Enantioselective Hydrogenation of Trimethylindolenine in Ionic Liquids

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Dedicated to Prof. J. Bargon on the occasion of his 65th birthday.

Abstract: The enantioselective hydrogenation of trimethylindolenine (**1**) has been carried out in a variety of ionic liquids using an Ir-XYLIPHOS catalyst. Compared to the reaction in conventional organic media, slightly higher temperatures (50 °C) are required, which is mainly due to the higher viscosities of the ionic media. Under these conditions we were able to identify three reaction media that gave ees comparable to the conventional process in toluene with greatly reduced reaction time (15 h as opposed to 23 h for 100% conversion; 91% conversion after 8 h). The sensitivity of the reaction system towards oxygen was also reduced significantly.

Keywords: asymmetric catalysis; imine hydrogenation; ionic liquids; iridium; P ligands; XYLIPHOS

Introduction

In the last few years, ionic liquids have been established as neoteric solvents for organic synthesis.[1] Their success for numerous applications originates mainly from the fact that their properties can be tuned to each and every specific reaction with little effort. Thus, ionic liquids are frequently called designer solvents: it seems obvious that for any given reaction a matching ionic liquid can be found which will promote the turnover towards higher yields, better selectivity, and so on. The main challenge that remains is to find the "right" one.

The enantioselective hydrogenation of imines is a synthetically valuable reaction, since it leads to chiral amine compounds which play a major role in natural product chemistry (such as α-amino acids). Many pharmaceuticals and crop protection agents contain chiral amine functionalities. Therefore, it would be beneficial and economically attractive to be able to perform this reaction easily and controllably in an enantioselective fashion. But although few industrial processes utilize this reaction step,[2] the reaction is far from being well understood and mastered for general application.[3] Major problems include limited choice of solvents (all of which are toxic and volatile), long reaction times, extremely high sensitivity of the reaction towards air, and poor reproducibility of yields and enantiomeric excesses. The use of ionic liquids as the solvent for imine hydrogenation is an obvious possibility to tackle these challenges. Most of these reaction media are non-toxic, all are non-volatile; they are quite polar which results in good solubility of the reaction components, and the right choice of a weakly coordinating anion can promote the activity of the catalyst. The ionic catalyst solution may be recycled and re-used, the solubility of hydrogen in these media can potentially be tuned,[4] and it has been shown that some reactions are less sensitive towards air when run in an ionic liquid.[5]

Results and Discussion

To be able to compare our results with an already established process, we chose the enantioselective hydrogenation of trimethylindolenine with Ir-XYLIPHOS as a test reaction (Figure 1).[6]

To judge the effects of the ionic liquid, a variety of ionic liquids with different physicochemical properties was synthesized according to known literature procedures[7–9] with slight modifications where necessary. Our "ionic liquid construction kit" consists of three basic building blocks that, taken together, form the ionic liquid: (a) the cation, (b) the substituent in the cation, and (c) the anion (cf. Figure 2). As cations, imidazolium- and pyridinium-based systems were used, since the imidazolium cation is quite C–H acidic[10,11] while pyridinium is not. In combination with either a short (butyl) or a long (decyl) alkyl substituent, lipophilic cation effects could be probed as well. As the anions, we decided for tetrafluoroborate, which is some kind of a "standard" anion in ionic liquid chemistry, but which is also known to be slightly unstable when in contact with water and to always con-

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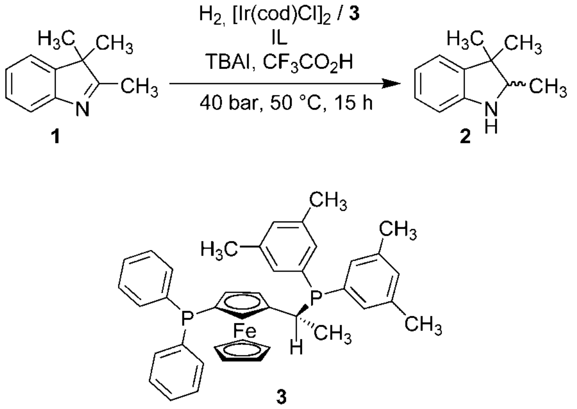

Figure 1. Enantioselective hydrogenation of trimethylindolenine.

Table 1. Enantioselective hydrogenation of **1** following the literature procedure.[6]

Entry	Solvent	Conversion [%]	ee [%][a]
1	Toluene[b]	100	87
2	Toluene	25	88
3	[bmim][BF_4]	18	n.d.
4	[bmpy][BF_4]	7	30
5	[C_{10}mim][BF_4]	30	83
6	[C_{10}mpy][BF_4]	10	59
7	[bmim][BTA]	1	n.d.
8	[bmpy][BTA]	2	n.d.
9	[C_{10}mim][BTA]	65	77

Reaction conditions: 0.4% catalyst loading, 40 bar H_2, 30 °C, 23 h.

[a] (*S*)-enantiomer.

[b] Result taken from Blaser et. al.[6]

tain traces of fluoride anions.[12–14] The second anion of choice was bis(trifluoromethylsulfonyl)amide (BTA), which is air- and moisture-stable and gives ionic liquids with low viscosities. Additionally, we expected the grade of fluorination in the anion to have an effect on hydrogen solubility in these media.

We ended up with a basic set of eight different ionic liquids (four different cations combined with two anions; Figure 2). The result of the first screening of these media in the enantioselective imine hydrogenation under the reaction conditions that were used by Blaser et. al.[6] are shown in Table 1. The only difference to the literature was that our reaction mixture came shortly into contact with air while transferring it into the autoclave. Entries 1 and 2 demonstrate that under these conditions we were unable to reproduce the literature results, which was not too surprising since the reaction was known to be extremely sensitive towards oxygen. The other results from Table 1 show comparably bad results – only 65% conversion in the case of [C_{10}mpy][BTA] and almost none in all the other cases.

It is noteworthy that all of the ionic liquids are highly viscous at 30 °C when used in pure and water-free form. For hydrogenation reactions, this might be the limiting factor because of strongly limited gas transfer into the solution.[15] Thus, since the viscosity of ionic liquids is strongly temperature-dependent, we chose to raise the reaction temperature from 30 to 50 °C. As a result, we were able to shorten the reaction time from 23 h to 15 h. Additionally, the reactions were now prepared strictly oxygen-free in a drybox. Under these conditions, we were not only able to reproduce the literature results in toluene (Table 2, entry 1), but the reactions in ionic liquids were substantially faster. At this point, though, we had still some difficulties to obtain reproducible results in different runs (cf. Table 2, entries 3–8).

Constant reproducibility was finally achieved by allowing more time for catalyst preformation. Up to this point, we had mixed all reaction components in the ionic liquid directly before the reaction was started as described by Blaser et. al.[6] Now, only the catalyst components (iridium source, ligand) and the promoters (acid, TBAI) were added and given time (1 h) to form the active precatalyst (we later found that 0.5 h formation time was also sufficient). The substrate was added directly before

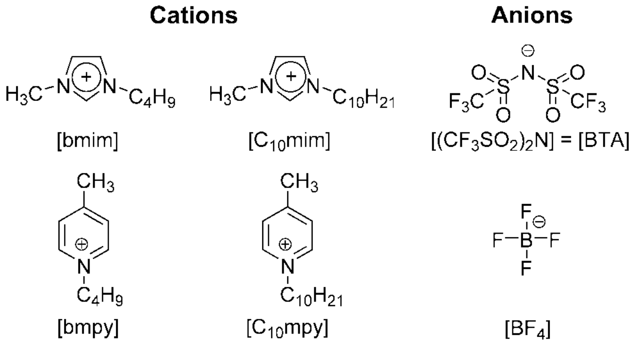

Figure 2. Cation and anion combinations that were used as ionic liquid media for the enantioselective hydrogenation of imines.

Table 2. Enantioselective hydrogenation of **1** at 50 °C under strictly anaerobic conditions.

Entry	Solvent	Conversion [%]	ee [%][a]
1	Toluene[b]	100	90
2	Toluene[c]	98	86
3	[bmim][BF_4]	100	56
4	[bmim][BF_4]	45	56
5	[bmim][BTA]	100	70
6	[bmim][BTA]	91	68
7	[C_{10}mim][BTA]	100	76
8	[C_{10}mim][BTA]	100	72

Reaction conditions: 0.4% catalyst loading, 40 bar H_2, 50 °C, 15 h.

[a] (*S*)-enantiomer.

[b] 23 h reaction time, 30 °C.

[c] 15 h reaction time, 50 °C.

the reaction was started. The result of this screening is shown in Table 3.

Under these reaction conditions, four ionic liquids with a conversion of 100% could be identified, three of them with ees of 80% and above. It is noteworthy to say that the best result (in [C_{10}mim][BF_4]) is comparable to the best examples in toluene that are known from the literature in terms of yield and ee. The reaction time was significantly shorter (15 h as opposed to 23 h), while the toluene reaction at the same conditions yielded 98% conversion with a slight drop in ee. Comparing the different ionic liquids, a more lipophilic medium (with a long alkyl chain in the cationic component) seems to promote this reaction while the choice of anion seems to have little effect.

To test the performance of the ionic liquid system, two more sets of reactions have been carried out. First, we repeated the reaction in the three reaction media that had worked best so far (Table 4). The most enantioselective reaction of the 15 h screening (cf. Table 3) was not the fastest one – in terms of speed, entries 1 and 2 changed places, but the ees were identical to those of prior reactions. Quite surprising was the fact that the reaction in [C_{10}mim][BTA], also giving 100% conversion after 15 h, showed a major induction period and thus had barely started after 8 h.

Finally, we wondered if the reaction in ionic liquids was really as sensitive to air as the reaction in toluene or if the initially bad results (Table 1) were due to the preparation of the catalyst. We repeated experiments 1 and 2 from Table 3 in a fashion that, like in our very first screening, the transfer of the readily prepared reaction mixture into the autoclave was done with short contact to air. The results are given in Table 5.

In comparison to oxygen-free transfer in the drybox, a slight drop in conversion as well as in selectivity was found. Nonetheless, the drop is far from being as dramatic as in the reaction in toluene. This effect might well be due to the higher viscosities of the ionic media, but it shows that the reaction is more robust when run in ionic liquids.

Table 3. Enantioselective hydrogenation of **1** with preformed catalyst.

Entry	Solvent	Conversion [%]	ee [%][a]
1	[C_{10}mim][BF_4]	100	86
2	[C_{10}mpy][BTA]	100	82
3	[C_{10}mim][BTA]	100	80
4	[bmpy][BTA]	100	72
5	[C_{10}mpy][BF_4]	91	74
6	[bmim][BTA]	79	74
7	[bmpy][BF_4]	75	74
8	[bmim][BF_4]	51	58

Reaction conditions: 0.4% catalyst loading, 40 bar H_2, 50 °C, 15 h.
[a] (*S*)-enantiomer.

Table 4. Enantioselective hydrogenation of **1** after 8 h reaction time.

Entry	Solvent	Conversion [%]	ee [%][a]
1	[C_{10}mpy][BTA]	94	82
2	[C_{10}mim][BF_4]	56	86
3	[C_{10}mim][BTA]	30	n.d.

Reaction conditions: 0.4% catalyst loading, 40 bar H_2, 50 °C, 8 h.
[a] (*S*)-enantiomer.

Table 5. Enantioselective hydrogenation of **1** after transfer of the reaction mixture to the autoclave through air.

Entry	Solvent	Conversion [%]	ee [%][a]
1	[C_{10}mim][BF_4]	98	84
2	[C_{10}mim][BTA]	92	76

Reaction conditions: 0.4% catalyst loading, 40 bar H_2, 50 °C, 15 h.
[a] (*S*)-enantiomer.

Conclusions

The enantioselective hydrogenation of imines can be readily run in suitable ionic liquids. The reaction time is reduced from 23 h for 100% conversion in toluene to less than 15 h in [C_{10}mim][BF_4] with no loss of selectivity, although the ionic media require slightly higher reaction temperatures, mainly due to their high viscosities. In [C_{10}mpy][BTA], the reaction had reached 94% conversion after only 8 h.

Experimental Section

Preparation of Ionic Liquids Containing Halide Anions

The halide ionic liquids were synthesized by direct alkylation of *N*-methylimidazole or 4-methylpyridine, respectively at 80 °C. The crude product was dissolved in acetonitrile and crystallized by adding dropwise to toluene at 0 °C. The product was dried in high vacuum at 60 °C.

Preparation of Ionic Liquids Containing the Tetrafluoroborate Anion

The corresponding bromide or chloride was dissolved in acetone. The solution was stirred at room temperature for 24 h with one equivalent of sodium tetrafluoroborate. The white solid which precipitated during the reaction (NaBr or NaCl) was removed by filtration. The solvent was removed under reduced pressure and the crude product was washed with small amounts of water until the extract was halide-free. Activated charcoal was added and the mixture was stirred for 24 h. The ionic liquid was dissolved in dichloromethane and the charcoal was removed by filtration. The solution was filtered through aluminium oxide. The solvent was evaporated and the product was dried at 60 °C in high vacuum.

Preparation of Ionic Liquids Containing the Bis-Triflic Amide Anion

The corresponding bromide or chloride was dissolved in water and heated to 70 °C. One equivalent of lithium bis-triflic amide was dissolved in water and added dropwise. The reaction mixture was stirred for one hour at 70 °C then for 24 h at room temperature. The product formed a second phase which was separated off and washed with small amounts of water until the extract was halide-free. Activated charcoal was added and the mixture was stirred for 24 h. The product was dissolved in dichloromethane and the charcoal was removed by filtration. The solution was filtered through aluminium oxide. The solvent was removed under reduced pressure and the product was dried at 60 °C in high vacuum.

Typical Procedure for Enantioselective Hydrogenation of Trimethylindolenine

The ionic liquid (1 mL) was heated to 60 °C in high vacuum for 4 h to remove water and dissolved oxygen. During this time the IL was frequently ventilated with argon and evacuated again. Under an argon atmosphere 0.8 mg (1.19 μmol, 0.2 mol%) $[Ir(cod)Cl]_2$, 1.6 mg (2.51 μmol, 0.4 mol%) (*R*)-(*S*)-XYLIPHOS **3**, 2.4 mg (6.5 μmol, 1.05 mol%) tetrabutylammonium iodide (TBAI) and 10 μL (14.8 mg, 0.13 mmol, 20.9 mol%) trifluoroacetic acid were added. The mixture was stirred vigorously for 1 h. 99.5 μL (98.7 mg, 0.62 mmol) of substrate **1** were added and the solution was transferred into the autoclave under a dry argon atmosphere (glovebox). The pressure vessel was filled with 20 bar of hydrogen and vented back three times, then set under 40 bar and heated to 50 °C. After 15 h the solution was extracted three times with 5 mL *n*-pentane each. Conversion and enantiomeric excess were determined by chiral GC analysis with bromobenzene as internal standard (Column: Chrompack WCOT-FS CP-Chirasil-Dex CB, $T = 90\,^\circ C$, retention times: 59.9, 62.1 min).

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