# Organic solvent nanofiltration in asymmetric hydrogenation: enhancement of enantioselectivity and catalyst stability by ionic liquids

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**This communication describes the enhancement of the enantioselectivity and the stability of Ru-BINAP with the ionic liquid trihexyl(tetradecyl)phosphonium chloride (CyPhos101), and the use of organic solvent nanofiltration for the efficient separation of the catalyst and ionic liquid from the hydrogenation product, followed by simultaneous recycling of the catalyst and ionic liquid.**

The use of ionic liquids[1] (ILs) has been shown to improve catalyst stability and product regio- and enantio-selectivity in some reactions.[2–5] However, pure ILs can hinder reaction rates due to poor mass and heat transfer characteristics arising from their high viscosities. It has recently been demonstrated that single-phase mixtures of IL and solvent can improve catalyst stability without compromising reaction rates.[6,7] In parallel, organic solvent nanofiltration (OSN) has recently been used in the effective separation of reaction products from ILs.[8,9] In this communication, we report for the first time the application of OSN for the simultaneous recycling of asymmetric hydrogenation catalysts and ILs. A surprising and significant increase in the enantiomeric excess was observed in the presence of ILs.

An off-the-shelf catalyst (Ru-BINAP) was chosen over others with more sophisticated ligands[10,11] to demonstrate the possibility of using a lower-cost catalyst and improving its performance *via* the addition of ILs. The asymmetric hydrogenation[12] of dimethyl itaconate (MW DMI = 158 g mol$^{-1}$) to dimethyl methylsuccinate (MW DMMS = 160 g mol$^{-1}$) with Ru-BINAP (MW Ru-BINAP = 794 g mol$^{-1}$) (Fig. 1) was selected as the model system. A range of ILs with varying structures and molecular weights were investigated.[13] A solvent resistant polyimide OSN membrane, Starmem™ 122 (MWCO[14] 220 g mol$^{-1}$), was used in this work to retain the catalyst and IL whilst allowing the permeation of the product.

Previous studies have reported hydrogenation of DMI with recycling of Ru-BINAP using OSN membranes, either using high catalyst loadings (S/C[15] = 800),[10] or lower initial loadings (S/C = 4000) accompanied by addition of further catalyst (at S/C = 20 000) in subsequent reactions.[16] In this work, an initial S/C was chosen at 6000 to demonstrate the improvement of IL on the catalyst stability and recyclability.

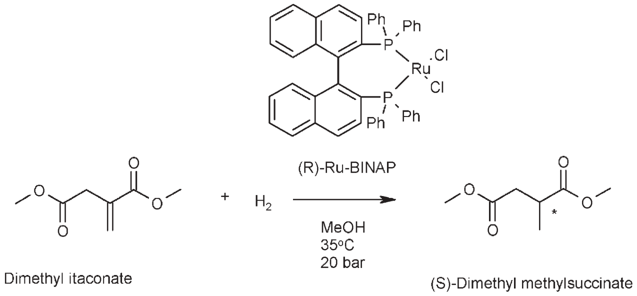

**Fig. 1** Asymmetric hydrogenation of DMI to DMMS with Ru-BINAP.

Methanol (MeOH), IL, substrate (80:10:10 wt%) and catalyst were initially added to a stirred cell fitted with the OSN membrane (Fig. 2). $H_2$ supplied in excess served as the $H_2$ source for the reaction and as the pressure driving force for the product/IL recovery stage by OSN. Consecutive reaction–filtration cycles could be carried out by the re-addition of fresh substrate and solvent to the cell as shown in Fig. 2.

The results for the screening of different MeOH/IL systems are shown in Fig. 3, which plots process yield and enantiomeric excess (ee)[17] as a function of the number of reaction-filtration cycles carried out. Reactions in the MeOH/CyPhos101 and MeOH/TBACl (Fig. 3, entries 2 and 9) systems showed a surprising and significant selectivity enhancement, increasing the ee from 75 to 95% over the pure MeOH system (Fig. 3, entry 1). For MeOH/CyPhos101, the yield was low due to a low rate of reaction in the initial two cycles—when the reaction was allowed to run for longer it reached completion in 20 h. This effect was more pronounced for the reaction in the MeOH/TBACl system, which, although achieving high ee, exhibited decreasing process yields in consecutive 3.5 h

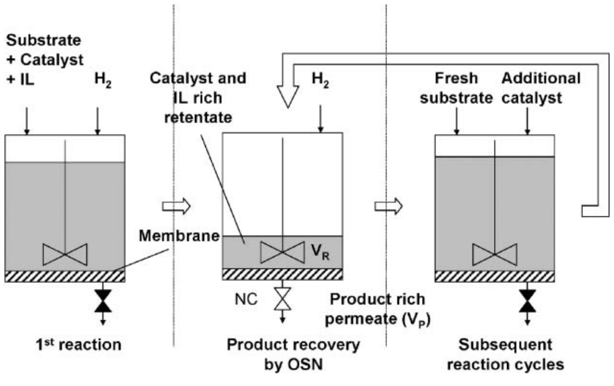

**Fig. 2** Reaction–filtration cycle for catalyst and IL recycle.

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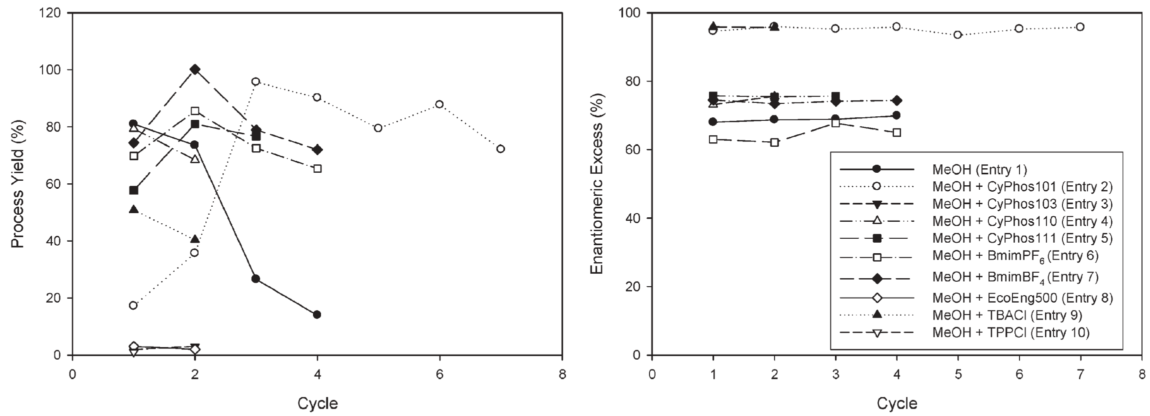

**Fig. 3** Screening of IL/MeOH mixtures for the conversion and EE after 3.5 h. *Reaction conditions*: 10 wt% DMI, 10 wt% IL, S/C 6000, 20 bar and 35 °C. The standard deviations of process yield and enantiomeric excess for repeated reactions are within 5 and 1%, respectively.

cycles. The remaining systems had no or even negative effects on process yield in comparison to the pure MeOH reaction. Reactions with CyPhos103, EcoEng500 and TPPCl achieved negligible process yields in 3.5 h and hence the ee was not measured. In the remainder of the solvent systems, the reaction cycles mainly followed the trend of high process yields for the first two cycles and a subsequent decline in the third and fourth cycles. This might be due to catalyst instability in the MeOH/IL system or to the loss of the active catalytic species through the membrane in the filtration work-up between cycles.

The process yield for the MeOH/CyPhos101 system was observed to increase over the first two cycles, suggesting that the catalyst requires a period of activation in the presence of CyPhos101. Further investigation of this system showed that after a first reaction for 20 h, enhanced reaction rates were achieved for the following cycles resulting in quantitative process yields in 3.5 h (Fig. 4, entry 11). High ee was maintained for all cycles (ee >95%) and the reaction was able to proceed for eight cycles with a slower decline in catalytic activity compared to the reaction in pure MeOH (Fig. 4, entry 1). This corresponds to an increase in the cumulative turnover number (TON[18]) to 43 500 in the MeOH/CyPhos101 system as compared with 13 500 in the MeOH system, demonstrating a marked improvement in the recyclability of the catalyst in the presence of CyPhos101. Subsequently, catalyst re-addition at S/C 60 000 after each reaction–filtration cycle was found to be sufficient to ensure no decline in catalytic activity or selectivity after eight cycles (Fig. 4, entry 12). The re-addition of CyPhos101 to each cycle was not necessary due to its high rejection[19] (>92%). This procedure illustrates how the beneficial effects of ILs can be exploited together with catalyst recycling *via* the use of OSN in asymmetric hydrogenations.

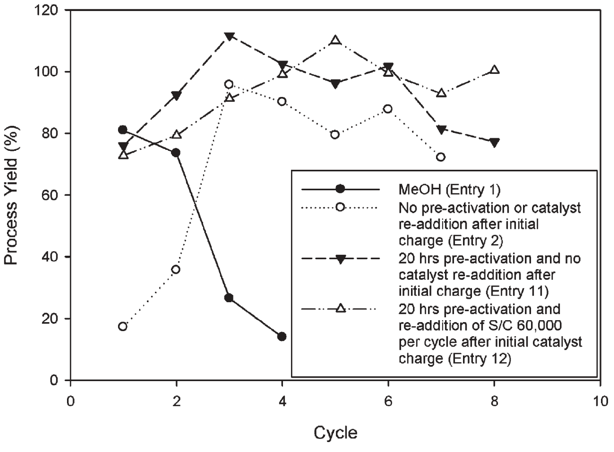

**Fig. 4** Effect of catalyst pre-activation and catalyst re-addition on process yield at 3.5 h (ee >95% for runs with CyPhos101). *Reaction conditions*: 10 wt% DMI, 10 wt% CyPhos101 (entries 2, 11 and 12), S/C 6,000, 20 bar and 35 °C.

Whilst the catalyst pre-activation resulted in high process yields in the first six reactions, this also suggests that the IL imposes a rate limiting effect on the system (Table 2). A compromise between the ee and reaction rates could be achieved by decreasing the IL concentrations. Experiments with the MeOH/CyPhos101 system and TPPCl at reduced IL concentrations in the feed solution showed a similar trend (Table 1). It was observed that for both ILs, quantitative yield was reached without an initial catalyst pre-activation phase. The results also indicate that a minimum amount of IL was required to interact with the catalyst precursor to achieve a high enantioselectivity. The performance in the reaction of CyPhos101 and TPPCl could be attributed to the similarity between the structures of the ILs. However, as shown in Fig. 3, variations in the anion in the other ILs (CyPhos103, 110 and 111) resulted in drastically different results with little or no improvement of enantiomeric excess and process yield, suggesting that the anion may also affect the interaction between the IL and the catalyst. Furthermore, reaction in the presence of LiCl (Table 1) also suggests that the enantioselectivity enhancement of

**Table 1** Effect of IL concentration on process yield and ee after 3.5 h. *Reaction conditions*: S/C 6,000, 20 bar and 35 °C

| IL | IL Conc. (wt%) | Process yield (%) | ee (%) |
|---|---|---|---|
| CyPhos101 | 10 | 17 | 95 |
| CyPhos101 | 1 | 68 | 96 |
| CyPhos101 | 0.1 | 76 | 92 |
| CyPhos101 | 0.01 | 81 | 75 |
| TPPCl | 10 | 0.7 | — |
| TPPCl | 1 | 77 | 93 |
| TPPCl | 0.1 | 73 | 93 |
| LiCl | 0.1 | 80 | 78 |

**Table 2** Effect of catalyst concentration on rate of hydrogen uptake in pure methanol and 10 wt% CyPhos101/methanol systems. *Reaction conditions*: 3.5 h, 20 bar and 35 °C

| System | S/C | Rate of $H_2$ uptake/bar $h^{-1}$ | ee (%) |
|---|---|---|---|
| MeOH | 6000 | 15 | 80 |
| MeOH | 3000 | 32 | 78 |
| MeOH | 1500 | 225 | 78 |
| MeOH/CyPhos101 | 6000 | 3 | 96 |
| MeOH/CyPhos101 | 1500 | 6 | 96 |

**Table 3** Ru-BINAP and IL rejection across OSN membrane

| IL | IL Conc. (wt%) | Catalyst rejection[a] (%) | IL Rejection[c] (%) |
|---|---|---|---|
| No IL | — | 99.9[b] | — |
| CyPhos101 | 10 | 99.9[b] | 98.1 |
| CyPhos101 | 1 | 99.4 | 92.5 |
| CyPhos101 | 0.1 | 95.1 | 93.1 |
| CyPhos101 | 0.01 | 97.6 | — |
| CyPhos103 | 10 | 96.9 | 93.5 |
| CyPhos110 | 10 | 99.9[b] | 95.5 |
| TBACl | 10 | 45.4 | — |
| $BmimPF_6$ | 10 | 95.6 | −35.4 |
| $BmimBF_4$ | 10 | 97.2 | — |
| EE500 | 10 | 98.4 | — |

[a] Based on Ru rejection. [b] Catalyst concentration below detectable limit of 0.01 mg $L^{-1}$ in the permeate. [c] Based on P rejection.

CyPhos101, TPPCl and TBACl is attributable to the whole ionic liquid and not the anion alone.

Further work on the variation of catalyst concentration from S/C 1500 to 6000 in the MeOH/CyPhos101 system also saw no change in the ee (ee > 95%) although the reaction rates increased with decreasing S/C as shown in Table 2. From this and other tests, we are confident that the reaction at S/C = 6000 was not limited by $H_2$ mass transfer.

Similarly, no significant improvement in the selectivity was observed for reactions in pure MeOH when the amount of catalyst was increased; the ee remained at low values (80–78%) when the S/C was decreased from 6000 to 1500. We therefore speculate that the increase in ee observed for CyPhos101, TPPCl and TBACl is due to an interaction between the catalyst precursor and the IL.

Analysis[20] on the permeate and retentate samples (Table 3) shows that the majority of the ILs lower the catalyst rejection. Low catalyst rejection for TBACl also corroborates the declining process yields observed in Fig. 3. Ru:P ratios for the reaction in pure MeOH saw a (mol) ratio of 0.55 in the retentate and 0.08 in the permeate. For the retentate, the 0.55 ratio is close to the stoichiometrically expected ratio of 0.5. The low Ru:P ratio in the permeate suggests that the (deactivated) catalyst does not pass through the membrane in its original form but breaks down with the P segment preferentially passing across the membrane.

This work has demonstrated the enhancement of the catalyst enantioselectivity of Ru-BINAP using CyPhos101, TBACl and TPPCl. This enhancement of selectivity and catalyst stability was clearly illustrated for the MeOH/CyPhos101 system where recycling the catalyst and IL over eight cycles with catalyst re-addition gave a TON of 28 000 with no loss of activity or enantioselectivity. This may be further improved to a value closer to 60 000 by increasing the number of recycles. Although improved catalytic performance has been shown for this particular reaction, the generality of this phenomenon has yet been explored. We believe that whilst the enhanced enantioselectivity may be system specific, the use of solvent/IL systems to improve catalyst stability can be extended to other systems. OSN has been also proven to offer an effective and simple alternative for the separation of ILs and the catalyst from the product in a single phase mixture.

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12 The single-phase reactions were carried out in a stainless steel reactor (METcell, www.membrane-extraction-technology.com); 8.0 g (50 mM) of DMI and 8.0 g of IL were dissolved in 80 ml of MeOH and degassed *via* the Schlenk technique with Ar before charging into the reactor. 6.7 mg (0.0084 mM) of Ru-BINAP (CAS: 132071-87-5) was then added to the reactor and heated to 35 °C. After each cycle, 80 ml of permeate was taken (in approximately 16 min) and fresh feed was added to make up a feed solution of 100 ml with fresh substrate. The membrane was 'washed' with the reaction solvent between each run.
13 CyPhos101: Trihexyl(tetradecyl)phosphonium chloride (MW 519 g $mol^{-1}$); CyPhos110: trihexyl(tetradecyl)phosphonium hexafluorophosphate (MW 629 g $mol^{-1}$); CyPhos111: trihexyl(tetradecyl)phosphonium tetrafluoroborate (MW 570 g $mol^{-1}$); CyPhos103: trihexyl (tetradecyl)phosphonium decanoate (MW 655 g $mol^{-1}$); $BmimBF_4$: 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (MW 228 g $mol^{-1}$); $BmimPF_6$: 1-butyl-3-methylimidazolium hexafluorophosphate (MW 287 g $mol^{-1}$); EcoEng500: Peg-5 cocomonium methosulfate (MW 546 g $mol^{-1}$); TBACl: tetrabutylammonium chloride (MW 278 g $mol^{-1}$); TPPCl: Tetraphenylphosphonium chloride (MW 375 g $mol^{-1}$).
14 STARMEM™ is a trademark of W. R. Grace and Co. Molecular weight cut-off is defined by the molecular weight for which 90% rejection of the solute is achieved by the membrane.
15 S/C: Substrate to catalyst ratio: S/C = mol substrate/mol catalyst.
16 D. Nair, H. T. Wong, S. J. Han, I. F. J. Vankelecom, L. S. White, A. T. Boam and A. G. Livingston, *Org. Process Res. Dev.*, 2006, in press.
17 The process yields were determined using GC analysis by the equation: $Y_{i,\mathrm{rxn}}$ = mol of DMMS in permeate/mol of DMI fed to reaction × 100; ee is defined by the equation $([S] - [R])/([S] + [R])$ and was determined using a Chiralcel OD-H column with 90:10 (hexane–IPA) as the mobile phase.
18 TON is defined by the following equation: TON = Total mol DMMS over all cycles/mol catalyst added.
19 Rejection is defined by the equation $R = 1 - (C_{P,i}/C_{R,i})$ where $C_{P,i}$ is the concentration of species $i$ in the permeate and $C_{R,i}$ is the concentration of $i$ in the retentate.
20 Catalyst and IL rejections were determined by first digesting samples in a MARS microwave digester followed by measuring the Ru and P concentrations *via* ICP-OES.