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Notes on the Asymmetric Hydrogenation of Methyl Acetoacetate in Neoteric Solvents

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Abstract Asymmetric hydrogenation of methyl acetoacetate to methyl *(R)*-3-hydroxybutyrate by [*(R)*- RuCl(binap)(p-cymen)]Cl has been studied in methanol-ionic liquid and methanol- dense CO_2 solvent systems. The ionic pairs triethylhexylammonium and 1-methylimidazolium with bis(trifluoromethane sulfonyl) imide and hexafluorophosphates were used. The role of ionic pairs on the kinetic parameters and (enantio)selectivity has been demonstrated. Although the CO_2 expanded methanol system suffered from a reduction in both reaction rate and product selectivity, this changed in the presence of water. The high selectivity of the optimized methanol-CO_2-water-halide system was designed as a consequence of observed additive effects.

Keywords Asymmetric hydrogenation · Ru-BINAP · β-Ketoesters · Ionic liquid · Ionic pairs · Dense gas expanded solutions

1 Introduction

It is well known that many organometallic complexes are excellent homogeneous catalysts [1, 2] and those with chiral centres may even provide multiple enantioselective recognition. It qualifies them as attractive homogeneous catalysts for various types of stereoselective reactions [3–5]. Chiral complexes containing halogen with empirical formula [RuX(aren)(BINAP)]*Y* (*X* = halogen, *Y* = halogen or BF_4) have dominated in asymmetric hydrogenations yielding valuable optically pure intermediates for many fine chemicals [6]. This type of the homogeneous hydrogenation catalysts has revealed exquisite properties in stereoselective transformation of molecules with keto groups [7] located either in the β- or γ- position to the carboxyl function [5]. Of course the general problem with homogeneous catalysts is the difficulty in efficiently separating and recycling. Recently many new alternatives have appeared such as the three-dimensional entrapment of the catalyst [8] (based on the electrostatic catalyst-polyelectrolyte attraction), utilisation of magnetite nanoparticles [9] or immobilization of the complex in thin films of ionic liquids deposited on silica beads [10]. Also various types of ionic liquids (IL) have been considered as reaction co-solvents for selective accommodation of the catalytic phase [11–15]. Due to their physical properties and variable phase behaviour separation of the catalyst from the reaction mixture is feasible. Currently the most popular types of ILs used for such purposes are imidazolium cations combined either with hexafluorophosphate or

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tetrafluoroborate, and quaternary ammonium cations (such as n-alkyl-triethylammonium) combined with the bis(trifluoromethane sulfonyl) imide anion [14–17].

Another possibility [18–20] is the use of carbon dioxide, either dense phase (subcritical) or supercritical. If the enantioselectivity parameter *ee* depends on the reaction gas concentration then the CO_2 phase may lead to significantly increased optical yields [21, 22]. Carbon dioxide (even when supercritical) is relatively non-polar and it is a poor solvent for dissolving most transition metal complexes. Its combination with other co-solvents, referred to as the CO_2 expanded liquids (CXLs) [23], might be accepted as an option. CXLs combine the compressed CO_2 phase (often subcritical) with another solvent, typically an organic solvent or a suitable ionic liquid [24, 25]. Addition of such solvents [26] allows the dissolution of homogeneous metal catalysts, whilst CO_2 brings an improved mass transfer and increased solubility for other reactive gases. In the case of organic solvents addition of pressurised CO_2 can be added at the end of the reaction and it acts as an "anti-solvent" for precipitation of the catalyst. Regarding involvement of ILs, these are insoluble even in supercritical CO_2, therefore the reaction products can be simply extracted from the ionic liquid (catalyst) phase [24, 27].

In this paper we report on stereoselective hydrogenation of achiral methyl acetoacetate (MAA) to optically pure methyl-3-hydroxybutyrate (MHB) over the *(R)*-Ru-BINAP catalyst ([*(R)*- RuCl(binap)(p-cymen)]Cl) in methanol, MeOH-IL, MeOH-CO_2, MeOH-CO_2-H_2O and MeOH-CO_2-H_2O-QUATS (QUATS = quaternary ammonium salts) reaction systems. Four different ionic liquids were employed, each of them structurally resulting from combinations of the four appearing ionic pairs.

Quaternary ammonium and imidazolium based ILs combining hexafluorophosphate and bistriflamide anions were prepared. Depending on the choice of ions, the ionic liquids reveal different physical properties such as melting points, phase behaviour, solvation properties, etc. Upon a contact with a particular IL the metallic centre of the catalytic complex is re-coordinated with the Lewis anions of the IL [28]. Alternatively metathesis of the complex [29, 30] and the migration of the IL's anions might be taken into account together with various steric effects. It leads to conformation modifications of an active centre and/or to blocking the substrate access. All these factors could significantly contribute to the magnitude of the achieved parameter of enantioselectivity. This kinetic parameter is generally understood as the key indicator of the stereoselective reaction progress.

To summarise the performed reactions were carried out separately in pure methanol, in methanol combined with 1-butylimidazolium bis(trifloromethylsulfonyl)imide (bmimTf_2N), 1-butylimidazolium hexafluorophosphate (bmimPF_6), triethylhexylammonium bis(trifloromethylsulfonyl)imide $[N_{6222}][Tf_2N]$) or triethylhexylammonium hexafluorophosphate ($[N_{6222}][PF_6]$), and finally with addition of CO_2. Despite quite a few $scCO_2$ enhanced reaction systems have been reported [26, 31–33] those including a chiral Ru-BINAP complex in the asymmetric hydrogenation have not been published yet.

This paper is a continuation of our recent works focused on the role of the alkyl chain length in the alkylammonium salts ILs on the progress of MAA hydrogenation and on the overall design of the asymmetric hydrogenation experiment [15, 34, 35]. We believe that from the general point of view the strategy described here might be useful for a practical design of an effective asymmetric synthesis via the hydrogenation reaction with a homogeneous chiral Ru-BINAP complex.

2 Experimental

2.1 Chemicals

The organometallic catalytic complex Ru-BINAP, chemically ([2,2′-bis (diphenylphosphino)-1,10-binaphthalene] chloro(*p*-cymene)ruthenium chloride) was supplied as the "Noyori *(R)* type" (Aldrich). Other chemicals were purchased in analytical p.a. grades—methyl acetoacetate, 1-bromohexane, 1-chlorobutane (Aldrich), KPF_6, triethylamine, and 1-methylimidazole and 1-butylimidazolium hexafluorophosphate ([bmim][PF_6]) (Fluka), Li bis (trifluormethanesulfonyl)imide ($LiTf_2N$) (SynQuest Laboratories), methanol, dichloromethane, ethyl acetate, acetonitrile, diethylether (Penta), CO_2 (BOC, SCF grade).

2.2 Preparation of ILs

1-Butylimidazolium bis(trifloromethylsulfonyl)imide ([bmim] [Tf_2N]), triethylhexylammonium bis(trifloromethylsulfonyl)imide ($[N_{6222}][Tf_2N]$) and triethylhexylammonium hexafluorophosphate ($[N_{6222}][PF_6]$) were prepared. The precursor salts, triethylhexylammonium bromide and 1-methylimidazolium chloride were prepared as described previously [36].

2.3 Preparation of $[N_{6222}][Tf_2N]$ and $[Bmim][Tf_2N]$

Synthesis of ILs was performed in 1-L Erlenmayer flask equipped with a magnetic stirrer. The mixture of $[N_{6222}]Br$ (0.51 mol) in water (50mL) was added drop wise to the solution of $LiTf_2N$ in water (0.52 mol, 70mL). After effective mixing (for 10 h), 150 mL of CH_2Cl_2 was added. Next, the organic phase was twice washed with 70 mL of ultrapure water to remove any water soluble impurities.

Presence of halides was tested by $AgNO_3$ (1M solution) until no precipitation of AgBr was observed. Then the organic phase was once washed with 30 mL of water. Finally, the suspense was filtered off with help of a short Brockmann alumina column, evaporated and dried under vacuum at 333K (attained yield 98%). The $BmimTf_2N$ IL was prepared analogously with an identical yield.

2.4 Preparation of $[N_{6222}][PF_6]$

The 250 mL flask was charged with KPF_6 (60 mmol) and water (30 mL), and CH_2Cl_2 (20mL). The $[N_{6222}]Br$ (60 mmol) in water (20 mL) was added drop wise. The two phase reaction mixture was stirred intensively for 8 h at room temperature. The purification was performed as described previously for $[N_{6222}][Tf_2N]$ (attaining a yield of 98%).

2.4.1 Hydrogenation Reactions

The catalytic reactions were carried out in two types of reactors. The first reaction system enabled periodical sampling. The second system was designed for experiments in the dense CO_2 phase. Hydrogenation experiments with methanol and with methanol-IL phase were performed in a stainless autoclave (25 mL, Parr; only ever used for Ru-BINAP reaction tests). The typical amount of Ru-BINAP introduced to the reaction was 10 mg in the IL/methanol mixture (7 mL). It was loaded to the reactor with help of Ar overpressure by means of a sampling tube. The complex was activated for 1 h in hydrogen at 333 K and 5 MPa. The same temperature and pressure were also used in the reactions. MAA (2 g) was introduced to the reactor in methanol (10 mL) similarly as the catalyst through the sampling probe. Samples of the reaction mixture were periodically withdrawn and analysed. Repeated runs were performed analogously. MHB and other products were washed out with water. The Ru complex remained preserved in the IL phase and then introduced with the appropriate amount of methanol and the substrate to the reactor again.

Experiments with CO_2 were carried out in a 100 mL Hastelloy C276 magnetically stirred pressure reactor equipped with a large oblong quartz-window to enable observation of the phase behaviour. The autoclave loaded with Ru-BINAP (15 mg) had been flushed out with nitrogen for 15 min dried for 15 min before degassed MeOH (15 mL) was added. The catalyst was pre-treated for 1 h in the hydrogen pressure at 333 K followed by addition of the degassed MAA (3 g) carried with liquid CO_2 by high-pressure piston pump. In the meantime the reactor was pressurized. The reaction was started by switching the stirrer on (at 333 K temperature level). The constant hydrogen pressure was maintained by a forward pressure regulator connected to a hydrogen ballast vessel.

Turn-over frequencies (TOF), selectivities (*S*) to MHB and enantioselectivities (*ee*) to the (*R)* isomer were evaluated as the principal kinetic parameters. The TOF, *ee* and the selectivity were always determined at 90% conversion (experiments with IL) or at the 75th min (experiments with CO_2) of the experimental run. In this case the continuous sampling of reaction mixture was disabled to avoid changes of the liquid–gas reaction mixture composition. The 75th min was established due to the experimentally observed higher level of MAA conversion. The *ee* parameter is defined:

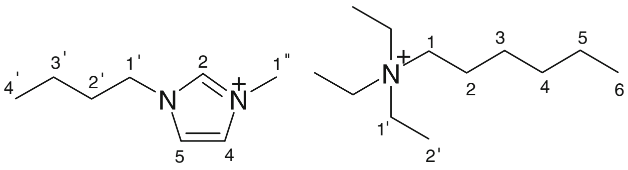
$$ee = [R] - [S]/([R] + [S]) \times 100 \quad (1)$$

The general selectivity parameter *S* to MHB reflected formation of acetals in the presence of methanol as described previously [34, 37].

$$S = [R] + [S]/([R] + [S] + [AC]) \times 100 \quad (2)$$

2.4.2 Analytical

Samples of the reaction mixture were chromatographically analysed with a chiral GC column MN Hydrodex-β-3P (50 m × 0.25 mm × 0.25 µm). NMR spectra were recorded on a Bruker Avance III—400 MHz spectrometer (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) in CD_3OD at 303 K. Residual signal of the solvent was used as an internal standard (δ_H 3.330 ppm, δ_C 49.30 ppm). ^{1}H, ^{13}C, gCOSY and proton-edited gHSQC spectra were recorded using the standard manufacturer's software. ^{1}H NMR spectrum was zero filled to fourfold data points and multiplied by a two-parameter double-exponential Lorentz-Gauss function before Fourier transformation to improve the resolution. The numbering used is depicted below.



$[bmim][PF_6]$

^{1}H NMR: 0.976 (3H, t, J = 7.4 Hz, H-4′), 1.383 (2H, m, H-3′), 1.877 (2H, m, H-2′), 3.914 (3H, s, H-1″), 4.198 (2H, t, J = 7.4 Hz, H-1′), 7.486 (1H, dd, J = 1.8, 1.8 Hz, H-4), 7.546 (1H, dd, J = 1.8, 1.8 Hz, H-5), 8.697 (1H, m, H-2); ^{13}C NMR: 13.87 (C-4′), 20.52 (C-3′), 33.12 (C-2′), 36.62 (C-1″), 50.77 (C-1′), 123.70 (C-5), 125.00 (C-4), 137.84 (C-2)

[bmim][Tf_2N]

^{1}H NMR: 0.997 (3H, t, $J = 7.4$ Hz, H-4′), 1.398 (2H, m, H-3′), 1.888 (2H, m, H-2′), 3.933 (3H, s, H-1″), 4.217 (2H, t, $J = 7.4$ Hz, H-1′), 7.532 (1H, dd, $J = 1.9, 1.9$ Hz, H-4), 7.599 (1H, dd, $J = 1.9, 1.9$ Hz, H-5), 8.831 (1H, m, H-2); ^{13}C NMR: 13.89 (C-4′), 20.62 (C-3′), 33.24 (C-2′), 36.70 (C-1″), 50.86 (C-1′), 121.45 (q, $J_{C,F} = 320.6$ Hz, CF_3) 123.86 (C-5), 125.15 (C-4), 137.9 (broad signal, C-2)

[N_{6222}][PF_6]

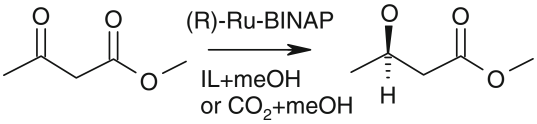
^{1}H NMR: 0.951 (3H, m, H-6), 1.304 (9H, tt, $J = 7.3$ Hz, J(^{14}N,^{1}H) = 1.9 Hz, H-2′), 1.406 (6H, m, H-3, H-4, H-5), 1.694 (2H, m, H-2), 3.184 (2H, m, H-1), 3.322 (6H, q, $J = 7.3$ Hz, H-1′); ^{13}C NMR: 7.87 (C-2′), 14.48 (C-6), 22.80 (C-2), 23.74 (C-5), 27.30 (t, J(^{14}N,^{13}C) = 1.9 Hz, C-3), 32.56 (C-4), 54.11 (t, J(^{14}N,^{13}C) = 3.0 Hz, C-1′), 58.39 (t, J(^{14}N,^{13}C) = 2.9 Hz, C-1)

[N_{6222}][Tf_2N]

^{1}H NMR: 0.947 (3H, m, H-6), 1.302 (9H, tt, $J = 7.3$ Hz, J(^{14}N,^{1}H) = 1.9 Hz, H-2′), 1.401 (6H, m, H-3, H-4, H-5), 1.692 (2H, m, H-2), 3.183 (2H, m, H-1), 3.322 (6H, q, $J = 7.3$ Hz, H-1′); ^{13}C NMR: 7.91 (C-2′), 14.45 (C-6), 22.82 (C-2), 23.71 (C-5), 27.28 (t, J(^{14}N,^{13}C) = 1.3 Hz, C-3), 32.53 (C-4), 54.16 (t, J(^{14}N,^{13}C) = 3.0 Hz, C-1′), 58.44 (t, J(^{14}N,^{13}C) = 2.9 Hz, C-1), 121.48 (q, $J_{C,F} = 320.6$ Hz, CF_3)

3 Results and Discussion

The primary intention of this work was to evaluate and compare (positive and negative) aspects of various arrangements of the *(R)*-methyl 3-hydroxybutyrate synthesis from achiral methyl acetoacetate by means of the stereoselective hydrogenation [11, 12, 14] with the chiral Ru-BINAP complex. These arrangements comprised the standard homogeneous experiment with methanol as a solvent, the mixed solvent system of methanol-IL or methanol-CO_2 and finally the methanol-CO_2 with additives - water and organic chlorides. In parallel the role of the ion-pairs combination was also elucidated.



Scheme 1 Methyl acetoacetate hydrogenation

The reaction course expressed in the form of a formal reaction scheme (Scheme 1) has been reported repeatedly [34, 37, 38]. It comprises a series of steps and formation of a series reaction intermediates. When the reaction is performed in the alcohol environment appearance of acetals cannot be omitted. It should be emphasized that especially the acidic properties of Ru-BiNAP play a significant important role toward the extent of their appearance [39]. It is noteworthy there is a clear reflection of this phenomenon on the magnitude of the selectivity parameter S. Also the mechanistic model of the Ru-BINAP catalytic cycle has already been introduced [40], however, for the reaction system without the ionic liquid phase.

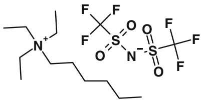
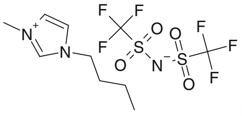
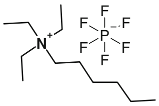
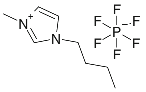
3.1 The Role of Ion Pairs

To elucidate the effect of combination of four ionic pairs, [bmim][Tf_2N], [N_{6222}][Tf_2N] and [N_{6222}][PF_6] were prepared and carefully purified to avoid a role of the trace contamination (mostly organic or inorganic halides, metallic salts, triethylamine and 1-methylimidazole). The kinetic data were compared with those obtained in pure methanol (Table 1). It is seen the TOF at the 90% conversion surpassed well the reaction systems involving ILs, however, with distinctive differences among them. On the other hand, as already introduced, due to high content of alcohol, this reaction environment was very much affected by the formation of acetals (reflected in the S_{90} parameter). Evidently the bistriflamides based ILs revealed much less negative effect on the reaction rate than the hexafluorophosphates. This is an important finding due to the broadband utilisation of [bmim][PF_6] in reactions of this type [11, 13]. The TOF was in average three times lower with the [Tf_2N] anion in comparison to the standard experiment in methanol, and nearly six times lower in the case of the [PF_6] anion.

Generally, there are two major reaction rate limiting factors: hydrogen gas solubility and/or structural modifications of the active catalytic centre with the anionic pair (Figs 1 and 2). Both factors are considered as similarly important. Solubility of hydrogen is generally low in the ionic liquids phase. It is believed that each Ru-BINAP molecule is selectively entrapped by the IL molecules. The effect of anion's type of the IL predominated the effect of the cation's type as illustrated in the Fig. 3. The reaction proceeded in generall faster with the quaternary amonium based ILs, in comparison with the imidazolium based ILs. The observed induction period might be attributed to the expulsion of a ligand providing the catalytically active centre [26].

Unlike the TOFs the *ee* values achieved with the [TF_2N]$^-$ based ILs were quite high, especially with [bmim][TF_2N] (Table 1). It should be emphasized that its value was nearly comparable with the *ee* evaluated for the

Table 1 The ionic pairs effect

IL	TOF_{90} (h^{-1})	ee_{90} (%)	S_{90} (%)	$ee^{re\text{-}use}$ (%)
MeOH	1100	98	79	
 $N_{6222}Tf_2N$	390	93	87	54
 bmimTFN	340	97	91	54
 $N_{6222}PF_6$	210	55	86	–
 6 $bmimPF_6$	160	78	88	32

Reaction conditions: 2 g MAA, 17 mL solvent IL-MeOH 1/1 wt., S/C = 1580, 333 K, 50 bar H_2

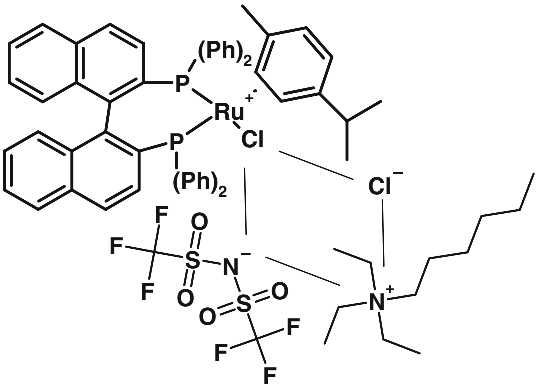


Fig. 1 Proposed "weak" catalyst-IL ionic pairs interaction

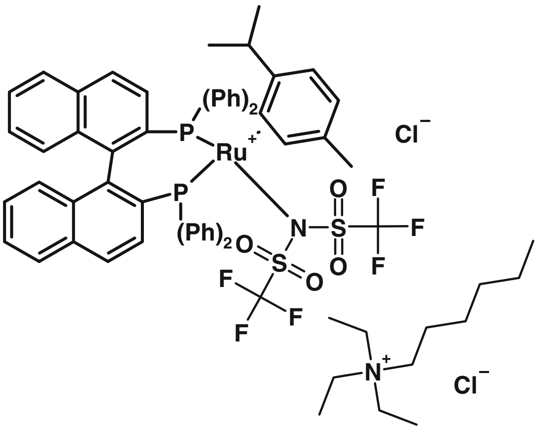


Fig. 2 Proposed catalyst-IL ionic pairs re-coordination

standard methanol experiment. On the other hand these parameters (for the PF_6 anion based ILs) were rather low.

As introduced in the experimental section the structure and the "origin" of ILs had been determined by NMR. It is of note here that the J(^{14}N,^{13}C) and J(^{14}N,^{1}H) couplings were observed due to the symmetry of the N_{6222} cation. The NMR data displayed almost no change depending on the anion's type. It must be emphasized that no relation of the ionic pairs to the catalytic course were observed from the ^{1H}NMR or ^{13C}NMR point of view. Hence, it should be noted that the extended positive charge delocalization of the imidazolium's cation may play a certain role in the catalytic course when compared to the aromatic-less ammonium IL, and considering the aromatic nature of the BINAP and *p*-cymene ligands.

As might be seen in Fig. 4 the parameter of enantioslectivity typically revealed an increasing tendency with the progress of the reaction and this phenomenon was even

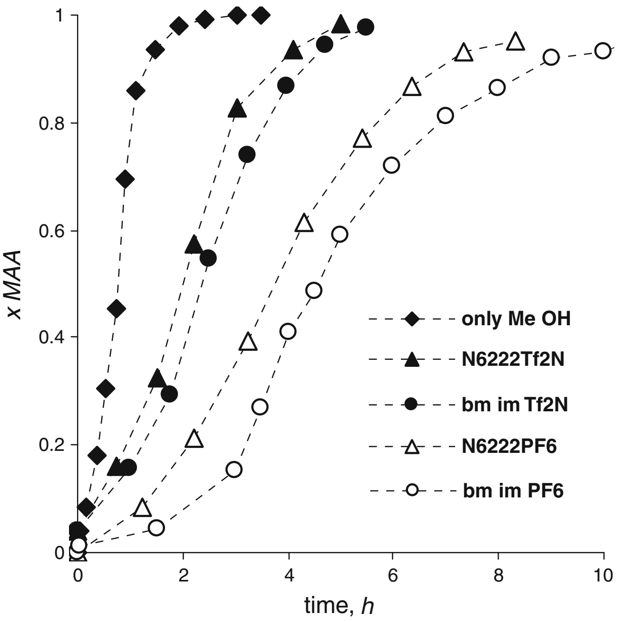


Fig. 3 Effect of IL pairs IL on the conversion of MAA

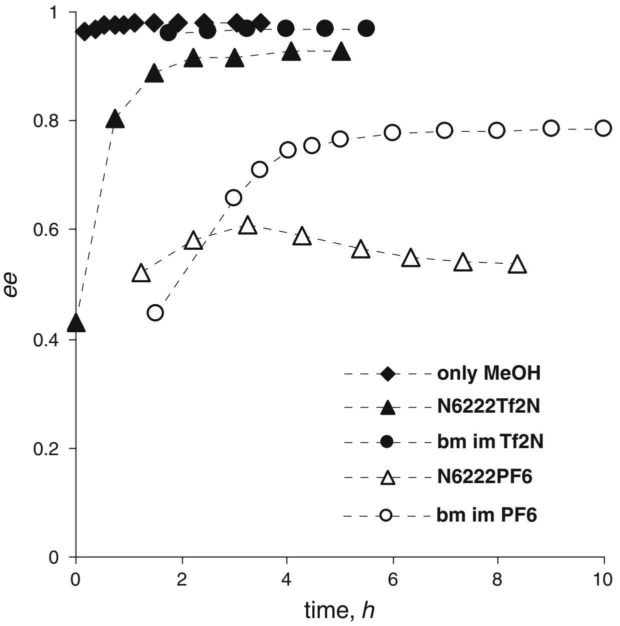


Fig. 4 Ionic pairs effect on the enantioselectivity

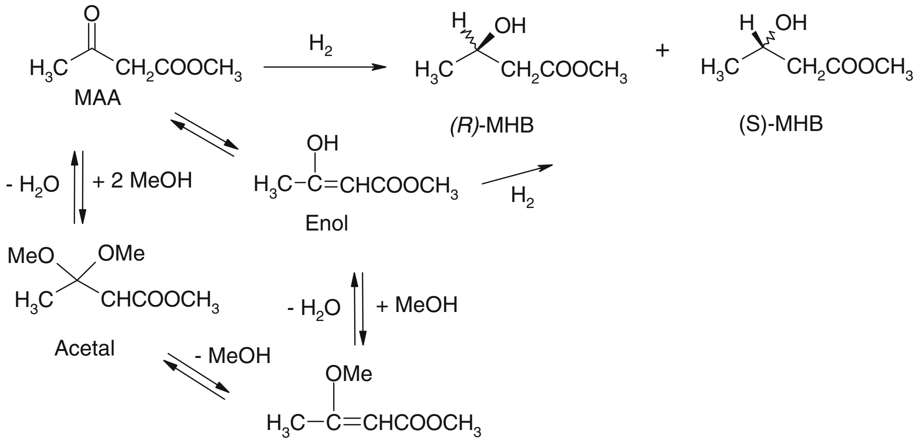
more pronounced with reactions in the IL/methanol phase. Some interpretation might be sought in terms of formation of highly unstable enolic intermediate (Scheme 2) in the presence of pure methanol. The enol form is much less stereospecific than MAA and thus a lower ratio of the (*R*) to *(S)* isomers could be expected [41]. By analogy to this explanation the hydrogenation of acetals [36] might be also considered. Obviously highly reversible enol and acetals formation is significant especially at low MAA conversion. At higher conversions concentration of enols is lower and thus *ee* increases. When the ionic liquid is present in the methanol phase the reaction rate is much lower as already described and also the enol and acetal intermediates are formed at much lower extent (Fig. 5). This in turn may cause indirect suppression of the magnitude of *ee*. In other words the lower S_{90} at more rapid reactions may indicate much higher *ee*. The maximum of acetals formation was in all cases higher in the presence of imidazolium cation. It might be attributed to the hydrogen acidic properties of imidazolium [42, 43]. In spite of the lower acidity of IL in comparison with methanol the imidazolium based IL are more acidic than ammonium.

3.2 The Effect of CO_2

To investigate the effect of CO_2 the reactor with a large oblong quartz window was used, enabling the in situ observation of the phase behavior of the solvent system. As described earlier the used metal complexes reveal a tendency not to be well soluble in dense or $scCO_2$. Therefore the influence of added CO_2 pressure to the methanol system was examined. The addition of relatively small pressure increment can lead to the improved solubility of other gases such as H_2. Furthermore, at the end of the reaction further increase in the CO_2 pressure can lead to the precipitation of the catalyst from the reaction mixture. The expansion of the liquid (solvent methanol and MAA) by CO_2 resulted in a single liquid phase. The presence of MeOH was essential due to the virtually zero catalyst's solubility in MAA and liquid CO_2. It must be noted that with this arrangement the mixture sampling was not considered to avoid the undesired composition changes. Hence the reaction parameters were always elucidated at the 75th min of the reaction run.

Under the studied conditions the incremental increase of the solvent swelling was observed as a consequence of increasing the partial pressure of CO_2. However, it was also expected that increasing the pressure could increase the reaction rate due to improved mass transfer. However, it was found that the reaction rate was actually suppressed in the presence of CO_2 (Table 2). (Note: The same trend was indicated in [31] for a similar system but for synthesis of naproxen *via* enantioselective hydrogenation). The explanation might be potentially sought in terms of the poisoning of the catalyst with CO originated from CO_2 reduction observed [44] in the enantioselective hydrogenation of ethyl pyruvate *via* heterogeneous Pt/Al_2O_3. However, such deactivation has never been indicated for homogeneous Ru-phosphines catalyzed reactions and thus we suppose it only as a hypothetical explanation. The molecular competitive interaction of the carbonyl groups of the substrate and CO_2 on the Ru-BINAP active centre is more plausible

Scheme 2 Proposed reaction intermediate formation



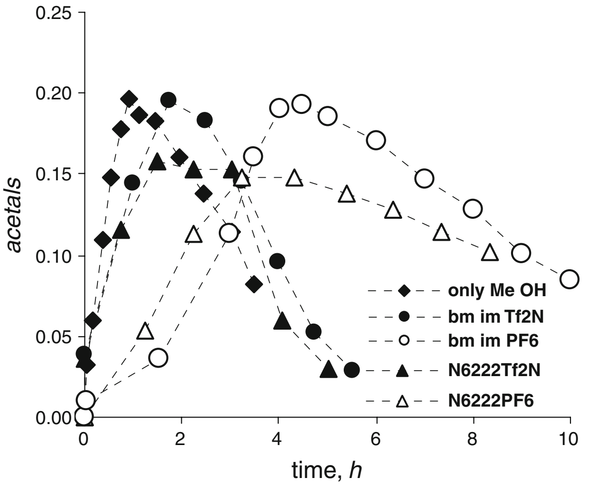


Fig. 5 Ionic pairs effect on the formation of by-products

Table 2 Effect of the CO_2 partial pressure

Entry	p_{H2} (bar)	p_{CO2} (bar)	x_{MAA}	$TOF_{1.25}$ (h^{-1})	$ee_{1.25}$ (%)	$S_{1.25}$ (%)
1	4.4	–	0.38	470	98.6	14
2	4.4	30	0.19	240	98.6	3
3	10	–	0.37	440	98.6	23
4	9.2	25	0.25	300	98.6	23
5	33	–	0.51	680	98.6	56
6	33	30	0.37	470	98.6	53
7	50	–	0.97	1300	98.7	78
8	50	30	0.72	930	98.8	72
9	50	51	0.70	830	98.9	69
10	20	80	0.28	350	99.0	68
11	80	20	0.996	1300	98.6	83

Reaction conditions: 3 g MAA, 25 mL MeOH, S/C = 1580 (mol/mol), 333 K, $t = 1.25$ h

but no quantification of the relative binding strength of CO_2 vs. MAA (or ester) on ruthenium phosphines was available. When considering the reduction of CO_2 with H_2 catalyzed by ruthenium phosphines complexes [50] formic acid is generally formed. On one hand, in the presence of acids [40], the TOF and the selectivity enhancements had been achieved, on the other hand the TOF and *ee* decreased dramatically in the presence of carboxylates $N_{4444}OAc$ or $N_{4444}OOPh$ (20mol. eq. to catalyst). In the presence of CO_2 neither significant TOF increase nor drop of *ee* was indicated. In principle, the esters (substrates) are not assumed as deactivants (taking into account the possible formation of methyl formate).

Another possible explanation is the dilution effect. It is expected to be prevailing at higher pressures of CO_2 [55, 56]. Experiments carried out at much lower pressures, it means at the level when virtually no expansion took place, did not point out on any contribution of diluting to the drop of the reaction rate. We believe that at moderate pressures used in our tests the contribution of dilution is plausible, but likely accompanied with some other mechanism. The effect of the CO_2 presence on the selectivity was rather negative, the *ee* value was influenced in minimal, rather positively and specifically at higher carbon dioxide partial pressures.

3.3 Optimization of the CO_2 System with Water

A certain role of the pH in acceleration of the MAA transformation over Ru-BINAP has been reported [40, 45]. In the presence of slightly acidic H_2CO_3—formed from carbon dioxide pH decrease might be expected [46] as well as the formation of methyl carbonic acid from CO_2 and methanol, reported by Eckert and Liotta [54]. The very positive effect of water on the reaction rate and especially selectivity had been described elsewhere [6, 34, 51–53]. The reversible formation of acetals, producing H_2O, is in

Table 3 Effect of the additives in H_2–CO_2 hydrogenation systems

Entry	p_{H2} (bar)	p_{CO2} (bar)	Additive/amount	x $_{MAA}$	$TOF_{1.25}$ (h^{-1})	$ee_{1.25}$ (%)	$S_{1.25}$ (%)
7	50	–	–	0.97	1300	98.7	78
12	50	–	H_2O/0.4 mL	0.52	660	98.3	55
13	50	–	choline chloride[a]	1		99.2	90
9	50	51	–	0.70	830	98.9	70
14	50	50	H_2O/0.4 mL	0.79	960	98.6	94
15[b]	50	50	H_2O/0.4 mL	1		98.6	99.6
16	50	50	H_2O/0.9 mL	0.90	1100	98.1	96
17	50	50	H_2O/2.35 mL	0.76	960	97.4	98
18	50	50	Choline chloride[a]	1		99.1	90
19	50	50	Betaine hydrochloride	0.86	1100	98.9	77
20	50	50	H_2O/0.4 mL choline chloride[a]	1		98.8	98

Reaction conditions: 3 g MAA, 25 mL MeOH, S/C = 1580 (mol/mol), 333 K, *t* = 1.25 h

[a] Additive/catalyst = 20 (mol/mol)

[b] 3h

the presence of water suppressed, thus the ratio substrate/acetals is higher such as the yield of the product.

Thus to verify it the "catalytic amounts" of water (0.4, 0.9, 2.3 mL) were added to the reaction mixture containing 25 mL of methanol. The very impressive reaction rate enhancement is showed in Table 3, revealing a clear maximum for the addition of 0.9 mL of water, indicating an optimum of pH in some cases. This "water effect" is evidently very much limited to only low volumes of water. The parameter of selectivity S increased significantly with increasing the water content, up to the level of 98%. It should be emphasized that such high values of the selectivity are achieved in the standard (methanol) reaction system at much longer reaction times (on the account of the reversible formation of acetals). Nevertheless, the value of *ee* decreased by 1.5% with increasing the concentration of water as observed elsewhere [34] with CO_2 free solvents. The results obtained in the methanol/water system (without CO_2; catalyst's precipitation signs) offer a clear evidence of the positive effect of CO_2—water.

3.4 Tuning the Reaction System

In transition metal catalysis the halide effect had been described [47–49]. The preliminary experiments pointed out the very essential role of organic halides positively influencing [35] the TOF as well as the (enantio)selectivity. The effect of cation's structure of chlorides or bromides on the reaction rate has been studied in every detail and this subject will be covered in our next communication. Here we wish briefly draw attention on the extraordinary role of the choline chloride reaction additive. As shown in Table 3 in the presence of choline chloride all monitored kinetic parameters were enhanced. It is seen that the value of *ee* increased by 0.5–99.2% when MeOH/choline chloride was used. The selectivity increased to 12% in comparison with the standard experiment. The CO_2/MeOH system (entry 13) turned very positively when choline chloride was added (entry 18). Comparing this system with MeOH/choline chloride, the *ee* was slightly negatively influenced by CO_2 and the role of CO_2 seemed to be negligible. We attempted to design "a new reaction system" for the studied hydrogenation: MeOH/water/CO_2/choline chloride, resulting from optimisation of all preceding systems. Although the presence of the water-carbon dioxide component depressed slightly the *ee*, this parameter was (98, 8%) was virtually on the same level as for the standard experiment. The total conversion and very high selectivity 97.8% (as a consequence of CO_2-water effect) might even satisfy requirements of a practical process.

4 Conclusion

Two homogeneous reaction systems were considered. The first, methanol-ILs system is able to satisfy catalyst's recovery requirements, the latter, methanol-CO_2 modified system offers high reaction rate and (enantio) selectivity, but it in parallel offers the possibility of the catalyst separation. Also the choice of an ionic pairs in the molecule of IL plays an important role in the asymmetric hydrogenation of MAA. Indeed, the reaction rate revealed to be strongly influenced in the presence ionic liquids, but the *ee* decrease as the most important parameter. The modified reaction system was designed to explain ee increase accentuated in the presence of ILs. In the second part the standard (methanol) system was modified by $scCO_2$. Even the solvent swelling effect on the mass transport was diminished by catalyst's inactivity in the presence of CO_2, the reaction was tuned by synergic water effect. Finally, the reaction parameters were optimized with respect to the positive effects of additives—CO_2/water and halides. This high-selectivity optimized system might be a challenge in practical asymmetric β-ketoesters hydrogenations.

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References

1. Akutagawa S (1995) Appl Catal A 128:171
2. Xia Y-Q, Tang Y-Y, Liang Z-M, Yu C-B, Zhou X-G, Li R-X, Li X-J (2005) J Mol Catal A: Chem 240:132
3. Saito T, Yokozawa T, Ishizaki T, Moroi T, Sayo N, Muira T, Kumobayashi H (2001) Adv Synth Catal 343:264
4. Huang HL, Liu LT, Chen SF, Ku H (1998) Tetrahedron Asymmetr 9:1637
5. Ratovelomanana-Vidal V, Girard C, Touati R, Tranchier JP, Hassine BB, Genêt JP (2003) Adv Synth Catal 345:261
6. Wolfson A, Vankelecom IFJ, Geresh S, Jacobs PA (2003) J Mol Catal A: Chem 198:39
7. Blaser HU, Spindler F, Studer M (2001) Appl Catal A 221:119
8. Köckritz A, Bischoff S, Morawsky V, Prüße U, Vorlop K-D (2002) J Mol Catal A: Chem 180:231
9. Hu AG, Yee GT, Lin WB (2005) J Am Chem Soc 127:12486
10. Fow KL, Jaenicke S, Muller TE, Sievers C (2008) J Mol Catal A: Chem 279:239
11. Pugin B, Studer M, Kuesters E, Sedelmeier G, Feng X (2004) Adv Synth Catal 346:1481
12. Guernik S, Wolfson A, Herskowitz M, Greenspoonc N, Geresh S (2001) Chem Commun 2314
13. Wolfson A, Vankelecom IFJ, Jacobs PA (2005) J Organomet Chem 690:3558
14. Starodubtseva EV, Vinogradov MG, Pavlov VA, Gorshkova LS, Ferapontov VA (2004) Russ Chem Bull 53:2172
15. Cerna I, Kluson P, Drobek M, Cajthaml T, Bartek L (2007) Chem Listy 101:994
16. Brown RA, Pollet P, McKoon E, Eckert CA, Liotta CA, Jessop PG (2001) J Am Chem Soc 123:1254
17. Malhotra SV, Kumara V, Parmarb VS (2007) Curr Org Synth 4:370
18. Olivier-Bourbigou H, Magna L (2002) J Mol Catal A: Chem 419:182–183
19. West KN, Hallett JP, Jones RS, Bush D, Liotta CL, Eckert CA (2004) Ind Eng Chem Res 43:4827
20. Solinas M, Pfaltz A, Cozzi PG, Leitner W (2004) J Am Chem Soc 126:16142
21. Pestre N, Meille V, Bellefon C (2006) J Mol Catal A: Chem 252:85
22. Landis CR, Halpern J (1987) J Am Chem Soc 109:1746
23. Jessop PG, Subramaniam B (2007) Chem Rev 107:2666
24. Webb PB, Sellin MF, Kunene TE, Williamson S, Slawin AMZ, Cole-Hamilton DJ (2003) J Am Chem Soc 125:15577
25. Kuhne E, Santarossa S, Perez E, Witkamp GJ, Peters CJ (2008) J Supercrit Fluids 46:93
26. Dong X, Erkey C (2004) J Mol Catal A: Chem 211:73
27. Fredlake CP, Muldoon MJ, Aki SN (2004) Phys Chem Chem Phys 6:3280
28. Daguenet C, Dyson PJ (2004) Organometallics 23:6080
29. Daley CJA, Bergens SH (2002) J Am Chem Soc 124:3680
30. Abbel R, Rashid KA, Faatz M, Hadzovic A, Lough AJ, Morris RH (2005) J Am Chem Soc 127:1870
31. Combes G, Coen E, Dehghani F, Foster N (2005) J Supercrit Fluids 36:127
32. Berthod M, Mignani G, Lemaire M (2004) Tetrahedron Asymmetr 15:1121
33. Hu Y, Birdsall DJ, Stuart AM, Hope EG, Xiao J (2004) J Mol Catal A: Chem 219:57
34. Bartek L, Drobek M, Kuzma M, Kluson P, Cerveny L (2005) Catal Commun 6:61
35. Floris T, Kluson P, Bartek L, Pelantova H (2009) Appl Catal A 366:160
36. Sun J, McFarlane DR, Forsyth M (1997) Ionics 3:356
37. Ochsner E, Etzold B, Junge K, Beller M, Wasserscheid P (2009) Adv Synth Catal 351:235
38. Matteoli U, Beghetto V, Scrivanti A (1999) J Mol Catal A: Chem 140:131
39. Kou Y, Yamada N, Akutagawa S, Zhang G, Tanabe K (1991) Bull Chem Soc Jpn 64:133
40. Wolfson A, Vankelecom IFJ, Geresh S, Jacobs PA (2004) J Mol Catal A: Chem 217:21
41. Sun Y, Wang J, LeBlond C, Landau RN, Laquidara J, Sowa JR, Blackmond DG (1997) J Mol Catal A: Chem 115:495
42. Wang Y, Li H, Han S (2006) J Chem Phys 124:044504
43. Avent AG, Chaloner PA, Day MP, Seddon KR, Welton T (1994) J Chem Soc Dalton Trans 3405
44. Minder B, Mallat T, Pickel KH, Steiner K, Baiker A (1995) Catal Lett 34:1
45. King SA, Thompson AS, King AO, Verhoeven TR (1992) J Org Chem 57:6689
46. Toews KL, Shroll RM, Wai CM, Smart NG (1995) Anal Chem 67:4040
47. Fagnou K, Lautens M (2002) Angew Chem Int Ed 41:26
48. Jiang Q, Jiang Y, Xiao D, Cao P, Zhang X (1998) Angew Chem Int Ed 37:1100
49. Vogl EM, Gröger H, Shibasaki M (1999) Angew Chem Int Ed 38:1570
50. Jessop PG, Joó F, Tai C-C (2004) Coord Chem Rev 248:2425
51. Mashima K, Kusano KH, Sato N, Matsumura Y, Nozaki K, Kumobayashi H, Sayo N, Hori Y, Ishizaki T, Akutagawa AS, Takaya H (1994) J Org Chem 59:3064
52. Gelman F, Avnir D, Schumann H, Blum J (1999) J Mol Catal 146:123
53. Wan KT, Davis ME (1993) J Chem Soc Chem Commun 1262
54. West KN, Wheeler C, McCarney JP, Griffith KN, Bush D, Liotta CL, Eckert CA (2001) J Phys Chem A 105:3947
55. Couchi D, Gourgouillon D, Courel M, Vital J, Ponte MN (2001) Ind Eng Chem Res 40:2551
56. Milewska A, Banet Osuna AM, Fonseca IM, Nunes da Ponte M (2005) Green Chem 7:726