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Beneficial effect of water as second solvent in ionic liquid biphasic catalytic hydrogenations

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Abstract—When reactions take place in ionic liquids, a solvent is normally used to extract the products after reaction. It is reported here how the presence of the solvent during the reaction already can seriously improve the catalytic performance. Above all, employing water as the added solvent enhanced the catalytic activities significantly, ascribed to the creation of a well mixed 'emulsion-like' system. The reductions of methyl 2-acetamidoacrylate with Rh–EtDuPHOS and of 2-cyclohexen-1-one with Wilkinson's catalyst in bmimPF_6 were thus successfully performed in the presence of water. The complexes were easily recycled and Rh–EtDuPHOS was even no longer air sensitive.

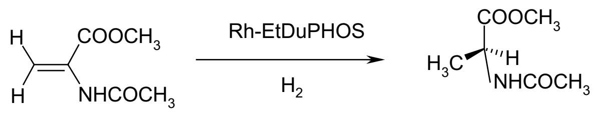
1. Introduction

Ionic liquids (ILs) have received increasing attention as green solvents due to their unique physical and chemical properties.[1–7] ILs usually contain imidazolium or ammonium cations with a variety of organic and inorganic non-coordinating anions.[4] Their properties, such as low melting temperature, low vapor pressure, polarity and high thermal stability, can be tuned by changing the type of anion or cation. Furthermore, they readily dissolve many organic, inorganic and organo-metallic compounds, that is, transition metal complexes (TMCs). ILs thus have the potential to act as high-performance green solvents for organic synthesis.[1–7] In addition, stabilization of the TMCs and their improved performance in ILs have already been reported.[4,8] Products are mostly separated from the reaction mixtures via extraction with a solvent or via distillation.

In spite of some successes, a general breakthrough of biphasic catalysis with TMCs in ILs has been hampered. The activities of these catalytic systems are often lower than with the corresponding homogeneous systems. It can be attributed to: (1) the absence of an organic solvent which makes the catalytic cycle less efficient; (2) a lower concentration of the reagent in the catalyst phase; or (3) mass transfer limitations in the highly viscous ILs.

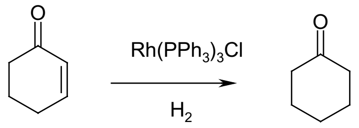
This letter reports an unexpectedly beneficial effect of water as the second solvent in biphasic catalysis with ILs. Water serves as extraction medium, but is present already during the reaction. The positive water effect will

1.



Asymmetric hydrogenation of methyl 2-acetamidoacrylate

2.



Hydrogenation of 2-cyclohexen-1-one

Figure 1. (a) Asymmetric reduction of methyl 2-acetamidoacrylate with Rh–EtDuPHOS; (b) hydrogenation of 2-cyclohexen-1-one with Wilkinson's complex.

Keywords: Ionic liquid; Hydrogenation; Catalyst recycling; Transition metal complexes; Biphasic reactions.

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be illustrated for the asymmetric hydrogenation of methyl 2-acetamidoacrylate with Rh–EtDuPHOS (Fig. 1a) and the hydrogenation of 2-cyclohexen-1-one with Wilkinson's catalyst (Fig. 1b) in the most commonly used IL, 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6).

2. Results and discussion

The hydrogenation of enamides with Rh–EtDuPHOS (Fig. 1a) was the first system studied, being an industrially relevant reaction to produce enantiopure α-amino acid derivatives.[9–11] Since protic solvents are known to induce the highest activities, the reaction in methanol was taken as the homogeneous reference reaction (Table 1, entry 1). Aiming at an IL-based system for easy product recovery and catalyst recycling, bmimPF_6 was selected as IL-phase. Although it dissolves Rh–EtDuPHOS very well, the homogeneous reaction in this solvent did not yield any activity (entry 2). This can possibly be explained by the need for a protic solvent in the catalytic cycle, or by the low concentration of hydrogen in bmimPF_6 under the low operational hydrogen pressure.[12,13] Hence, this type of reaction clearly needs the presence of another solvent, not only for the extraction, but already during reaction. Based on the reactions in organic solvents, methanol would be preferred, but this solvent is fully miscible with bmimPF_6 and would thus not allow catalyst recycling. Hence, other solvents, which all form a biphasic system with bmimPF_6, were screened.

The effect of such a second solvent on the catalytic activity was first investigated in the absence of IL. Changing the solvent in the homogeneous reaction from methanol to isopropanol resulted in a small drop in activity and enantioselectivity (entries 1 and 3). Since the solubility of the complex in hexane or water is negligible, water and hexane were added to methanol to examine their effect on the catalytic performance (entries 4 and 5). The activity dropped in both solvents, but the enantioselectivity remained unchanged. Full immiscibility with methanol prevented such reference reaction to take place in diethyl ether.

Table 1. Homogeneous and biphasic asymmetric reductions of methyl 2-acetamidoacrylate with Rh–EtDuPHOS in different solvents[a]

Entry	Solvent (s)	Conversion (%) (re-use)	ee (%) (re-use)
Homogeneous			
1	Methanol	54	97
2	BmimPF_6	0	0
3	Isopropanol	49	96
4	Methanol + water[b]	43	97
5	Methanol + hexane[b]	23	97
Biphasic			
6	BmimPF_6/hexane	0	0
7	BmimPF_6/diethyl ether	12 (12)	96 (96)
8	BmimPF_6/isopropanol	31 (30)	95 (94)
9	BmimPF_6/water	68 (66)	96 (97)

[a] Reaction conditions: Homogeneous, 2 mL solvent, 1 μmol complex, S/C = 500, 5 bar H_2, 20 °C, 5 min. Biphasic, 2 g bmimPF_6, 2 mL solvent, 1 μmol complex, S/C = 500, 5 bar H_2, 20 °C, 20 min.

[b] 1 mL of each solvent.

In the biphasic reaction system, hexane as second solvent did not allow any reaction (entry 6), while the combinations of bmimPF_6 with diethyl ether, isopropanol and water all yielded activity (entries 7–9). Moreover, In contrast with the homogeneous reactions, the catalyst could now be recycled successfully and was even found to be air stable.[8] Re-use of the catalyst was done after removing the upper solvent layer from the reactor, followed by a number of supplementary extractions with the same solvent as the one present already during the catalytic run to remove product and substrate.

Employing water as second solvent the reaction rate in the biphasic system yielded much higher reaction rates than with the other solvents. The special effect of water makes this approach the best Rh–DuPHOS recycling reported till now. Previous heterogenizations have been realized by occlusion in polydimethylsiloxane[14] and polyvinyl alcohol[15] membranes, or by anchoring to heteropoly acids.[16,17] While the polymeric systems yielded only low activities and had to be operated in aqueous solutions to prevent leaching of the complex, the anchored complex was recyclable and yielded even higher activities than the reference homogeneous reactions, but these reference values were much lower than those of similar homogeneous experiments reported elsewhere.[10,11]

The important effect of water on the catalytic performance can possibly be explained in three ways: water could be essential in the catalytic cycle, could change the concentration of the substrate in the IL catalytic phase or could influence the mixing of the two phases. The two first effects can be eliminated here. Indeed, although water can allow the catalytic cycle to proceed,[13,14] no higher activity of the homogeneous reaction was found when water was added to methanol (entry 4). Furthermore, the amount of reagent in the catalyst containing IL-phase was found to increase in the order diethyl ether > water > isopropanol (Table 2). Increased amounts of solvent further decreased the amount of substrate in the IL-phase (entries 2–4 and 5–7). Hence, if a higher concentration of the substrate

Table 2. The effect of solvent type and amount of solvent on the distribution of methyl 2-acetamidoacrylate in the (solvent/bmimPF_6)-biphasic systems[a]

Entry	Solvent	(Solvent/bmimPF_6)-ratio (v/v)	Amount of methyl 2-acetamidoacrylate in bmimPF_6 (mg)
1	Diethyl ether	1	36.2
2	Water	1	32.7
3	Water	2	22.7
4	Water	3	22.2
5	Isopropanol	1	28.1
6	Isopropanol	2	22.8
7	Isopropanol	3	19.8

[a] 1 g bmimPF_6, 45 mg methyl 2-acetamidoacrylate, room temperature.

in the IL catalytic phase would be the reason for the higher reaction rate, the reaction should proceed faster in diethyl ether than in water, which is clearly not the case.

The superior reaction rate of the (water/bmimPF_6)-biphasic system can thus mainly be attributed to the excellent mixing in this system. In fact, visual observations supported this suggestion (Fig. 2). The combination of bmimPF_6 with hexane or isopropanol resulted in visibly big droplets of the organic solvent in the IL-continuous phase. The addition of water to the bmimPF_6 phase on the other hand resulted in a much better dispersed system, as reflected in the turbid aspect of the mixture, indicating the presence of smaller droplets. The different mixing of the various IL-biphasic systems can be explained by the different mutual solubility of the three solvents with bmimPF_6.[18] While hexane has negligible solubility in the ionic liquid due to its insignificant polarity and hydrogen bonding character, isopropanol has higher solubility in bmimPF_6 and water, which is the most polar solvent of the three, has the highest solubility in bmimPF_6. The solubility of water in bmimPF_6 and of bmimPF_6 in water were found to be around 2 wt %.[19]

A further optimization of this (water/bmimPF_6)-biphasic system in the asymmetric reduction of methyl 2-acetamidoacrylate with Rh–EtDuPHOS was done by changing the (water/bmimPF_6) volume ratio. It resulted in a maximum reaction rate at a ratio around 1 (Fig. 3), while enantioselectivities remained 96% at all ratios. It seems that after the maximum, the reaction rate decreases because less substrate resides in the IL catalytic phase, as shown in Table 3 (entries 2–4).

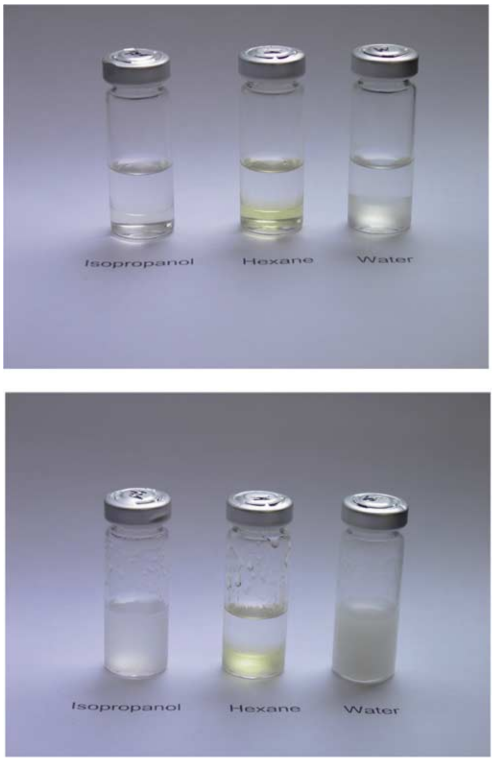

Figure 2. Biphasic systems with bmimPF_6 before mixing (top) and a few seconds after mixing (bottom).

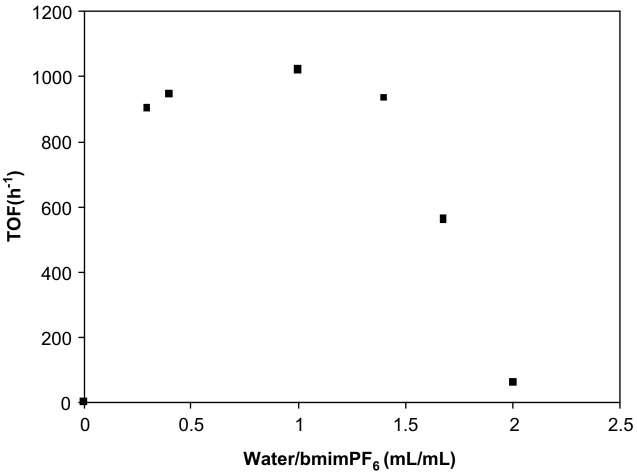

Figure 3. The effect of (water/bmimPF_6) volume ratio on the activity of the asymmetric reduction of methyl 2-acetamidoacrylate with Rh–EtDuPHOS. Reaction conditions: 1 μmol complex, S/C = 500, 2 g bmimPF_6, 5 bar H_2, 20 °C, 20 min.

A second illustration of the beneficial effect of water during reaction was found in the hydrogenation of 2-cyclohexen-1-one with Wilkinson's catalyst (Fig. 1b). Homogeneous reference reactions were done first in dichloromethane (DCM), ethanol, and tetrahydrofurane (THF) (Table 3, entries 1–3). While the complex dissolved well in DCM and THF, its solubility in ethanol was low. Nevertheless, the activity was higher in ethanol, due to the protic character of this solvent. On the other hand, the selectivity to cyclohexanone was much lower in ethanol, and many different by-products were found. Water was previously reported to enhance the activity in homogeneous reactions with Wilkinson's catalyst.[20] Since the solubility of the complex in aqueous medium is negligible, a reference system was created by adding water to the homogeneous THF solution (entry 4). This increased the activity fivefold when compared to the reaction in pure THF.

Table 3. Homogeneous and biphasic hydrogenations of 2-cyclohexen-1-one with Wilkinson's complex in different solvents[a]

Entry	Solvent	Conversion (%) (re-use)	Selectivity (%)[b] (re-use)
Homogeneous			
1	DCM	17	100
2	Ethanol	100	27
3	THF	6	100
4	THF + water[c]	32	100
Biphasic			
5	BmimPF_6/diethyl ether	4 (4)	100 (100)
6	BmimPF_6/hexane	7 (7)	100 (100)
7	BmimPF_6/water	26 (26)	90 (90)

[a] Reaction conditions: Homogeneous, 2 mL solvent, 1 μmol complex, S/C = 140, 5 bar H_2, 30 °C, 3 h. Biphasic, 2 g bmimPF_6, 2 mL solvent, 1 μmol complex, S/C = 140, 5 bar H_2, 30 °C, 3 h.

[b] Selectivity to cyclohexanone.

[c] 1 mL of each solvent.

Biphasic reactions were first done with diethyl ether and hexane. Both systems yielded full selectivity to cyclohexanone but low hydrogenation activity (entries 5 and 6). On the other hand, again the use of water as second solvent yielded a much higher activity (entry 7). The product yield of the biphasic water system was thus even close to the best yields obtained in the homogeneous reactions. Apart from a slight decrease in activity for the biphasic water system, possibly due to some solubility of the IL (with some catalyst) in water,[19] the same performance was observed upon re-use of all biphasic systems.

Even though water is a very cheap and green solvent, its utilization in catalytic organic reactions has been limited so far. The homogeneous TMCs frequently employed as catalysts, show negligible solubility in water, unless modified accordingly.[21,22] The generally low reaction rates found in biphasic (water/organic)-catalysis also limit the practical feasibility of these systems. The reported 'emulsion-like' (water/IL) combination could offer a practically feasible green alternative.

3. Conclusion

The recycling of Rh–EtDuPHOS and Wilkinson's catalyst in bmimPF$_6$ was performed successfully without any prior modification of the complexes. Besides separation of the product and recycling of the catalyst, the use of water as the second solvent in biphasic IL-reactions had a clear beneficial effect on activities due to the creation of a well mixed 'emulsion-like' system. Higher reaction rates than with other solvents were thus realized and the Rh–EtDuPHOS catalyst even became air stable.

4. Experimental

The homogeneous and biphasic reactions were done in 10 mL stainless steel pressure reactors. Reaction proceeded at room temperature under 5 bar hydrogen pressure. The air sensitive Rh–EtDuPHOS (Strem) was handled under nitrogen atmosphere. In the homogeneous reaction, 1 μmol of Rh–EtDuPHOS and 71.5 mg of methyl 2-acetamidoacrylate (Fluka) were added to 2.5 mL of the corresponding solvent. In the IL-biphasic reactions, the same amount of complex was added to 2 g of bmimPF$_6$ (Fluka) before the addition of a mixture of 71.5 mg of methyl 2-acetamidoacrylate in 2.5 mL solvent. Hydrogen was fed into the reactors after nitrogen flushing. Samples were withdrawn and analyzed to determine conversion and selectivity via GC-analysis. Re-use of the complex in the IL-biphasic systems was done by extraction of the IL phase after the first run with the same solvent that was used during reaction to remove the residual product and substrate. A fresh substrate solution was then added to the IL-phase. Atomic absorption spectroscopy was done on the collected extractant phases (Rh detection limit 0.05 μg/mL), but metal traces were never found.

For the reduction of 2-cyclohexenone with Wilkinson's catalyst, 1 μmol of complex was used with 13.44 mg of substrate and 2 mL of solvent in the homogeneous reaction. In the heterogeneous systems, 2 g bmimPF$_6$ was added. Hydrogen was fed at a pressure of 5 bar to the reactor, which was kept at 30 °C. Before starting the stirring and heating of the reactor, it was first flushed with nitrogen, followed by hydrogen.

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References and notes

1. Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Weinheim: Wiley-VCH, 2003.
2. Welton, T. *Chem. Rev.* **1999**, *99*, 8.
3. Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391.
4. Olivier-Bourbigou, H.; Mangna, L. *J. Mol. Catal.* **2002**, *182–183*, 419.
5. Sheldon, R. A. *Chem. Commun.* **2001**, *23*, 2399.
6. Gordon, C. M. *Appl. Catal. A* **2001**, *222*, 101.
7. Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157.
8. Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun.* **2001**, *22*, 2314.
9. Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: New York, 1989.
10. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
11. Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.
12. Berger, A.; de Souza, R. F.; Delgado, M. R.; Dupont, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1825.
13. Anthony, J. L.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2002**, *106*, 7315.
14. Wolfson, A.; Janssens, S.; Vankelecom, I. F. J.; Geresh, S.; Gottlieb, M.; Herskowitz, M. *Chem. Commun.* **2002**, 388.
15. Wolfson, A.; Geresh, S.; Gottlieb, M.; Herskowitz, M. *Tetrahedron: Asymmetry* **2002**, *13*, 465.
16. Tanielyan, S. K.; Augustine, R. *Chem. Ind. Dekker* **1998**, *75*, 101.
17. Augustine, R.; Tanielyan, S.; Anderson, S.; Yang, H. *Chem. Commun.* **1999**, 1257.
18. Reichert, W. M.; Holbrey, J. D.; Huddleston, J. G.; Rogers, R. D. Abs. 2269, 206th Meeting: The Electrochemical Society; 2004.
19. Anthony, J. L.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2001**, *105*, 10942.
20. Joo, F.; Csiba, P.; Benyei, A. *Chem. Commun.* **1993**, *21*, 1602.
21. Joo, F.; Toth, Z.; Beck, M. T. *Inorg. Chim. Acta* **1977**, *25*, L61.
22. Herrmann, W. A.; Eckl, R. W. *Aqueous Organometallic Catalysis*; Wiley-VCH: Weinheim, Germany, 1998.