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Enantioselective Hydrogenation of Imines in Ionic Liquid/Carbon Dioxide Media

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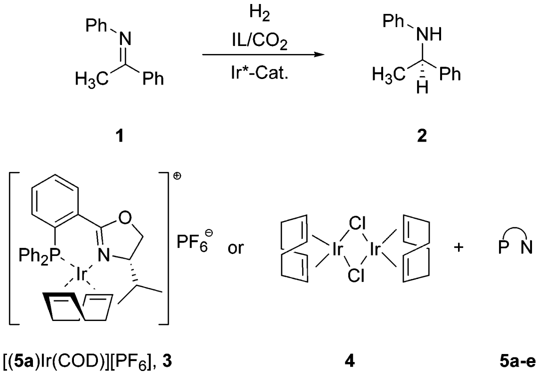
Abstract: The enantioselective hydrogenation of *N*-(1-phenylethylidene)aniline using cationic iridium complexes with chiral phosphinooxazoline ligands was studied as a chemical probe to assess the potential of ionic liquid/carbon dioxide (IL/CO_2) media for, multiphase catalysis. The biphasic system leads to activation, tuning, and immobilization of the catalyst that would be impossible in classical organic solvent systems or in either of the two unconventional media separately. In particular it is demonstrated that (i) the presence of CO_2 can be beneficial or even mandatory for efficient hydrogenation in the IL; (ii) the precursor is activated in the IL by anion exchange allowing one to use in situ catalysts; (iii) the anion of the IL greatly influences the selectivity of the catalyst; (iv) the products are readily isolated from the catalyst solution by CO_2 extraction without cross contamination of IL or catalyst; and (v) the IL leads to enhanced stability of the catalyst. These results are corroborated and rationalized on the basis of the physicochemical properties of the biphasic medium and the chemical characteristics of the catalytic systems.

Introduction

Innovative methodologies for immobilization and efficient recycling of organometallic catalysts are finding ever increasing interest for the development of environmentally benign and economically viable homogeneously catalyzed processes.[1] Stimulated by the seminal paper of Brennecke and Beckman[2] on the phase behavior of mixtures of ionic liquids (ILs)[3] and supercritical carbon dioxide ($scCO_2$),[4] several groups have shown recently that the combination of these two media offers a highly attractive approach to this problem.[5,6] In the present paper, we present our recent results on the activation, tuning, and immobilization of chiral iridium catalysts in IL/CO_2 for the enantioselective hydrogenation reaction of imines (Scheme 1).[7]

Scheme 1. Enantioselective Hydrogenation of *N*-(1-Phenylethylidene)aniline (**1**) in IL/CO_2 and Catalytic Systems Used in the Present Study[a]



[a] For the definition of ligands **5b**−**e**, see Scheme 3.

The enantioselective hydrogenation of imines provides an attractive route to enantiomerically enriched chiral secondary amines as applied in the industrial production of (*S*)-metolachlor.[8] The chiral (phosphanodihydrooxazole)iridium catalyst

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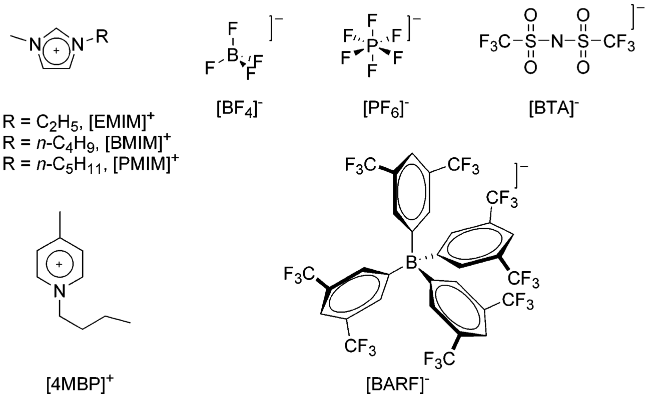
Scheme 2. Set of Cations and Anions Used in the Present Work



3 yields high levels of asymmetric induction in the hydrogenation of prochiral *N*-alkyl and *N*-aryl imines[9] as well as in the hydrogenation of carbon−carbon double bonds.[10] Some of us have recently shown that this type of complexes can be used as homogeneous catalysts for the hydrogenation of imines in $scCO_2$ upon appropriate modification especially of the counterion.[11] Although the product and the catalyst could be readily separated using the CESS (catalysis and extraction using supercritical solvents) procedure, an efficient immobilization of the catalyst was not possible because of noticeable deactivation during the recycling process.

Here, we describe how the combination of ILs and $scCO_2$ does not only allow one to overcome this problem, but permits one to exploit fully the benefits of both systems through the combination of the molecular interaction of the stationary IL phase with the catalyst and the mass transfer properties of the mobile CO_2 phase. In particular, we observe that (i) the presence of CO_2 is beneficial or in certain cases even mandatory for efficient hydrogenation in the IL at comparable partial pressures of hydrogen; (ii) dissolving the catalyst in the IL leads to activation by anion exchange and allows one to use in situ systems that would not be applicable in conventional solvents; (iii) the choice of the anion of the IL greatly influences the selectivity of the catalyst; (iv) the products are readily removed and isolated from the catalyst solution by CO_2 extraction without cross contamination of IL or catalyst; and (v) the IL leads to greatly enhanced long-term stability of the iridium catalyst.

These results are corroborated and rationalized on the basis of the physicochemical properties of the biphasic medium and the chemical characteristics of the catalytic systems.

Results and Discussion

The hydrogenation of *N*-(1-phenylethylidene)aniline (**1**) to give (*R*)-phenyl-(1-phenyl-ethyl)-amine (**2**) was used as a benchmark reaction throughout the course of this study (Scheme 1). The set of cations and anions displayed in Scheme 2 was used to assess the influence of the structural diversity of ILs for the process. The cationic complex **3** containing $[PF_6]^-$ as the counterion was used as a precatalyst in the initial phase of the study. In a typical experiment, the appropriate ionic liquid (2.0 mL), the iridium complex **3** (3×10^{-3} mmol) and the substrate **1** (**1**/**3** = 500/1) were loaded under argon in a window-equipped stainless steel autoclave ($V = 12$ mL). The reactor was then pressurized with H_2 and the desired amount of CO_2 followed by heating under stirring to 40 °C for a standard reaction time of 22 h. The products were collected for offline GC and HPLC analysis from screening experiments by extraction of the IL phase with hexane after cooling and venting, or alternatively isolated by CO_2 extraction as described below. Representative results are summarized in Table 1.

Table 1. Enantioselective Hydrogenation of *N*-(1-Phenylethylidene)aniline (**1**) to (*R*)-Phenyl-(1-phenyl-ethyl)-amine (**2**) in IL/CO_2 Systems[a]

entry	IL	cat.	*T* [°C]	H_2 [bar]	CO_2 [g]	*t* [h]	conversion [%]	ee [%]
1	[EMIM][BTA]	3	40	30		22	3	
2	[EMIM][BTA]	**3**[b]	40	100		22	97	58
3	[EMIM][BTA]	3	40	30	8.9	22	>99	56
4	[4MBP][BTA]	3	40	30		22	>99	53
5	[4MBP][BTA]	3	40	30	9.8	22	>99	52
6	$[PMIM][PF_6]$	3	40	35	7.5	22	>99	61
7	$[PMIM][PF_6]$	3	25	30	8.0	22	>99	65
8	$[PMIM][PF_6]$	**4**/**5a**[c]	40	30	8.6	22	>99	62
9	$[PMIM][PF_6]$	**4**/**5a**[d]	40	30	9.2	22	>99	64
10	$[BMIM][BF_4]$	3	40	30	7.6	22	92	30
11	[EMIM][BARF][e]	3	40	30	8.9	22	>99	78
12	[EMIM][BARF][e]	3	0	30	9.0	22	54	76

[a] Standard conditions unless noted otherwise: **1**/Ir = 500/1, *V*(reactor) = 12 mL, *V*(IL) = 2.0 mL. [b] **1**/Ir = 100/1. [c] **1**/**5a**/Ir = 250/1/1, preformation in CH_2Cl_2. [d] **1**/**5a**/Ir = 250/1/1, in situ protocol. [e] [EMIM][BARF] = 0.7−0.8 g.

The ionic liquid ethyl-methyl-imidazolium bis(trifluoromethylsulfonyl)imide ([EMIM][BTA]) was used to assess the influence of CO_2 on the hydrogenation process using **3** as the catalyst precursor. In the absence of CO_2, conversion was only marginal under standard conditions ($p(H_2) = 30$ bar, $T = 40$ °C), and significant conversion required the use of hydrogen pressures as high as 100 bar. However, quantitative formation of the hydrogenation product was observed at a hydrogen partial pressure of 30 bar in the presence of 8.9 g of CO_2 under otherwise identical conditions (Table 1, entries 1−3). Within experimental error, there was no influence of CO_2 on the enantiomeric excess (Table 1, entries 2/3 and 4/5).

A similar beneficial effect of added CO_2, albeit far less dramatic, was observed with other ILs. Using the 4-methyl-*N*-butyl pyridinium bis(trifluoromethylsulfonyl)imide ionic liquid ([4MBP][BTA]), quantitative conversion was observed with and without CO_2 under 30 bar of hydrogen within the standard reaction time of 22 h (Table 1, entries 4 and 5). However, the effect of the CO_2 pressure was reflected again at shorter reaction times. The hydrogenation of **1** in [4MBP][BTA] in the absence of carbon dioxide with 30 bar of H_2 pressure gave 25% of conversion in 2 h reaction time (TOF = 44 h^{-1}), while at the same condition, but with the presence of supercritical carbon dioxide, 34% of conversion (TOF = 60 h^{-1}) was obtained (Table 2, entries 3 and 4). At lower temperatures and in $[BMIM][PF_6]$, the conversions again followed the same trend but were too small to allow for quantitative conclusions. In this set of screening experiments, the highest activities were achieved in the presence of $scCO_2$ at 40 °C in $[PMIM][PF_6]$, reaching several hundreds turnover per hour at low catalyst loading.

In conventional solvents, the hydrogenation of **1** with catalyst **3** does not show a direct proportionality to the hydrogen

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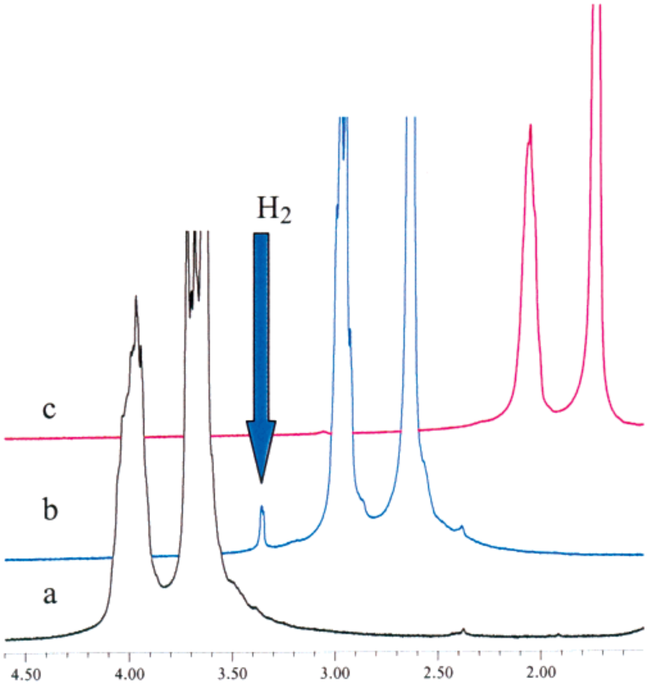

Figure 1. Part of the high pressure ^{1}H NMR spectra of [EMIM][BTA] under hydrogen pressure of $p(H_2) = 30$ bar (trace a), upon addition of CO_2 to a total pressure of 120 bar (trace b), and after release of the system pressure (trace c); the measurements were performed at $T = 297 \pm 2$ K.

Table 2. Effect of the Carbon Dioxide Pressure on the Rate of Imine Hydrogenation with Catalyst **3** in Various ILs

entry	IL	sub./cat.	T [°C]	H_2 [bar]	CO_2 [g]	t [h]	conversion [%]	TOF [h^{-1}]
1	[EMIM][BTA]	500/1	40	30		22	3	<1
2	[EMIM][BTA]	500/1	40	30	8.9	22	>99	>20
3	[4MBP][BTA]	350/1	40	30		2	25	44
4	[4MBP][BTA]	350/1	40	30	8.6	2	34	60
5	[BMIM][PF_6]	360/1	25	30		1	5	18
6	[BMIM][PF_6]	360/1	25	30	8.8	1	8	29
7	[BMIM][PF_6]	450/1	40	30	8.6	3	92	138
8	[PMIM][PF_6]	1160/1	40	30	7.2	0.5	14	327

pressure. The exact reaction order is not known. However, it has been noticed that the chiral iridium catalysts used in the present study react quite sensitive on hydrogen availability influenced by mass transfer properties of the system.[9,10c,12] The apparent "activation" of the catalytic system upon adding CO_2 can thus be related to an improved H_2 availability in the IL, which may result from a strongly increased H_2-solubility[6g,13,14] and/or reduced viscosity[15] in the presence of compressed CO_2. In the present case, we were able to assess these features qualitatively and quantitatively by using high-pressure NMR spectroscopy (Figure 1).

When a high-pressure sapphire single-crystal NMR tube[16] was charged with a pure sample of [EMIM][BTA] and then pressurized with 30 bar of H_2, the characteristic signal of dissolved dihydrogen (ca. 4.0−4.5 ppm) could not be detected even after prolonged shaking to ensure that the equilibrium concentration was reached (Figure 1, trace a). On the basis of the sensitivity of the NMR method, we estimate that the concentration of hydrogen must be below $c(H_2) \approx 0.01$ mol L^{-1} under these conditions. This is in line with the low solubility of H_2 in ILs determined recently through independent investigations by Dyson et al.[17] After carbon dioxide was added to the system, reaching a total pressure of 120 bar, the signal related to the molecular hydrogen was clearly observed with a chemical shift of 4.3 ppm (Figure 1, trace b). At the same time, the viscosity of the ionic liquid decreased drastically, resulting in an improved resolution of the NMR peaks. Once the CO_2 pressure was released, a complete disappearance of the hydrogen signal was observed (Figure 1, trace c). From integration of the dihydrogen signal and the signals of the methylene protons in the imidazolium cation, the concentration of hydrogen in this system could be estimated to $c(H_2) = 0.14$ mol L^{-1}. This value compares well with the solubility of hydrogen in common organic solvents at the same conditions and is approximately an order of magnitude larger than in common ionic liquids in the absence of CO_2.[17]

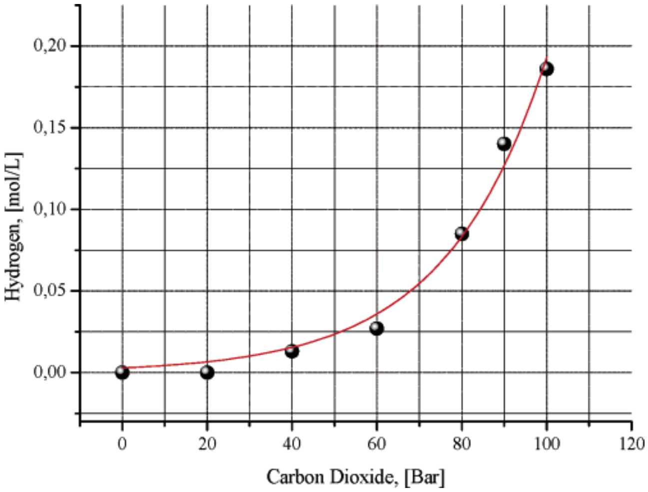

Figure 2. Solubility of hydrogen in [EMIM][BTA] at a constant partial pressure $p(H_2) = 30$ bar as a function of the added CO_2 pressure as determined by high-pressure ^{1}H NMR spectroscopy ($T = 297 \pm 2$ K; concentrations below the estimated detection limit of 0.01 mol L^{-1} were set to zero).

The high-pressure NMR technique allows one to quantify the enhancement of hydrogen solubility in ionic liquid by the effect of carbon dioxide more systematically. As shown in Figure 2, the H_2 concentration in [EMIM][BTA] was found to increase continuously at constant hydrogen pressure (30 bar) with the additional pressure of carbon dioxide in the sapphire NMR tube. In the range of CO_2 pressure investigated here, the net concentration of molecular hydrogen in the IL expressed in [mol L^{-1}] follows with good approximation ($R^2 = 0.989$) an exponential curve of the type:

$$[H_2] = [H_2]^0 + Ae^{P_{CO_2}/b}$$

where $[H_2]^0$ is the concentration in the absence of CO_2 (defined

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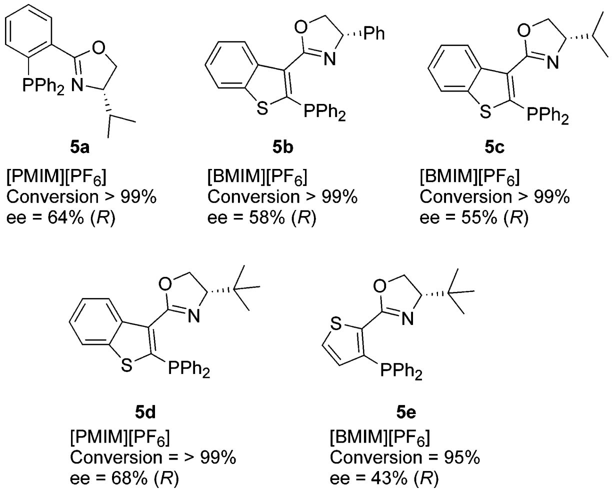
here as zero) and the constants have been calculated as $A = (3.0 \pm 0.9)$ mmol L^{-1} and $b = (23.8 \pm 2.0)$ bar. Obviously, the concentration would be finally limited by the total amount of hydrogen available, which is approximately 1 mol L^{-1} within the total volume of the tube.

As revealed quantitatively in Figure 2, the system [EMIM][BTA]/H_2/CO_2 exhibits a remarkable deviation from Henry's law, which predicts the hydrogen solubility in the liquid solvent to be only a function of the H_2 partial pressure. It has been demonstrated very recently that the solubility of hydrogen in a series of pure ionic liquids does indeed obey this rule and is directly proportional to the H_2 pressure.[17] In our experiments, the partial pressure of hydrogen is fixed to 30 bar, but its solubility in [EMIM][BTA] ironically increases as it is diluted with CO_2. This result can be related to the exceptional solubility properties of carbon dioxide which is largely soluble in ionic liquids[13] and in all proportions miscible with hydrogen.[4a] Beyond arguments related to the hydrogen solubility, it is known that the viscosity of ionic liquids is decreased by the effect of the carbon dioxide pressure.[15] The enhancement of hydrogen availability in the ionic liquid resulting from the combined effects in the presence of CO_2 leads to a higher reaction rate or, as in the case of [EMIM][BTA], even in a surpassing of the threshold concentration to make the catalytic cycle possible. This net "activation" of the catalytic system illustrates nicely the potential benefits arising from the combination of the two media.

In addition to the physicochemical properties, interactions on the molecular level can also be used to activate and tune the catalytic system through the choice of the anion in the IL/CO_2 medium. Again, the cationic iridium catalysts used in the present study serve as an illustrative example, as they are known to respond very sensitively to the nature of the counterions in some cases.[10,11,18] To exploit this tuning effect in conventional solvents, the synthesis of individual catalyst precursors of type **3** with varying anions is necessary. Using ILs as catalyst support opens the possibility to use the same precursor and to introduce the variation of the counterion with the choice of the IL. This requires that the counterion of the catalyst precursor is fully dissociated and effectively "diluted" in the pool of the ionic solvent system. As shown in Table 1, this is indeed the case, and remarkable effects are observed on the stereoselectivity of the reaction upon variation of the anion in the IL using the $[PF_6]^-$-containing precursor of **3** in all cases. The ee values vary from 30% with $[BF_4]^-$ up to 78% with $[BARF]^-$. As a general trend, the performance of the catalyst improves with decreasing coordinating ability of the counterion of the IL.[19]

Taking this one step further, the anion exchange with the IL allows one to even use a simple catalyst formed directly from the air-stable precursors $[Ir(COD)(Cl)]_2$ (**4**) and the free ligand **5a** in the appropriate molar ration (**5a**:Ir = 1:1). It is important to note that mixtures of the two components **4**/**5a** do not lead to active catalysts in conventional solvents as the coordination strength of chloride is too high, thus poisoning the active site.[20,21]

Scheme 3. Screening of a Small Ligand Library **5a**−**e** for Enantioselective Hydrogenation of **1** in IL/CO_2 Using the in Situ Catalyst **4**/**5a**−**e**



Two different methods for the direct generation of the catalyst were tested. In the first case, **4** and **5a** were mixed in CH_2Cl_2 for 1 h at 50 °C, the solvent was removed, and the chloride iridium complex was redissolved in the appropriate ionic liquid. In an in situ protocol, the desired amount of metal precursor and the ligand were dissolved directly in a mixture of 25%/75% vol/vol of CH_2Cl_2 with the appropriate ionic liquid.[22] The organic solvent was removed under high vacuum before starting the hydrogenation reaction. Almost identical results are observed with either the direct preformation or the in situ protocol in [PMIM]$[PF_6]$ as compared to the isolated complex **3** in the same IL (Table 1, entries 6, 8, and 9).

The simple and straightforward in situ protocol opens a rapid and effective way to test libraries of structurally diverse ligands in the enantioselective hydrogenation of imines. This was verified for the series of ligands **5a**−**e**[23] as shown in Scheme 3. All catalytic solutions were prepared from **4**/**5a**−**e** following the in situ protocol in a 12 mL stainless steel reactor. After charging the catalytic solution with substrate, H_2 (30 bar), and CO_2 (8−9 g), the reaction was allowed to proceed at 40 °C. All catalysts **4**/**5a**−**e** showed high activity, and >90% conversion was obtained within a standard reaction time of 22 h. The enantioselectivities varied between 44% and 68%, and the (*R*)-enantiomer was obtained as the major isomer. Interestingly, the relative selectivities in the $[PF_6]^-$-containing ionic liquid (**5d** > **5a** > **5b** > **5c** ≫ **5e**) are not identical to those observed with the isolated $[BARF]^-$ complexes in conventional solvents (**5a** ≅ **5c** > **5d** > **5e** ≫ **5b**). In the case of **5b**, the in situ protocol leads even to slightly higher ee even though the opposite trend would be expected from the usual behavior of the $[PF_6]^-$- and $[BARF]^-$-based catalysts.

Probably the most general interest in the system IL/CO_2 relates to the recycling and immobilization of the organometallic catalyst. Indeed, this new biphasic system provides by far the most effective methodology to immobilize the cationic iridium

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(21) Chloride anions also poison the catalyst in IL, but only at much higher levels than those introduced in the in situ protocol. It proved necessary, however, to check the ILs for their chloride content and to remove any chloride impurities as described in the Experimental Section.

(22) The low solubility of the iridium precursor **4** in pure ionic liquids prevented the complete elimination of organic solvents during the preformation step. More benign alternatives to CH_2Cl_2 such as methanol or acetone may also be used.

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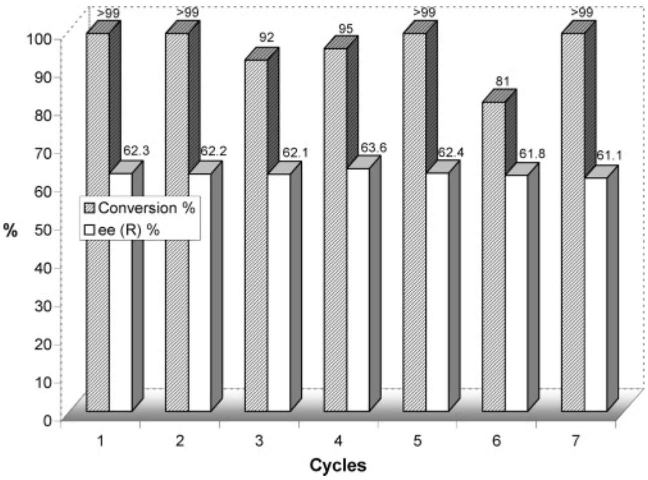

Figure 3. Batch-wise catalyst recycling for hydrogenation of imine **1** using catalyst **3** in the system [BMIM][PF_6]/$scCO_2$.

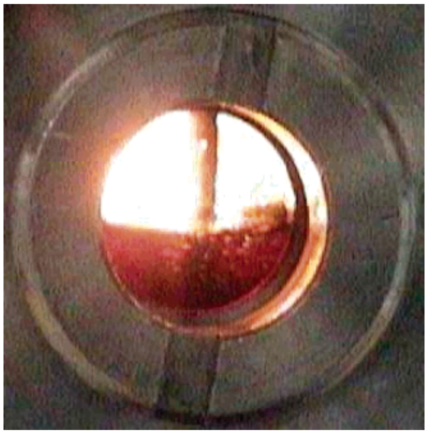

Figure 4. Biphasic system IL/$scCO_2$ during the extraction step of the batch-wise recycling process. CO_2 is bubbled through the intensively red IL/catalyst solution via the capillary, extracting the product **2** into a colorless solution leaving the reactor at the top for downstream processing.

catalysts of type **3** known to date. For the representative set of experiments shown in Figure 3, a solution of [BMIM][PF_6] containing the catalyst **3** was used at $T = 40$ °C and $p(H_2) = 40$ bar in the presence of $scCO_2$ ($d = 0.68$ g mL^{-1}). The reaction time was reduced to only 3 h from the screening procedures, still leading to complete conversion in the first cycle. This corresponds to an average turnover frequency of TOF > 150 h^{-1}. Supercritical CO_2 was shown to be effective at moderate temperatures and pressures for the quantitative extraction of product **2** after the hydrogenation reaction from the catalyst solution. Figure 4 shows a view of the biphasic mixture in the high pressure cell during the extraction process with the intensively red IL-catalyst phase on the bottom and the colorless CO_2-product phase on top. The capillary used for introduction of CO_2 and the bubbles purging through the IL phase are also visible. Following the extraction, the reactor was charged again with another batch of imine **1** for the successive hydrogenation reaction. The catalyst solution showed stable activity and enantioselectivity under these conditions for at least seven cycles. With one exception, conversion remained above 90% in all runs and the enantiomeric excess stayed constant at 62% ± 1%.

The long-term stability of the catalytic solution is in positive contrast to the previous CO_2-based immobilization method for catalysts of type **3** using the CESS procedure, where a significant deactivation occurred after the fourth cycle.[11] This deactivation was attributed to the sensitivity of the active intermediates to adventitious oxygen during the batch-wise recycling. Indeed, it was found that IL solutions of catalyst **3** are significantly less air sensitive than solutions of **3** in conventional organic solvents.[24] A closer inspection of the data summarized in Figure 3 shows that only 81% conversion was achieved in run #6. This was due to a leak in the high-pressure setup resulting in loss of the pressurized gases including the reactant hydrogen. Consequently, the catalyst solution was exposed to air for a short period of time. Despite this, the catalyst solution showed the same performance as in the previous runs again in run #7. Following this serendipitous observation, catalyst solutions [EMIM][BTA]/**3** were found to be remarkably stable even upon prolonged exposure to air (75% conversion and 56% ee after 20 h in air under standard reaction conditions), indicating that the ionic liquid environment helps to stabilize the catalytically active intermediates.

In addition to the catalyst recycling, CO_2 extraction provides also a very convenient method for product isolation. Upon depressurization, compound **2** was isolated directly from the CO_2 stream in a solvent-free and analytically pure form as a colorless crystalline material. In the experiments summarized in Figure 3, 98% of the employed material was recovered with the total number of turnovers exceeding TON = 3000. No signals associated with the IL were detected during NMR and HPLC analyses of the material. Samples from each run were analyzed by ICP measurement, demonstrating that the iridium content was below the detection limit of the instrument (<1 ppm) in all cases and that no significant leaching of metal compounds into the product had occurred. Although the relative amount of CO_2 used for the isolation of a certain amount of **2** is still quite high in the batch procedure, this could be greatly reduced under continuous-flow operation.[5a,6c,f] The engineering aspects of this approach are the subject of ongoing studies and will be reported separately.

Experimental Section

Safety Warning. The handling of pressurized gases and supercritical fluids requires the use of suitable high-pressure equipment and must be carried out under rigorous safety conditions only.

General Procedures and Materials. All manipulations of air- and moisture-sensitive material were carried out under a positive pressure of argon. Solvents were dried and purified according to standard methodologies prior to use. The gases H_2 (99.999) and CO_2 (99.995) were used without further purification. The syntheses of *N*-(1-Phenylethylidene)aniline **1**[9,25] and the phosphanodihydrooxazole-iridium catalyst **3**[9] were carried out according to literature procedures. Ionic liquids were synthesized according to known procedures[26] or obtained from Solvent Innovation.[27] In addition to standard purification, all ILs were tested for chloride impurities which were removed by washing CH_2Cl_2 solutions of the IL with water until the washing tested negative for Cl^- with $AgNO_3$. ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded in deuterated solvents on a Bruker DPX 300 spectrometer. GC-MS analyses were performed on a HP-MASS 5973 chromatograph. HPLC analyses were performed with a JASCO PU-2080 chromatograph

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(24) A similar observation was made for a Rh-MeDuPHOS-based catalyst: Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun.* **2001**, 2314.

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(27) http://www.solvent-innovation.com.

equipped with a MD-2010 detector using a CHIRACEL OD-H column. Values for conversion and ee's from representative single experiments are quoted in the tables. Reproducibility of the catalytic runs was checked for selected examples and was found to be well within 5% relative experimental error.

Hydrogenation of *N*-(1-Phenylethylidene)aniline 1 in IL/CO$_2$ Using Catalyst 3. In a typical experiment, a 12 mL window equipped stainless steel reactor was charged under argon atmosphere with the appropriate IL (2 mL), substrate **1** (293 mg, 1.5 mmol), and catalyst **3** (2.5 mg, 3.0×10^{-3} mmol). The reactor was pressurized with 30 bar of hydrogen followed by addition of 8.5 g of CO$_2$ using a compressor (corresponding to a total pressure of 150 bar at room temperature). The reactor was warmed to 40 °C, and the reaction was allowed to proceed for 22 h. After cooling to room temperature, all volatiles were vented through a cold trap (−70 °C). The IL was recovered from the autoclave and extracted several times with *n*-hexane until complete recovery of the reaction product. The contents of the cold trap and the extracted material were combined and analyzed by GC-MS and HPLC to determine conversion and enantiomeric excess, respectively.

Hydrogenation of *N*-(1-Phenylethylidene)aniline 1 in IL/CO$_2$ Using the in Situ Catalysts 4/5a−e. In a typical experiment a 12 mL window equipped stainless steel reactor was charged under argon atmosphere with [Ir(COD)Cl]$_2$ (**4**, 7.8 mg, 12×10^{-3} mmol) and the appropriate ligand **5a**−**e** (24.2×10^{-3} mmol, **5a**−**e**/Ir = 1:1). A mixture of the appropriate IL (2 mL) and CH$_2$Cl$_2$ (0.7 mL) was added, and the resulting solution was stirred for 1−3 h at 50 °C. The organic solvent was removed by evacuating the reactor for 2 h under stirring. Next, substrate **1** (1.17 g, 6.0 mmol) was introduced under argon, and the reactor was pressurized with 30 bar of hydrogen followed by addition of ca. 8.5 g of CO$_2$ using a compressor. The reactor was allowed to proceed at 40 °C for 22 h followed by workup and analysis as described above.

Recycling Experiments. A 24 mL window equipped stainless steel autoclave was charged, under argon atmosphere, with [BMIM][PF$_6$] (3.2 mL), substrate **1** (0.87 g, 4.46 mmol), and catalyst **3** (8.2 mg, 0.01 mmol). The reactor was subsequently pressurized with hydrogen (40 bar) and filled with 13.7 g of CO$_2$ using a compressor (total pressure = 145 bar at 22 °C). The reaction was allowed to proceed at 40 °C for 3 h. The product **2** of the reaction was extracted by flushing CO$_2$ through the reactor at 160 bar and 45 °C for 3 h with an exit flow set to approximately 700−800 mL min^{-1}. The product was collected in two sequential cold traps kept at 0 and −60 °C, leading to greater than 95% recovery in all cases. In the cases of quantitative conversion, the product was recovered as a colorless microcrystalline material. Samples were analyzed for conversion and ee as described above with additional ICP analysis to assess the iridium content. After the extraction, the reactor was charged again with the same amount of substrate, hydrogen, and CO$_2$ for the subsequent catalytic cycle.

High-Pressure NMR Investigation. A high-pressure sapphire NMR tube (outer diameter = 5 mm, $V = 0.9$ mL) was charged, under argon atmosphere, with [EMIM][BTA] (0.5 mL) and one drop of C$_6$D$_6$ for the lock signal. The NMR tube was placed inside a cylindrical safety shield made from polycarbonate, pressurized at room temperature with 30 bar of H$_2$, and agitated by gentle shaking behind a second safety shield. The tube was lowered into the magnet directly from the polycarbonate cylinder using a home-built device. After the ^{1}H NMR spectrum was recorded at ambient temperature (297 ± 2 K), the tube was removed from the spectrometer into the safety cylinder, connected to a CO$_2$ supply, and pressurized stepwise up to a total pressure of 130 bar with CO$_2$ at room temperature.

Summary and Conclusion

In the present work, the iridium-catalyzed hydrogenation of imines was used as a chemical probe to evaluate systematically the potential of ionic liquid/supercritical CO$_2$ reaction media for multiphase catalysis. It is demonstrated that the application of the biphasic system leads to activation, tuning, and immobilization of the catalyst system that would be impossible in classical organic solvent systems or in either of the two unconventional media separately.

Using imine hydrogenation as a benchmark transformation, it was possible to rationalize the observed effects on the basis of the physicochemical and molecular characteristics of the reaction system. Whereas the unique properties of the supercritical phase are particularly important for aspects such as mass transfer, gas availability, and product isolation, the ionic environment of the catalyst phase provides beneficial molecular interactions with the cationic organometallic intermediates. Most intriguingly, certain disadvantages of one medium can be ameliorated through the complementary characteristics of the other one. Among the most striking examples for this paradigm is the significant increase of hydrogen solubility in the IL in the presence of compressed CO$_2$ that was quantified in this work by high-pressure NMR. Another example is the feeble solvent power of scCO$_2$ for cationic catalysts that is turned into an advantage as the catalyst is immobilized through a virtually quantitative partitioning into the IL phase.

In summary, the results presented in this study emphasize the remarkable potential of the IL/CO$_2$ biphasic system for the future development of multiphase catalysis. They provide also guidelines for how to exploit the characteristics of this system by focusing on certain benefits offered by the unique set of complementary properties. This type of information is required to assess the scope and limitations of individual techniques as the number of novel approaches for biphasic catalysis based on scCO$_2$ as the mobile phase is increasing ("cartridge catalysis").[28]

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