Asymmetric Hydrogenation and Catalyst Recycling Using Ionic Liquid and Supercritical Carbon Dioxide

Richard A. Brown,[†] Pamela Pollet,[‡] Erin McKoon,[†]
Charles A. Eckert,[§] Charles L. Liotta,[‡] and Philip G. Jessop*,[†]

Department of Chemistry, University of California Davis, California 95616-5295
Schools of Chemistry and Chemical Engineering Georgia Institute of Technology, Atlanta, Georgia 30332-0100

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Asymmetric hydrogenation of tiglic acid catalyzed by $Ru(O_2CMe)_2$((*R*)-tolBINAP) in wet ionic liquid ([bmim]PF_6 with added water, bmim = 1-*n*-butyl-3-methylimidazolium) gave 2-methylbutanoic acid with high enantioselectivity and conversion. The product was extracted with supercritical CO_2 ($scCO_2$) giving a clean separation of product and catalyst. The catalyst/ionic liquid solution was then reused repeatedly without significant loss of enantioselectivity or conversion.

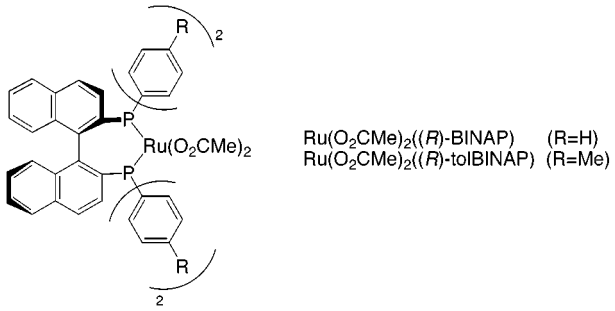
Biphasic solvent systems for homogeneous catalysis typically consist of a lower phase solvent that dissolves the catalyst and an upper phase solvent that carries the substrate into the reaction vessel and the products out. The ideal biphasic solvent system would consist of a lower solvent that is able to dissolve both the homogeneous catalyst and the substrate (for optimum rates) and an upper solvent that is environmentally friendly, can dissolve the substrate and products, can be easily removed from the products, and has negligible ability to extract the lower solvent or the catalyst. Aqueous/organic[1] or fluorous/organic[2] biphasic systems do not meet the environmentally benign requirements, fluorous/organic systems also have problems with partial solubility of the catalyst in the organic phase, and H_2O/$scCO_2$ systems[3] can have problems with pH.[3b] Finally, all of these systems when used for asymmetric catalysis employ sulfonated or fluorinated chiral ligands, which can be synthetically challenging. We have found that an ionic liquid/$scCO_2$ biphasic system, which meets all of these requirements without the need for a sulfonated or fluorinated ligand, can be used for asymmetric catalysis followed by facile product/catalyst separation and catalyst recycling.

Supercritical carbon dioxide[4,5] has been used as an alternative medium for a number of asymmetric hydrogenations,[6] although catalyst solubility, especially with the complexes of the highly aromatic ligand BINAP, has been a problem.[6a] Ionic liquids have not received as much attention until recently, but there has been an initial report by Monteiro et al. of their use as a solvent for enantioselective hydrogenation.[7] The possibility of combining ionic liquids and $scCO_2$ for chemical separations was first suggested by Blanchard et al.[8] It is our aim to demonstrate that the combination of ionic liquids and $scCO_2$ for catalysis can have substantial advantages over the use of either type of solvent alone.

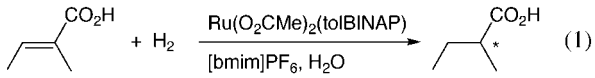
Table 1. The Asymmetric Hydrogenation of Tiglic Acid in [bmim]PF_6/H_2O Followed by Extraction with $scCO_2$ (Enantioselectivity and Conversion as a Function of the Number of Cycles)[a]

run no.	catalyst solution	% ee	% conversion
1	fresh	85	99
2	recycled from run 1[b]	90	98
3	recycled from run 2[b]	88	97
4	recycled from run 3[b]	87	98
5	recycled from run 4[b,c]	91	97

[a] Reaction conditions as described in ref 9. [b] Before each subsequent run, 1.1 mmol of tiglic acid was added to the catalyst/IL solution in the vessel. [c] The last reaction cycle was not stirred.



We found that the hydrogenation of tiglic acid using $Ru(O_2CMe)_2$((*R*)-tolBINAP) proceeds with good selectivity and excellent yield in [bmim]PF_6 (hereafter referred to as ionic liquid or IL) with some water added (eq 1, Table 1). The product was extracted from the IL by $scCO_2$.[9] Fortunately, the ionic liquid has no solubility whatsoever in $scCO_2$.[8] Equally fortunately, the tolBINAP complex is far more soluble in the IL than it is in the $scCO_2$, so that there is no tendency of the $scCO_2$ to extract the complex. One then obtains essentially pure product from the CO_2 effluent, contaminated with no ionic liquid or catalyst, and containing only some H_2O. The catalyst solution left behind in the vessel can be reused for at least four more runs. The ee (enantiomeric excess) of the product using recycled catalyst was higher than that obtained using fresh catalyst, and the ee and conversion remained high through the total of five cycles.



(1)

We further tested the hydrogenation of tiglic acid in [bmim]-PF_6 to explore the parameters which influence the enantioselectivity (Table 2). These tests were performed on a smaller scale than those in Table 1, and were not followed by $scCO_2$ extraction

* To whom correspondence should be addressed. Tel. (530) 754−9426. Fax. (530) 752−8995. email: jessop@chem.ucdavis.edu.
[†] University of California, Davis.
[‡] Georgia Institute of Technology, School of Chemistry.
[§] Georgia Institute of Technology, School of Chemical Engineering.

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(9) **Method for hydrogenation and extraction:** The [bmim]PF_6 (30 g, degassed, density 1.36 g/mL), water (10 mL), $Ru(O_2CMe)_2$(*R*-tolBINAP) (22 μmol), tiglic acid (1.1 mmol), and a stir bar were combined in a 160 mL steel vessel under nitrogen atmosphere. The reaction was performed over 18 h under 5 bar of H_2 at 25 °C. The vessel was then warmed to 35 °C and $scCO_2$ (175 bar, 1 mL/min) was bubbled through the solution and vented through a JASCO back-pressure regulator into a cold trap (approximately 18 h). Yields were higher (90% recovery) if the trap contained cold ^{i}PrOH. After several hours of extraction, the CO_2 flow was stopped, and the gas was vented from the vessel. The contents of the trap were analyzed by chiral capillary GC. More tiglic acid (1.1 mmol) was added to the ionic liquid solution remaining in the vessel, followed by H_2 gas. This was the start of the second reaction cycle.

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Table 2. The Asymmetric Hydrogenation of Tiglic Acid in [bmim]PF_6 Catalyzed by $Ru(O_2CMe)_2$(*R*-tolBINAP)[a]

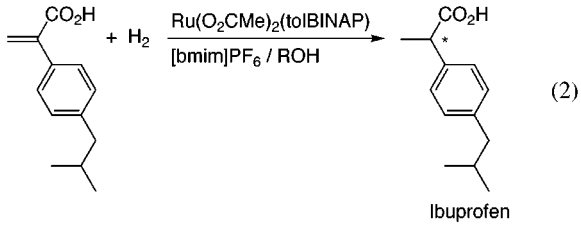
cosolvent (mL)	$P(H_2)$, bar	IL, g	additive	% ee	% conv
none	5	1.6		88	100
none	5	1.6	$MgSO_4$, 100 mg	88	98
H_2O (0.4)	8	1.6		88[b]	100
H_2O (0.4)	100	1.6		25	100
H_2O (0.8)	5	0		67	27
H_2O (0.8)	5	1.6	$AgPF_6$, 52 mg	81	9
H_2O (0.8)	5	1.6	*R*-tolBINAP, 1.8 mg	92	100
H_2O (0.8)	100	1.6		64	100
^{i}PrOH (0.8)	5	1.6		40	100
^{i}PrOH (0.8)	100	1.6		29	100
^{i}PrOH (2.0)	8	0		48	100

[a] Conditions: 25 °C, 1.1 μmol of $Ru(O_2CMe)_2$(*R*-tolBINAP), 1.6 g of [bmim]PF_6, S/C = 40 in a 1 dram vial held upright in a 160 mL vessel. Product extracted from IL with ^{i}PrOH. [b] Average of two runs.

of the product. At low H_2 pressure, the amount of water added had no effect on the ee; even adding a drying agent ($MgSO_4$) had no effect. However, at higher H_2 pressures, larger amounts of water improved the ee. Regardless of H_2 pressure, far greater enantioselectivity was observed when water rather than 2-propanol was used as the cosolvent in the IL. Using H_2O *instead* of IL gave poor enantioselectivity and poor conversion. Adding $AgPF_6$ in an attempt to trap trace chloride ions in the IL resulted in a drastic lowering of the conversion. The addition of excess (*R*)-tolBINAP to the catalyst in IL increased the enantioselectivity to 92%. This ee is higher than that reported for the same reaction in aqueous/organic biphasic media using a PEG-bound Ru BINAP catalyst (83% ee at 4 bar of H_2 in H_2O/ethyl acetate).[10]

The hydrogen concentration dependence of asymmetric catalysis with ruthenium BINAP complexes, usually in methanol solution, is known to depend on the substrate.[11] The substrates can conveniently be grouped into two categories: class I substrates such as atropic acid are hydrogenated in higher enantioselectivity at high H_2 concentration while class II substrates such as tiglic acid are hydrogenated in higher enantioselectivity at low H_2 concentration. In practice, the H_2 concentration in the MeOH is a function of the H_2 pressure[11] and the stir rate.[12] The finding by Monteiro et al.[7] that the hydrogenation of atropic acid (a class I substrate) in [bmim]BF_4/ROH mixtures has H_2-pressure *independent* enantioselectivity was most surprising. We found that the H_2 pressure dependence that is normally observed for tiglic acid in MeOH was also observed in the wet IL. The optimum ee was found at low H_2 pressure. The trend in IL/^{i}PrOH was similar but less pronounced.

The asymmetric hydrogenation of isobutylatropic acid (a class I substrate), giving the antiinflammatory drug ibuprofen, was also tested in IL: the enantioselectivity in wet ionic liquid was poor, but that in IL with methanol added was 85% at 100 bar of H_2 (eq 2). The enantioselectivity observed here is higher than that



(2)

reported for the same reaction in aqueous/organic biphasic media using the PEG-bound Ru BINAP catalyst (64% ee in H_2O/ethyl acetate, 47% in H_2O/toluene).[10] The complete results with isobutylatropic acid and other substrates in IL and $scCO_2$ will be published separately.

It is not clear why H_2O was such an effective cosolvent for the hydrogenation of tiglic acid while it was poor for the hydrogenation of isobutylatropic acid. The reason could be the differing solubilities of the acids in water, but is more likely to be the high solubility of H_2 in ^{i}PrOH. At 25 °C, the mole fraction solubility of H_2 in ^{i}PrOH is 19 times greater than that in H_2O.[13] If the same trend in H_2 solubility is found in IL/^{i}PrOH vs IL/H_2O mixtures, then class I substrate hydrogenations, which are more enantioselective when H_2 concentrations are high, would be expected to be more enantioselective in IL/^{i}PrOH than in IL/H_2O, as observed.

The phase behavior in these systems is complicated. IL and H_2O are not miscible in the proportions used (60% IL by volume). The partitioning of the substrates between the two liquids has not been studied, although benzoic acid is known to partition primarily into the IL phase in a IL/H_2O mixture (pH 6.5).[14] IL and ^{i}PrOH are also not miscible in the proportions used (60% IL by volume), although they become miscible if a small amount of water is added, a counter-intuitive result considering the immiscibility of IL and H_2O. IL and MeOH are miscible in the proportions used.

In conclusion, the asymmetric hydrogenation of tiglic acid proceeds readily in wet IL, with the H_2 pressure dependent enantioselectivity that is normally observed in MeOH. At least for tiglic acid, there is no need to add an alcohol or other organic solvent other than the IL itself, nor is there a need to prepare a fluorinated or water-soluble derivative of the catalyst. The products can be extracted from the IL by $scCO_2$, with no concomitant extraction of the IL or the asymmetric catalyst. The IL/catalyst solution can be reused several times without significant loss of enantioselectivity or activity.

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