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Ionic liquid-phase asymmetric catalytic hydrogenation: hydrogen concentration effects on enantioselectivity

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Abstract—Molecular hydrogen is almost four times more soluble in the ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMI·BF_4) than in its hexafluorophosphate (BMI·PF_6) analogue at the same pressure. The Henry coefficient solubility constant for the solution BMI·BF_4/H_2 is $K=3.0\times10^{-3}$ mol L^{-1} atm^{-1} and 8.8×10^{-4} mol L^{-1} atm^{-1} for BMI·PF_6/H_2, at room temperature. The asymmetric hydrogenation of (*Z*)-α-acetamido cinnamic acid and kinetic resolution of (±)-methyl-3-hydroxy-2-methylenebutanoate by (−)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate and dichloro[(*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl]ruthenium(II) complexes immobilised in BMI·PF_6 and BMI·BF_4 were investigated. Remarkable effects in the conversion and enantioselectivity of these reactions were observed as a function of molecular hydrogen concentration in the ionic phase rather than pressure in the gas phase.

1. Introduction

Molten salts based on the 1-alkyl-3-methylimidazolium cation exhibit a relatively wide electrochemically stable window, a broad range of room temperature liquid compositions, negligible vapour pressure, and excellent chemical and thermal stabilities. These materials have been used as the mobile phase in organometallic biphasic catalytic reactions ranging from Ziegler–Natta-type processes to hydroformylations.[1–3] However, in only a few cases, asymmetric organometallic catalytic reactions have been carried out in ionic liquids.[4–9] These studies essentially comprise hydrogenation processes.[4,5,9] In this respect, it was found that the hydrogenation of atropic acid by Ru-BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) complex immobilised in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMI·BF_4) furnishes e.e. essentially independent of the hydrogen-pressure.[5] In contrast, in the reduction of tiglic acid by the same catalyst dissolved in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (BMI·PF_6) ionic liquid, the e.e. is hydrogen-pressure dependent.[9] These apparently conflicting results are probably related to a different hydrogen solubility in the two ionic liquids. Moreover, it is well known that in various homogenous and heterogeneous asymmetric hydrogenations the solution concentration of hydrogen, rather than the pressure in the gas phase, is the kinetic variable that must be considered when evaluating the enantioselectivity data obtained under different gas–liquid mass transfer conditions.[10]

Herein, we report our results for the determination of the solubilities of molecular hydrogen in these imidazolium ionic liquids and the influence of the hydrogen concentration over the asymmetric hydrogenation of (*Z*)-α-acetamido cinnamic acid as well as the asymmetric kinetic resolution of (±)-methyl-3-hydroxy-2-methylenebutanoate by Rh(I)- and Ru(II)-catalyst precursors immobilised in BMI·PF_6 and BMI·BF_4 ionic liquids.[11]

2. Results and discussion

2.1. Hydrogen solubility in 1-*n*-butyl-3-methylimidazolium ionic liquids

The gas–liquid mass transfer coefficients and molecular hydrogen solubilities in the ionic liquids have been determined using a known procedure (see Section 4).[12] The Henry coefficient solubility constant for the solution BMI·BF_4/H_2 is $K=3.0\times10^{-3}$ mol L^{-1} atm^{-1} and 8.8×10^{-4} mol L^{-1} atm^{-1} for BMI·PF_6/H_2, at room tem-

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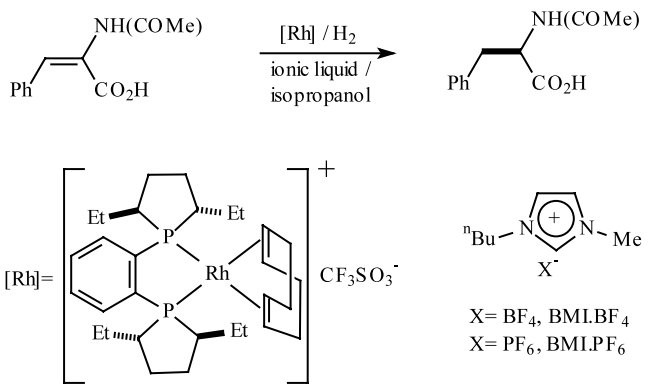
perature. Thus, the hydrogen solubility in these ionic liquids at different pressures can easily be determined, assuming ideal-gas behaviour, by the Henry equation: $M = K \times P$, where M is the gas solubility in mol L^{-1}, K the Henry constant in mol L^{-1} atm^{-1} and P is the gas partial pressure in atm. The K values indicate that molecular hydrogen is almost four times more soluble in BMI·BF_4 than in BMI·PF_6 under the same pressure.

2.2. Hydrogen pressure effects in Rh-catalysed asymmetric hydrogenation

The effect of the hydrogen concentration in the liquid phase was investigated in the asymmetric reduction of (*Z*)-α-acetamido cinnamic acid catalysed by (–)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate dissolved in *iso*-propanol, BMI·BF_4 and BMI·PF_6 (Scheme 1 and Table 1).

It is apparent that the conversion increases when the solubility of molecular hydrogen increases in the liquid phase (Table 1). This is most probably related to the availability of the hydrogen at the catalyst site. The relatively lower enantioselectivity in the case of BMI·PF_6 as compared to the other two liquids (BMI·BF_4 and *iso*-propanol) indicates that at 50 atm pressure there is not sufficient hydrogen in the ionic phase. Indeed, hydrogenation reactions performed at higher hydrogen pressures (100 atm) gave e.e. values similar to those observed in *iso*-propanol. These results demonstrate that the hydrogen concentration in solution determines the enantioselectivity in this system.



Scheme 1.

It is important to note that recovered ionic catalyst solutions could be re-used for further hydrogenations maintained the enantioselectivity, but after the fourth recycle a significant drop in the conversion was observed (from 73 to 35%). This loss of efficiency results from catalyst leaching from the ionic phase to the product/*iso*-propanol solution as verified by atomic absorption analysis.

2.3. Kinetic resolution catalysed by Ru-(tolyl-BINAP)

We also tested the influence of hydrogen pressure by investigating the kinetic resolution of (±)-methyl-3-hydroxy-2-methylenebutanoate by [$RuCl_2$-(*S*)-tolyl-binap]$_2$·NEt_3/BMI·BF_4-catalysed hydrogenation under various reaction conditions (Scheme 2 and Table 2).

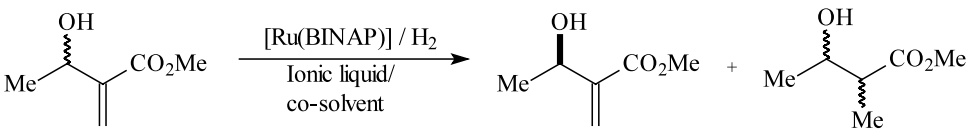
The best kinetic resolution was obtained at a reaction pressure of 40 atm where the unreacted substrate was recovered in 29% yield with 98% e.e. (entry 6, Table 2). Note that under homogeneous conditions, but at 50 atm, the yield and e.e of recovered substrate are of the same order of the magnitude as those observed in ionic liquid media, (Table 2, entry 9). Moreover, the sense of the diastereoselection was the same for the reactions performed either in methanol or in ionic liquid.

The degree of enantiomer differentiation (k_f/k_s) is considerably influenced by hydrogen pressure. Higher k_f/k_s values were obtained up to 40 atm hydrogen pressures (entries 1–6, Table 2). A significant drop was observed at higher pressure (entries 7 and 8). This trend is

Table 1. The asymmetric hydrogenation of (*Z*)-α-acetamido cinnamic acid: the effect of hydrogen concentration in the liquid phase on the conversion and the enantioselectivity[a]

Entry	Catalyst phase	*P* (atm)	Sol. H_2 (mol L^{-1})	Conversion (%)	E.e.[b] (%)
1	BMI·PF_6	5	4.4×10^{-3}	7	66
2	BMI·PF_6	50	4.4×10^{-2}	26	81
3	BMI·PF_6	100	8.9×10^{-1}	41	90
4	BMI·BF_4	50	1.5×10^{-1}	73	93
5	^{i}PrOH	50	129.3[c]	99	94

[a] Reactions performed at room temperature, 24 h, 950 rpm, 3 mL of the ionic liquid and 9 mL of *iso*-propanol, substrate/[Rh] = 100.
[b] Determined by chiral GC.
[c] Calculated from the data reported by Frolich.[13]



Scheme 2.

Table 2. Kinetic resolution of methyl-3-hydroxy-2-methylenebutanoate by Ru(tol-BINAP)/BMI·BF_4 catalysed asymmetric hydrogenation[a]

Entry	P (atm)	Sol. H_2 (mol L^{-1})	Time (min)	(%) recovery	E.e. (%)[b]	k_f/k_s[c]
1	20	6.0×10^{-2}	30	53	59	9
2	20	6.0×10^{-2}	145	47	75	11
3	30	9.0×10^{-2}	30	43	83	11
4	30	9.0×10^{-2}	145	39	87	10
5	40	1.2×10^{-1}	30	36	91	10
6	40	1.2×10^{-1}	145	29	98	10
7	50	1.5×10^{-1}	30	31	85	6
8	50	1.5×10^{-1}	145	27	89	5
9[d]	50	144.2[e]	150	37	97	14
10[d]	4	11.54[e]	660	24	99	16

[a] The reactions were carried out with 0.5 mL (4.1 mmol) of the substrate in 3 mL of the ionic liquid and 5 mL of *iso*-propanol at room temperature.
[b] E.e. of the unreacted substrate determined by GC.
[c] k_f/k_s (enantiomeric selection) calculated by Kagan's equation.[14]
[d] In 'homogeneous' conditions (methanol).[15]
[e] Calculated from the data reported by Frolich.[13]

consistent with other enantio-face discriminating homogenous hydrogenations where high e.e.s were obtained at lower pressures.[16]

3. Conclusions

In summary, our results show that classical homogeneous Rh(I)- and Ru(II)-catalysed asymmetric hydrogenations can be transposed to liquid–liquid two-phase systems using imidazolium based ionic liquids as the mobile phase. It is evident that the hydrogen concentration in the ionic phase rather than the hydrogen pressure in the gas phase, is the important kinetic parameter to be considered when comparing studies performed under different gas–liquid mass transfer conditions. This is particularly true for the 1-*n*-butyl-3-methylimidazolium ionic liquids, where the hydrogen solubility is almost four times larger in the hydrophilic tetrafluoroborate (BMI·BF_4) than in the hydrophobic hexafluorophosphate (BMI·PF_6) analogue, under the same pressure.

4. Experimental

4.1. General

All manipulations have been performed under dry, oxygen-free argon using standard techniques. All solvents were dried and distilled under argon prior to use. Hydrogenation reactions were carried out in a Parr 50 mL reactor with agitation speeds of 900–990 rpm and at room temperature. The hydrogen pressure was measured with electronic flow mass controller at 1 Hz. The kinetic resolution reaction product was analysed by gas chromatography on a Varian 3400 chromatograph equipped with a Beta Dex 120 column 30 m long, id 0.25 mm and 0.25 μm film thickness, equipped with a FID detector; H_2 was the carrier (2.3 mL/min); the temperature program was: 30°C (40 min) to 70°C (10 min) at a heating rate of 4°C/min. The products of (*Z*)-α-acetamido cinnamic acid were analysed using a Chirasil-Val III column 25 m long, id 0.32 mm, H_2 was the carrier (2.0 mL/min); the temperature program was: 90°C (20 min) to 110°C (30 min) at a heating rate of 4°C/min.

The ionic liquids[11] were prepared as described earlier and all other reagents were obtained from commercial sources (Strem or Aldrich).

4.2. Catalytic hydrogenation

The $[RuCl_2$-(*S*)-tolyl-binap$]_2\cdot NEt_3$ (6.8×10^{-3} mmol) or [Rh(cod)(2*R*,5*R*)-EtDuphos]CF_3SO_3 (1.22×10^{-2} mmol) catalyst precursors were dissolved in dichloromethane (2–3 mL) and then added to the ionic liquid (3 mL). After 15–30 min under agitation the volatiles were removed under reduced pressure (10^{-3} atm) at room temperature until the residue had constant weight. The ionic liquid catalyst solution was charged in the reactor and then a solution of the substrates ((±)-methyl-3-hydroxy-2-methylenebutanoate 4.1 mmol, or (*Z*)-α-acetamido cinnamic acid, 1.2 mmol) in *iso*-propanol (5 and 9 mL, respectively) were added and the reactor was pressurised with molecular hydrogen.

4.3. Gas–liquid mass transfer coefficients

Gas–liquid mass transfer coefficients and hydrogen solubilities in the ionic liquids were measured using a known procedure.[12] The ionic liquid (10 mL) was charged to the reactor and degassed, and the reactor was pressurised and isolated under hydrogen (20–50 atm). Agitation (990 rpm) was then initiated and pressure drop in the reactor was measured at the rate of 1 Hz, until constant pressure. The data was treated according to established methods.[10,12]

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References

1. Welton, T. *Chem. Rev*. **1999**, *99*, 2071.
2. Dupont, J.; Consorti, C. S.; Spencer, J. *J. Braz. Chem. Soc*. **2000**, *11*, 337.
3. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772.
4. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2698.
5. Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177.
6. Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837.
7. Song, C. E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun*. **2000**, 1743.
8. Comyns, C.; Karodia, N.; Zeler, S.; Andersen, J.-A. *Catal. Lett*. **2000**, *67*, 113.
9. Brown, R. A.; Pollet, P.; McKonn, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc*. **2001**, *123*, 1254.
10. Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc*. **1996**, *118*, 1348 and references cited therein.
11. Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217.
12. Deimling, A.; Karandikar, B. M.; Shah, Y. T.; Carr, N. L. *Chem. Eng. J*. **1984**, *29*, 140.
13. Frolich, P. K.; Tauch, E. J.; Hogan, J. J.; Peer, A. A. *Ind. Eng. Chem*. **1931**, *23*, 548.
14. Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc*. **1974**, *96*, 5152.
15. Kitamura, M.; Manabe, I. K. K.; Noyori, R.; Takaya, H. *J. Org. Chem*. **1988**, *53*, 708.
16. Landis, C. R.; Halpern, J. *J. Am. Chem. Soc*. **1987**, *109*, 1746.