Mixtures of Ionic Liquids and Water as a Medium for Efficient Enantioselective Hydrogenation and Catalyst Recycling

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Received: April 19, 2004; Revised: September 10, 2004; Accepted: September 13, 2004

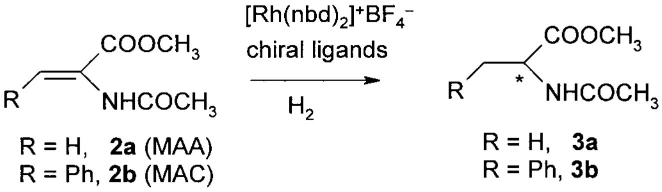
Abstract: In a screening of ligands, ionic liquids and reaction conditions in the Rh-catalyzed hydrogenation of enamides, a novel multi-phase reaction system consisting of an ionic liquid (IL) and water (wet ILs) was found to give the most promising results. In many cases such IL/water combinations were superior compared to conventional organic solvents and biphasic ILs/organic co-solvents media with respect to catalytic performance as well as to catalyst separation and recycling. So far, the best results were obtained with Rh-ferrocenyl-diphosphine catalysts (>99% ee). Generally, somewhat lower ees were observed at higher pressure. However, this effect was less pronounced with wet ILs than with conventional solvents. It is shown that IL/water combination allow repeated catalyst recycling without significant loss of activity and that industrially relevant turnover numbers of >10,000 can be obtained.

Keywords: asymmetric hydrogenation; catalyst recycling; homogeneous catalysis; ionic liquids; rhodium

Introduction

In the last few years, ionic liquids have been attracting much attention as "green and designer" media for chemical reactions.[1] Their application in catalysis has been extensively explored and found to be promising,[2,3] also in enantioselective hydrogenations.[4,5]

The goal of this work was to investigate the scope of ILs in enantioselective hydrogenation with various ligands/catalysts with respect to catalytic performance and to product/catalyst separation and to identify suitable reaction systems and conditions. To study the effects of ILs we performed a screening with various rhodium-diphosphine catalysts, using the two standard enamides test substrates methyl α-acetamidoacrylate (**2a**; MAA) and methyl α-acetamidocinnamate (**2b**; MAC) (Scheme 1), seven classes of diphosphine ligands (Fig. 1) and four imidazolium ILs (Fig. 2). These ILs were selected because they have different polarities and miscibilities with various inorganic and organic solvents and because they are supposed to be non-coordinating.[6] Pyridinium ILs and phosphonium ILs were considered but not chosen, because the first are solids at room temperature and the latter gave only very poor conversions in preliminary hydrogenation experiments.



Scheme 1. Enantioselective hydrogenation of enamides.

Results and Discussion

Before starting our screening, we investigated the influence of the quality of the commercial ILs. Significant differences in catalyst performance could be observed when different batches of ILs were used. We found no correlation between catalyst performance and the colour of the ILs, which can vary from yellow to deep orange depending on the batch. However, formation of a precipitate upon addition of aqueous $AgNO_3$ indicated that many batches of ILs were contaminated with significant amounts of Cl^- or Br^- anions, which have an important effect on catalyst performance. As a consequence, all commercial ILs were purified as described in the literature[7] before use. With such purified ILs, reproducibility was no longer a problem.

In Table **1** we summarize the results of hydrogenations that were carried out with the ferrocenyl-diphosphine li-

DOI: 10.1002/adsc.200404113

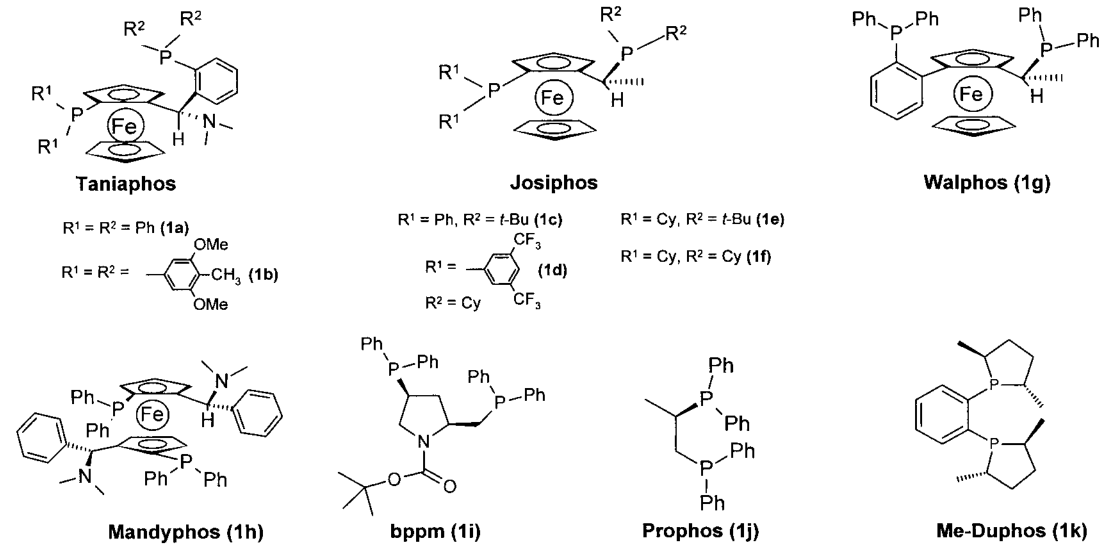
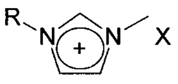


Figure 1. Structures of the ligands used for enantioselective hydrogenation in this study.



R	X⁻	name
n-Bu	BF_4	[bmim]BF_4
n-Bu	PF_6	[bmim]PF_6
n-Bu	Tf_2N	[bmim]Tf_2N
n-Oct	BF_4	[omim]BF_4

Figure 2. Ionic liquids used in this study.

gands **1a** and **1b**.[8] The classical solvents for cationic Rh-catalysts are alcohols (most often methanol). Reference reactions without ILs are given for the same ligands (Table 1, entries 1–4, 12, 13, 20, 26). Experiments with ligand **1a** illustrate the influence of the polarity of the solvent on catalytic performance: In alcohols good activities and enantioselectivties are obtained but they drop significantly with decreasing solvent polarity (Table 1, entries 1–4). It is also interesting to note that addition of water to MeOH has no negative effect (Table 1, entry 1).

ILs have been shown to have similar polarities as low alcohols.[9,10] Indeed, the reactions in ILs gave similar ees as in alcohol, but significantly lower rates (Table 1, entries 5, 6, 14, 21). It is known, that ILs have much lower hydrogen solubilities and higher viscosities than alcohols.[11] The lower rates may therefore be caused by a lower hydrogen concentration due to limited mass transport.

Addition of *i*-PrOH as co-solvents to [bmim]BF_4 and [bmim]PF_6 yields a known biphasic reaction system. In this medium the rates were generally higher than in pure ILs but lower than in alcohols (Table 1, entries 7, 8, 15, 16 and 22). Furthermore, the ees were significantly lower in several cases (Table 1, entries 7 and 8). The possibility to immobilize the catalysts in the IL phase of this biphasic reaction system was studied. We found that catalyst separation and recycling by simple decantation is in principle feasible, but unsatisfactory, since in most cases significant catalyst leaching occurred, as indicated by the yellow colour of the co-solvent phase (Table 1, entries 7 and 8). In addition, ^{1}H NMR measurements revealed significant leaching of ILs into the *i*-PrOH phase.

The promising results in the MeOH-H_2O mixtures mentioned above prompted us to study combinations of ILs with water. Mixtures of ILs and water in any ratio have been called “wet ILs” in the literature[12] and can be single or multi-phasic systems. Such “wet ILs” have been shown to give good results in several reactions such as fluorination with metal fluorides,[13] catalytic hydrogenation of alkynes,[14] and catalytic epoxidation of α,β-unsaturated carbonyl compounds.[15] In addition, several studies indicate that the presence of water can strongly affect the physical properties of ILs.[7,16]

The use of “wet ILs” in enantioselective hydrogenation has only been mentioned for the Ru-catalyzed hydrogenation of tiglic acid, where wet [bmim]PF_6 was reported to give better ees (up to 92%) than pure [bmim]PF_6 (88%) or *i*-PrOH/[bmim]PF_6 (up to 40%).[12] This beneficial effect was attributed to a lower hydrogen concentration in [bmim]PF_6 and wet [bmim]PF_6 than in the organic solvent. Unfortunately, this report gives only very little information about catalyst activity.

We tested this concept with two different biphasic systems. We thereby avoided the use of PF_6-ILs which are known to easily decompose in water.[17] We chose the more stable [omim]BF_4 and [bmim]Tf_2N which both have a poor solubility in water, in order to prevent a possible leaching of the IL into the water-phase and to simplify the following work-up. We also worked with another biphasic system, where one phase was a mixture of the

Table 1. Enantioselective hydrogenation of enamides catalyzed by Rh-Taniaphos in various Ils/water combinations and in conventional solvents.

Entry	Reaction Medium	Conversion [%]	ee [%]	Catalyst Separation	No of Phases
Reactions using ligand **1a**, substrate **2a**					
1	MeOH-H_2O[a]	100	98	–	1
2	MeOH	100	97	–	1
3	*i*-PrOH	92	95	–	1
4	Toluene	47	28	–	1
5	[bmim]BF_4	32	>99	–	1
6	[bmim]PF_6	6	91	–	1
7	[bmim]BF_4/*i*-PrOH	64	96	+	2
8	[bmim]PF_6/*i*-PrOH	12	93	+	2
9	[omim]BF_4/H_2O	100	>99	++	2
10	[bmim]Tf_2N/H_2O	97	>99	++	2
11	[bmim]BF_4-H_2O[b]/Toluene	100	>99	++	2
Reactions using ligand **1b**, substrate **2a**					
12	MeOH	53	97	–	1
13	*i*-PrOH	84	95	–	1
14	[bmim]BF_4	17	98	–	1
15	[bmim]BF_4/*i*-PrOH	43	99	++	2
16	[omim]BF_4/*i*-PrOH	47	98	++	2
17	[omim]BF_4/H_2O	70	>99	++*	2
18	[bmim]Tf_2N/H_2O	90	>99	++	2
19	[bmim]BF_4-H_2O[b]/Toluene	100	>99	++	2
Reactions using ligand **1a**, substrate **2b**					
20	*i*-PrOH	100	94	–	1
21	[bmim]BF_4	52	93	–	1
22	[bmim]BF_4/*i*-PrOH	100	93	+	2
23	[omim]BF_4/H_2O	100	95	++	2
24	[bmim]BF_4-H_2O[b]/Toluene	100	94	++	2
25	[omim]BF_4/H_2O[c]/Toluene	100	95	++	3
Reactions using ligand **1b**, substrate **2b**					
26	*i*-PrOH	100	99	–	2
27	[omim]BF_4/H_2O	100	>99	++	2

ILs: *ca.* 2 mL, co-solvents: *ca.* 2–3 mL, S/C = 200, [S] = 0.25 M in co-solvent, room temperature, P(H_2) = 1 bar, and t = 20 min. "–" no, "+" good (some leaching), "++" excellent (no leaching).

[a] v:v = 4:1.

[b] v:v = 6:1.

[c] v:v = 3:1.

* ICP-MS: 0.9 ppm Rh content in co-solvent.

water-soluble IL [bmim]BF_4 and water and the other a hydrophobic organic solvent such as toluene.

To our surprise, hydrogenation of **2a** with ligands **1a** and **1b** in [omim]BF_4/H_2O and [bmim]Tf_2N/H_2O combinations afforded in most cases improved ees and/or reaction rates compared to conventional organic solvents (Table 1, entries 9 and 10, 17 and 18, 23, and 27). In addition, the colourless water-phases and orange coloured ILs phases indicated no or only very low catalyst leaching.[18]

Since for more lipophilic substrates such as **2b** water is not a good solvent, ternary combinations of ILs, water and an organic solvent (toluene) were also tested (Table 1, entries 11, 19, 24 and 25). Here again, excellent results with respect to catalytic performance as well as to catalyst separation were obtained.

It is generally known that the ligand is one of the most important factors that governs the performance of a catalyst. To investigate the scope of this new reaction medium, a series of further ligands with and without ferrocenyl backbones **1c**–**1k** (see Figure 1) were tested in wet ILs. The results are given in Table 2.

The results indicate that the effect of ILs is strongly dependent on the ligands used. While all ferrocene-based ligands (**1c–1 h**)[19] give better ees and/or activities in wet ILs than in MeOH (Table 2, entries 1–16), the ligands with other backbones (**1i–1k**) give inferior results (Table 2, entries 17–25). So far, we have no explanation for this very different behaviour. With respect to catalyst separation and catalyst recycling, the IL-water system is superior to the conventional IL/isopropyl alcohol system for all ligands. This can be explained by

Table 2. Enantioselective hydrogenation of **2a** (MAA) with selected chiral diphosphine ligands.

Entry	Ligand	Reaction Medium	Conversion [%]	ee [%]	Catalyst Separation[a]	No of phases
1	**1c**	MeOH	8	48	–	1
2	**1c**	[bmim]PF_6/*i*-PrOH	23	29	+	2
3	**1c**	[omim]BF_4/H_2O	26	75	+ +	2
4	**1d**	MeOH	100	97	–	1
5	**1d**	[bmim]PF_6/*i*-PrOH	22	82	–	2
6	**1d**	[omim]BF_4/H_2O	100	>99	+ +	2
7[b]	**1d**	[omim]BF_4/H_2O	70	>99	+ +	2
8	**1e**	MeOH	99	14	–	1
9	**1e**	[omim]BF_4/H_2O	27	63	+ +	2
10	**1f**	MeOH	100	71	–	2
11	**1f**	[omim]BF_4/H_2O	100	72	+ +	2
12	**1g**	MeOH	100	93	–	1
13	**1g**	[omim]BF_4/H_2O	95	94	+ +	2
14	**1h**	MeOH	63	95	–	1
15	**1h**	[bmim]BF_4/*i*-PrOH	96	97	+	2
16	**1h**	[omim]BF_4/H_2O	100	99	+ +	2
17	**1i**	MeOH	100	87	–	1
18	**1i**	[bmim]BF_4/*i*-PrOH	100	66	+	2
19	**1i**	[omim]BF_4/H_2O	97	68	+ +	2
20	**1j**	MeOH	100	81	–	1
21	**1j**	[bmim]BF_4/*i*-PrOH	100	73	+	2
22	**1j**	[omim]BF_4/H_2O	90	68	+ +	2
23	**1k**	MeOH	100	99	–	1
24	**1k**	[bmim]BF_4/*i*-PrOH	87	99	+	2
25	**1k**	[omim]BF_4/H_2O	70	99	+ +	2

ILs: *ca.* 2 mL, co-solvents: *ca.* 2–3 mL, S/C =200, [S] =0.25 M in co-solvent, 25 °C, $P(H_2)=1$ bar, and $t=20$ min.

[a] "–" no, "+" good (some leaching), "+ +" excellent (colourless co-solvent phase).

[b] Performance of catalyst that has been re-used 6 times.

* ICP-MS: 0.9 ppm Rh content in co-solvent.

the solubility of the catalysts which is generally much lower in water than in alcohols if ligands without highly polar or charged groups are used.

The hydrogen concentration in the liquid phase is another factor that affects the reaction rate and, depending on the ligand, in many cases also the ee.[4,12,20] The higher ees observed with many ligands in wet ILs compared to organic solvents raises the question of whether this may be due to a different hydrogen concentration in wet ILs or to a solvent effect such as a different solvation of the catalyst and reactants.

The hydrogen concentration depends on factors such as hydrogen solubility in the solvent, applied hydrogen pressure and mass transfer effects. As mentioned above, hydrogen has a lower solubility in ILs than in organic solvents. Accordingly, as can be seen in Table 1, all hydrogenations that were performed in alcohols are faster than those in pure ILs. Interestingly, the results in Table 1 also show that the reaction rates in wet ILs are similar to those in organic solvents. Since the hydrogen solubility is also lower in water than in organic solvents this is a surprising result, demonstrating that a mixture of a IL and water can have different properties than its individual components.

To get further insight into this hydrogen concentration effect, a series of hydrogenations with selected ligands were compared at low (1 bar) and at high (10 bar) hydrogen pressure in wet ILs and in MeOH. The reactions were stopped before completion, so that average TOFs could be estimated. The results are given in Table 3. It is interesting to note that generally the ees tend to be lower at 10 bar than at 1 bar and that the decrease is less important in wet ILs than in organic solvents. This effect is most pronounced with ligand **1d** (entries 5–8) where differences in ees of 13% in MeOH and 7% in wet IL are observed. As expected, the average hydrogenation rates increase with increasing hydrogen pressure. The fact that with only one exception (entry 6) all rates ***and*** ees are higher in wet ILs than in methanol strongly indicates that this cannot be due to lower hydrogen availability but that this effect must rather be caused by a different solvation of the reactants in the wet ILs.

An important motive to use ILs is the possibility to separate and reuse the catalyst. Hydrogenation of **2a** in [omim]BF_4/H_2O with the Rh-**1d** complex was chosen as a model reaction to study catalyst recycling and the distribution of the product in the two phase system. Using our standard reaction conditions (see Table 1) the

Table 3. Hydrogenation of MAA in MeOH and H_2O/[omim]BF_4 at 1 bar and 10 bar hydrogen pressure.

Entry	Ligands	Solvents	Ionic liquids	TOF[a] [1/h]	ee [%]	$P(H_2)$ bar
1	**1a**	MeOH	No	480	98	1
2	**1a**	H_2O	[omim]BF_4	816	99	1
3	**1a**	MeOH	No	1645	95	10
4	**1a**	H_2O	[omim]BF_4	2229	98	10
5	**1d**	MeOH	No	1536	97	1
6	**1d**	H_2O	[omim]BF_4	636	>99	1
7	**1d**	MeOH	No	2365	84	10
8	**1d**	H_2O	[omim]BF_4	2846	92	10
9	**1b**	MeOH	No	318	97	1
10	**1b**	H_2O	[omim]BF_4	420	>99	1
11	**1b**	MeOH	No	1371	96	10
12	**1b**	H_2O	[omim]BF_4	3085	>99	10

S/C = 200, [S in co-solvent] = 0.25 M, room temperature.

[a] Average TOF during 1–5 minutes reaction time.

catalyst gave complete conversion and ees > 99% in 5 consecutive runs. In the 6th run some catalyst deactivation was observed (Table 2, entry 7), nevertheless, a seventh run with complete conversion and unchanged ee could be achieved when the reaction time was increased from 20 minutes to 40 minutes. In all runs, the separated aqueous phases were perfectly colourless. After the first run (entry 6), the Rh content in the water phase was checked by ICP-MS and found to be as low as 0.9 ppm. This corresponds to a catalyst leaching of only 0.5%. Based on these observations we attribute the observed loss of activity to catalyst deactivation, e.g., by contamination with traces of air during work-up, rather than to catalyst leaching.

Catalyst separation was performed by simple decantation of the colourless water phase. According to NMR and GC measurements 35–40% of the polar hydrogenation product **3a** remained in the IL phase. However, after the last run, the product could efficiently be extracted from the IL phase with *t*-butyl methyl ether.

For substrates with very low water solubility such as **2b**, wet ILs/apolar co-solvents combinations were used. Depending on the ILs and on the amount of water added, such systems are either biphasic {[bmim]BF_4-H_2O (v:v 6:1)/toluene; Table 1, entry 24} or triphasic {[omim]BF_4/H_2O (v:v 3:1)/toluene; entry 25}. In both systems the hydrogenations were fast and yield the lipophilic product **3b** with high ees. Here, the product **3b** could be isolated efficiently and without visible catalyst contamination by direct decantation of co-solvent(s).

To be of industrial interest, enantioselective Rh catalysts should achieve turnover numbers in the range of several thousands. To the best of our knowledge, enantioselective hydrogenations in ILs so far have only been performed with low S/C ratios (typically < 100). To check the limits of the wet IL system, we carried out a hydrogenation of **2a** with ligand **1b** with an S/C ratio of 10,000 in [omim]BF_4/H_2O at 10 bar hydrogen pressure. The hydrogenation gave quantitative conversion within 3 hours and yielded the product **3a** with 95% ee. A colourless water and a yellow IL phase indicated no significant leaching. Interestingly the catalyst in the IL phase was less but still active and could be reused for a second run without loss of enantioselectivity.

Conclusion

Wet ILs constitute a new class of solvents with their own new and interesting properties. This reaction medium has an interesting potential in enantioselective catalysis since it can give excellent catalytic performance, also at very high S/C ratios, and allow efficient catalyst separation and easy recycling. Not surprisingly, our screening showed that the effect of ILs on catalytic performance is not predictable and strongly depends on the ligand/catalyst system used.

Experimental Section

General Procedure for the Hydrogenations and for Catalyst Recycling

The ionic liquids [bmim]BF_4, [bmim]PF_6 and [omim]BF_4 were purchased from Solvent Innovation and purified as described in literature[7] before use. The ionic liquid [bmim]Tf_2N was obtained from Dr. R. Giernoth (the Institute for Organic Chemistry, University of Cologne) and directly used without further purification. The ligands BPPM, Prophos and Me-Duphos were purchased from STREM Chemicals. All manipulations were performed under Ar and with degassed solvents.

The hydrogenations at 1 bar were performed in a 25 mL vial equipped with a septum, a connection to Ar, vacuum and H_2 and a magnetic stirring bar. To a solution of the ligand (0.0034 mmol) in 2 mL IL, a solution of $[Rh(NBD)_2]BF_4$ (0.003 mmol) and a solution of the substrate in dichloromethane (total approx. 3 mL) was added. The dichloromethane was removed under reduced pressure and the co-solvent(s) added. Typically 2 mL IL and 2–3 mL co-solvent were used. Then the reaction mixture was set under H_2 (1 bar) and the hydrogenation started at room temperature by switching on the magnetic stirrer.

The reaction at 10 bar H_2 pressure were performed in a 50 mL autoclave equipped with a magnetic stirrer. Substrate concentration was 0.25 M except in the hydrogenation with an S/C 10,000 (1 M). Care was taken that the mixing in all cases was turbulent. Conversion and enantiomeric excess were determined by GC (CE instruments MFC 800, equipped with Chirasil-Val capillary column).

Acknowledgements

We would like to thank Novartis Pharma AG for financial support.

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[18] **Determination of catalyst leaching:** The only strongly coloured ingredient in the reaction mixtures is the orange-red catalyst. Based on our experience, the colouring of the aqueous phases can reliably be used for a qualitative assessment of the degree of catalyst leaching. In Tables 1–3, the sign "–" stands for no or very poor catalyst separation (co-solvent phase and IL phase have similar colours), the sign "+" for good catalyst separation (slightly collared co-solvent phase) and the sign "++" for excellent separation (colourless co-solvent phase). In one reaction (Table 2, entry 6), the Rh content in a colourless aqueous phase was checked by ICP-MS and found to be as low as 0.9 ppm. This corresponds to a catalyst leaching of only 0.5%.

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