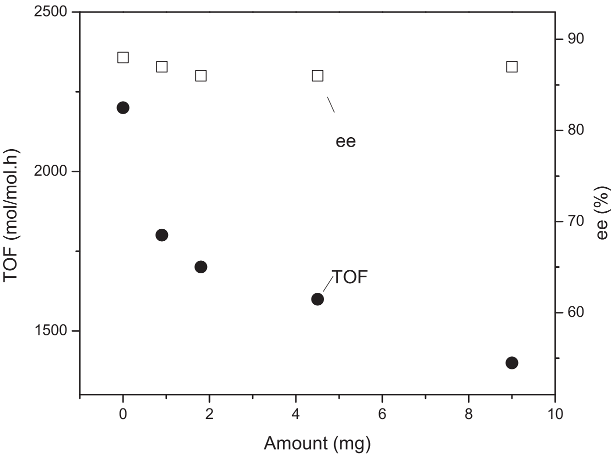


Fig. 2. The influence of [BMIm][BF_4] added to the reaction mixture before hydrogenation of **1** in acetic acid. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 3 ml AcOH, 2 mg CD, 20 bar, room temperature, 10 min reaction time.

The ILs applied in Table 1 as solvents may be divided into two categories. Those containing a cycloaliphatic cation ($[BMPr]^+$, $[MMMo]^+$, $[MMPp]^+$, Fig. 1) allow reasonably good ees, while the presence of the heteroaromatic cation $[BMIm]^+$ lowers the enantioselection and in particular the reaction rate. As concerns the low reaction rates in the presence of $[BMIm]^+$, there is an increasing amount of experimental indications to the poisoning effect of ILs, including imidazolium-based salts, in hydrogenation reactions on Pt-group metal catalysts [15,22,45,46]. It has been proposed that imidazolium-based ILs may react with Ir(0) nanoclusters and form "surface-attached carbenes", although deactivation due to strongly adsorbed, π-bonded imidazolium cations could not be excluded [47]. Not only the $[BMIm]^+$ cation but also some anions in the order $[PF_6]^- < [BF_4]^- < [CF_3SO_3]^-$ may be the origin of deactivation [48].

3.2. Ionic liquids as solvent components (reaction additives)

Due to the high cost of ILs as solvents, it is more attractive to apply them in small amounts as additives. The influence of [BMIm][BF_4] additive in acetic acid solvent is illustrated in Fig. 2. The poisoning effect is obvious: the higher the amount of IL in the system, the lower is the reaction rate. After the fast initial drop the deactivation was less pronounced. Multiplying the amount of IL from 9 to 90 mg resulted in only a relatively small decrease of TOF from 1400 to 1100 h^{-1} (not shown). Note that 90 mg of IL corresponds to 2.8 mass% of the solvent acetic acid. The effect of [BMIm][BF_4] as reaction additive on the enantioselectivity was negligible: all values in Fig. 2 varied in a narrow range of 87 ± 1%. A significant decrease to 84% was observed only by the tenfold increase (to 90 mg) of the amount of IL.

The effect of constant amounts of [BMIm][FEP] added to different organic solvents is illustrated in Table 2, under partly different conditions. In this series of experiments the amount of ILs (30 mg) was increased to a relatively high level compared to those in Fig. 2 in order to suppress the effect of the amount of ILs on the catalyst performance. In most solvents – excluding the alcohols – the enantioselectivity barely changed. In the weakly polar, aromatic

Table 2
Influence of small amounts of [BMIm][FEP] added to different solvents prior to the hydrogenation of **1**, using CD-modified Pt. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 1 mg CD, 3 ml solvent with or without [BMIm][FEP] (30 mg), 10 bar, room temperature.

Solvent	[BMIm][FEP]	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})	Relative rate
3-Pentanone	–	15	69	92	1700	1.00
	+	150	76	92	180	0.11
Tetrahydrofuran	–	15	75	87	1800	1.00
	+	150	21	86	50	0.03
Acetic acid	–	15	54	78	1300	1.00
	+	15	29	79	730	0.56
Ethyl acetate	–	15	43	90	1100	1.00
	+	90	57	93	240	0.22
1,2-Dichlorobenzene	–	60	63	90	380	1.00
	+	60	65	92	400	1.05
2-Propanol	–	15	39	76	910	1.00
	+	15	33	88	820	0.90
2-Butanol	–	15	82	84	2000	1.00
	+	15	50	92	1200	0.60

solvent 1,2-dichlorobenzene the influence of the IL is negligibly small: the change in the reaction rate and ee does not exceed the estimated experimental error. A tentative explanation for the missing influence is the strong π-bonding interaction between the aromatic ring of the solvent and the $[BMIm]^+$ cation, as described for imidazolium-based ILs and benzene or toluene [49–52]. This interaction with the solvent probably minimizes the amount of IL adsorbed on Pt. The TOFs are in general lower in the presence of the IL, probably indicating some site blocking at the Pt surface, as will be discussed later. In the extreme case, in tetrahydrofuran, ca. 1 mass% IL in the solvent diminished the hydrogenation rate of **1** by 97%. A surprising result is the 8–12% increase of enantioselectivity in alcoholic solvents by addition of [BMIm][FEP]. For comparison, hydrogenation of α-ketoesters in alcohols never provided outstanding ees, probably due to some hemiketal formation [31,53].

Next, we choose 3-pentanone as solvent and varied the chemical nature of the IL (Table 3). Clearly, both the cations and the anions influence the enantioselective hydrogenation of **1**. A significant negative effect on the enantioselectivity was observed only in the presence of $[BF_4]^-$ and $[PF_6]^-$ anions. Excluding these anions the ee barely changed, independent of the nature of the cation.

It is reasonable to assume that the lower reaction rate, compared to the reference reaction without IL, reflects the strong adsorption of the IL on the Pt surface resulting in site blocking. In other words, the IL, the substrate, and the chiral modifier compete for the same Pt^0 active surface sites. Based on this assumption we can conclude that heteroaromatic cations adsorb much stronger than the cycloaliphatic cations. The order of adsorption under these conditions is: $[BMIm]^+ > [BMPy]^+ > [BMPr]^+ \approx [MMPp]^+ \approx [MMMo]^+$. Also the nature of the anion affects the adsorption strength, as can be seen for example by comparing the effect of four different salts with $[BMIm]^+$ cation.

We have to consider that catalyst deactivation might also be caused by impurities. The striking, more than 100-fold deactivation in the presence of $[BF_4]^-$ anion might also be due to its hydrolysis and the formation of HF [54]. This side reaction is less facile with the $[PF_6]^-$ anion. Note that a small amount of water is always present at the catalyst surface at the beginning of the hydrogenation reaction originating from the reduction of oxygen impurities and surface oxygen on the catalyst. A further possibility is the hydrodehalogenation of the F-containing anions $[BF_4]^-$ and $[PF_6]^-$ that would result in the loss of hydrogenation activity of Pt.

A feasible conclusion from the results in Table 3 is that (non-reactive) ILs do not disturb the interaction of CD with **1**, the source of enantioselection, independent of the chemical nature of the cation. On the other hand, ILs containing heteroaromatic cations adsorb strongly on Pt, cover a considerable fraction of surface sites and diminish the reaction rate.

3.3. *Catalyst poisoning in cyclohexene hydrogenation: a comparison*

To support our assumption on the competitive adsorption of ILs on Pt, we repeated the experiments in Table 3 and substituted **1** and CD with cyclohexene. Hydrogenation of the C=C bond in cyclohexene is a facile reaction that – in contrast to the enantioselective reaction – does not require an extended ensemble of active sites [55]. The results in Table 4 demonstrate that this simple test reaction is poisoned stronger than the enantioselective hydrogenation of **1**. Here even the ILs possessing a cycloaliphatic cation diminish the activity of Pt by 38–62% and the poisoning effect of heteroaromatic cations with various anions may be higher than 99%. For each IL additive, the relative rate was lower in the hydrogenation of cyclohexene than in case of **1**.

An obvious explanation is the relatively weak adsorption of cyclohexene, compared to that of **1** (possessing electron-rich phenyl, carbonyl and ester groups) and in particular to CD [56–58]. A further probable component of catalyst poisoning by ILs is the hydrophobic character of cyclohexene, while the ILs adsorbed on the Pt surface are strongly hydrophilic and may hinder the adsorption of the olefin.

It has been found that addition of small amounts of ILs frequently improved the chemoselectivity but at the cost of the reaction rate [22,59]. Complete hydrogenation of highly reactive olefins such as 1-hexene [48] or cyclooctadiene [22] required 50–75 °C at medium pressures. In the absence of ILs these transformations occur on Pt-group metal catalysts already under ambient conditions [60].

3.4. *Ionic liquid–cinchona interaction: structural effects*

The data in Table 3 revealed no sign of influence of chemically stable ILs on the enantioselection, that is on the substrate–chiral modifier interaction. To better understand this critical point, we extended the study to *O*-arylated derivatives of CD. In the hydrogenation of various activated ketones PhOCD and NaphOCD afford the (*S*)-alcohols in excess, although the actual ee depended also on the reaction conditions [61]. Inversion of the major product was attributed to the steric hindrance by the bulky aryloxy group [62]. The use of these three modifiers provides an excellent opportunity

Table 3
The effect of small amounts of ILs added to 3-pentanone prior to hydrogenation of **1** on CD-modified Pt. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 1 mg CD, 3 ml solvent, 30 mg IL, 10 bar, room temperature.

Ionic liquid	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})	Relative rate
No	15	69	92	1700	1.00
Cycloaliphatic cation					
[BMPr][OTf]	15	40	89	980	0.58
[BMPr][FEP]	15	72	92	1700	1.00
[MMPp][NTf_2]	15	67	92	1600	0.94
[MMMo][NTf_2]	15	63	92	1500	0.88
Aromatic cation					
[BMIm][BF_4]	900	32	77	13	0.008
[BMIm][PF_6]	180	60	92	120	0.07
[BMIm][FEP]	150	76	92	180	0.11
[BMIm][NTf_2]	150	69	92	170	0.10
[BMPy][BF_4]	180	56	65	120	0.07
[BMPy][PF_6]	60	56	79	340	0.20

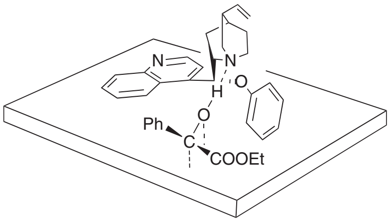


Fig. 3. Illustration of the N–H–O type interaction between the quinuclidine N atom of the alkaloid and **1** adsorbed on Pt, and the tilted position of the *O*-phenyl ring relative to the Pt surface.

to study structural effects, since aryl substitution at the OH function of CD induces only steric effects; the stereogenic centers of the modifiers and the N–H–O type interaction between the quinuclidine N of the chiral modifier and keto-carbonyl group of the substrate (Fig. 3) remain the same.

We repeated the experiments in Table 3 with the only difference that CD was substituted with PhOCD. The results in Table 5 show that ILs possessing cycloaliphatic cations barely reduced the ee to (*S*)-**2** (with the exception of [BMPr][OTf]), and the loss of catalyst reactivity was always less than 50%. The effect of heteroaromatic cations was much stronger: the ee dropped to one-half or even to one-fifth and the rate decreased by up to 99%.

Table 6 presents a comparison involving all three chiral modifiers. In this case the influence of only two typical ILs are compared, both possessing the heteroaromatic cation $[BMIm]^+$. There is no influence on the ee in case of CD, while the (negative) effect of ILs in the presence of PhOCD and NaphOCD is comparable. As concerns the reaction rate, the data indicate a small but significant poisoning effect of the $[PF_6]^-$ anion.

For the interpretation of the results we assume that a π–π bonding interaction between the aryloxy group of the alkaloid derivative and the heteroaromatic cation of the IL is responsible for the shift in the product distribution. Adsorption of the substrate on Pt involves the phenyl group and the two electron-rich carbonyl groups [63]. During interaction with the ketone substrate, also the quinoline ring of the alkaloid adsorbs strongly on Pt in (close to) parallel position. Hence, the $[BMIm]^+$ cation cannot interact with these electron-rich groups and the ILs have only minor or negligible influence on the ee when CD is applied. In case of PhOCD and NaphOCD the situation is different: the aryloxy function does not adsorb parallel to the Pt surface but rather in a tilted position [62] and thus it is available for interaction with the imidazolium ring of the IL. This interaction changes the shape and size of the chiral site available for adsorption of the ketone substrate and thus controls the ee. The existence of this type of π-bonding interactions has been evidenced between various ILs containing 1-alkyl-3-methylimidazolium cations and aromatic hydrocarbons such as benzene [49,51,52], toluene, [49,50] and 1-methylnaphthalene [64].

3.5. Supported ionic liquid layer or reaction modifier?

We have mentioned previously the disadvantages of applying ILs as solvents and in most cases we used them in small amounts as reaction additives. This is a very simple approach and many solvents dissolve small amounts of IL salts, but separation and recycling of the expensive additive may be a limiting factor. To evaluate

Table 4
Hydrogenation of cyclohexene: the influence of IL additives containing cycloaliphatic and aromatic cations in 3-pentanone solvent. *Conditions*: 120 mg (1.5 mmol) cyclohexene, 30 mg IL, 10 mg 5% Pt/Al_2O_3, 3 ml solvent, 3 bar, room temperature.

Ionic liquid	Time (min)	Conv. (%)	TOF (h^{-1})	Relative rate
No	15	66	1600	1.00
Cycloaliphatic cation				
[BMPr][OTf]	15	12	280	0.18
[BMPr][FEP]	15	40	990	0.62
[MMPp][NTf_2]	15	24	600	0.38
[MMMo][NTf_2]	15	15	360	0.23
Aromatic cation				
[BMIm][BF_4]	120	2.5	7.5	0.005
[BMIm][PF_6]	120	4.2	13	0.008
[BMIm][FEP]	120	6.1	19	0.012
[BMIm][NTf_2]	120	3.3	10	0.006
[BMPy][BF_4]	30	14	180	0.11
[BMPy][PF_6]	30	23	280	0.18

Table 5
The effect of small amounts of ILs on the hydrogenation of **1** to (*S*)-**2** in 3-pentanone, using PhOCD-modified Pt. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 1 mg PhOCD, 3 ml solvent, 30 mg IL, 10 bar, room temperature.

Ionic liquid	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})	Relative rate
No	30	42	66	510	1.00
Cycloaliphatic cation					
[BMPr][OTf]	30	22	49	270	0.53
[BMPr][FEP]	30	24	63	280	0.55
[MMPp][NTf_2]	30	39	63	470	0.92
[MMMo][NTf_2]	30	42	65	500	0.98
Aromatic cation					
[BMIm][BF_4]	900	8	13	4	0.008
[BMIm][PF_6]	900	15	22	6	0.012
[BMIm][FEP]	900	18	33	7	0.014
[BMIm][NTf_2]	900	19	32	8	0.016
[BMPy][BF_4]	180	29	18	59	0.12
[BMPy][PF_6]	120	26	22	79	0.15

Table 6
The critical role of the structure of the chiral modifier in the IL–modifier interactions during the hydrogenation of **1** in 3-pentanone. *Conditions*: 250 mg **1**, 10 mg 5% Pt/Al_2O_3, 1 mg modifier, 3 ml solvent, 30 mg IL, 10 bar, room temperature.

Modifier	Ionic liquid	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})	Relative rate
CD	No	15	69	92 (*R*)	1700	1.00
CD	[BMIm][PF_6]	180	60	92 (*R*)	120	0.07
CD	[BMIm][FEP]	150	76	92 (*R*)	180	0.11
PhOCD	No	30	42	66 (*S*)	510	1.00
PhOCD	[BMIm][PF_6]	900	15	22 (*S*)	6	0.012
PhOCD	[BMIm][FEP]	900	18	33 (*S*)	7	0.014
NaphOCD	No	60	45	44 (*S*)	270	1.00
NaphOCD	[BMIm][PF_6]	900	18	20 (*S*)	7	0.026
NaphOCD	[BMIm][FEP]	900	21	24 (*S*)	9	0.033

the other commonly used approach, we deposited 30 mass% of an IL as a separate layer onto the surface of the 5% Pt/Al_2O_3 catalyst and carried out the enantioselective hydrogenations in the weakly polar solvent toluene that is a poor solvent of ILs. An even less polar, hydrophobic hydrocarbon solvent would be a better choice, but the low solubility of cinchona alkaloids does not allow this choice. The study involves three ILs with heteroaromatic and cycloaliphatic cations and three different anions, and also two different chiral modifiers. The effect of the same ILs used as reaction additives in 3-pentanone are also included in Table 7 for comparison.

An important difference between the two series of experiments is the amount of IL on the catalyst surface. Using the supported IL layer approach, 13 mg catalyst contained 3 mg IL. This amount of salt probably remained there during reaction in toluene, although its distribution on the Pt and on the support is unknown. In the other series 30 mg IL was added to the reaction mixture and probably only a small fraction of this salt adsorbed onto the catalyst surface.

Analysis of the results reveals in Table 7 that independent of the approach applied, [BMPr][FEP] possessing a cycloaliphatic cation has negligible influence on the reaction, when CD is used as chiral modifier. In the presence of PhOCD the catalyst deactivation is more significant when [BMPr][FEP] is added to the solvent as a reaction additive, but the enantioselectivities are barely affected. A similar conclusion may be drawn for [BMIm] [FEP] and [BMIm][BF_4]: with

Table 7
Comparison of the effect of ILs as a supported layer on Pt/Al_2O_3 or as a reaction additive in the hydrogenation of **1**. *Conditions*: 250 mg **1**, 1 mg modifier, 3 ml solvent, 10 bar, room temperature; catalyst: 10 mg 5% Pt/Al_2O_3 and 30 mg IL, or 13 mg 5% Pt/Al_2O_3 covered by 30 mass% IL layer.

Ionic liquid	Modifier	Solvent	Time (min)	Conv. (%)	ee (%)	TOF (h^{-1})	Rel. rate
As a supported layer							
No	CD	Toluene	60	35	88 (*R*)	210	1.00
[BMPr][FEP]	CD	Toluene	120	65	88 (*R*)	200	0.95
[BMIm][FEP]	CD	Toluene	240	51	88 (*R*)	76	0.36
[BMIm][BF_4]	CD	Toluene	240	10	82 (*R*)	15	0.07
No	PhOCD	Toluene	120	24	44 (*S*)	73	1.00
[BMPr][FEP]	PhOCD	Toluene	120	22	41 (*S*)	68	0.93
[BMIm][FEP]	PhOCD	Toluene	120	14	31 (*S*)	43	0.59
[BMIm][BF_4]	PhOCD	Toluene	720	4	17 (*S*)	2	0.03
As a reaction additive							
No	CD	3-Pentanone	15	69	92 (*R*)	1700	1.00
[BMPr][FEP]	CD	3-Pentanone	15	72	92 (*R*)	1700	1.00
[BMIm][FEP]	CD	3-Pentanone	150	76	92 (*R*)	180	0.11
[BMIm][BF_4]	CD	3-Pentanone	900	32	77 (*R*)	13	0.008
No	PhOCD	3-Pentanone	30	42	66 (*S*)	510	1.00
[BMPr][FEP]	PhOCD	3-Pentanone	30	24	63 (*S*)	280	0.55
[BMIm][FEP]	PhOCD	3-Pentanone	330	8	25 (*S*)	9	0.02
[BMIm][BF_4]	PhOCD	3-Pentanone	900	8	13 (*S*)	4	0.008

both chiral modifiers the (negative) effect on the reaction rate and ee is stronger, when the IL is used as an additive in 3-pentanone. In addition, comparison of the data allows differentiation between the negative effect of the $[BMIm]^+$ aromatic cation and the poisoning of Pt by the $[BF_4]^-$ anion.

4. Summary and conclusions

In the enantioselective hydrogenation of **1** to (*R*)-**2** (Scheme 1) over CD-modified 5% Pt/Al_2O_3 the highest enantioselectivities (90–92%) were achieved in the organic solvents 3-pentanone, ethyl acetate and 1,2-dichlorobenzene (Table 1). Strongly basic solvents ceased the enantioselection and the commonly used solvents acetic acid and toluene were not advantageous. In the six different ILs tested as solvents, the ees varied in the range 46–87%. The ILs containing the heteroaromatic cation $[BMIm]^+$ (Fig. 1) reduced the ee and diminished the hydrogenation rate typical for polar organic solvents by more than two orders of magnitude. Interestingly, application of them as reaction additives in about 1 mass% improved the ee in some organic solvents, particularly in alcohols (Table 2, Fig. 2). The highest ee of 93% (without optimization) was obtained in an ethyl acetate–[BMIm][FEP] mixture. The significant shifts in the catalyst performance provide an indirect evidence for the location of ILs on the Pt surface during the hydrogenation reactions. In this respect, the effect of ILs on the reaction rate and enantioselectivity was qualitatively the same, independent of the method used to introduce them into the reaction mixture, i.e. whether they were deposited onto the catalyst surface as a thin supported layer prior to application in toluene that dissolves them poorly, or they were simply added to a good polar solvent in larger amount (Table 7).

An important target of the study was to understand the interaction of ILs with the substrate, the chiral modifier and the Pt surface. In general, IL additives possessing a cycloaliphatic cation (Fig. 1) had only a small effect on the performance of the Pt–CD system (Table 3). On the contrary, the heteroaromatic cations $[BMIm]^+$ and $[BMPy]^+$ were detrimental. The most probable explanation is the blocking of a fraction of surface Pt sites by the strongly adsorbed (π-bonded) cation [65,66]. This competition for the active surface sites was even more pronounced in the hydrogenation of cyclohexene under otherwise identical conditions (Table 4), which difference is probably linked to the different adsorption strengths of the IL, the substrate, and CD. Note that transformation (hydrolysis or hydrogenolysis) of the anions $[PF_6]^-$ and $[BF_4]^-$ under reaction conditions, and the resulting catalyst poisoning, may also contribute to the observed deactivation. Nevertheless, all data indicate that the changes in reactivity and enantioselectivity cannot be linked to a direct interaction of the IL with the substrate (**1** or cyclohexane) or CD. According to our general knowledge, the electron-rich phenyl and carbonyl groups of **1** and the extended aromatic ring system of CD adsorb (close to) parallel to the Pt surface during hydrogen uptake (Fig. 3) [30,67–70]. This strong interaction with the surface Pt atoms prevents the significant interaction of these species with the IL additive.

The situation is different, when an *O*-aryl function is introduced into CD. The *O*-aryl function is adsorbed in a tilted position relative to the Pt surface (Fig. 3) and can easily interact with the heteroaromatic cations of the ILs via π-bonding interactions. Similar interactions involving a heteroaromatic cation of an IL and an aromatic organic molecule have been confirmed by various spectroscopic methods [49–52,64]. As a result of this interaction the chiral space available for adsorption of the α-ketoester substrate changes, inducing a change in the substrate–chiral modifier interaction and in the enantioselectivity (Tables 5 and 6). This approach, the double modification of the Pt surface with a strongly adsorbing chiral molecule and an interacting IL offers a new possibility for tuning the enantioselectivity, especially for solvents usually allowing inferior ees.

Acknowledgement

Financial support by the Swiss National Science Foundation (Project 200020-131869) is kindly acknowledged.

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