

Asymmetric hydrogenation of 2-arylacrylic acids catalyzed by immobilized Ru-BINAP complex in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate molten salt

Adriano L. Monteiro, Fabiano K. Zinn, Roberto F. de Souza and Jairton Dupont *

Grupo de Catálise, Instituto de Química, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves, 9500, CEP 91501-970, Porto Alegre, Brazil

Abstract: The $[\text{RuCl}_2\text{-(S)-BINAP}]_2\cdot\text{NEt}_3$ catalyst precursor dissolved in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate molten salt is able to hydrogenate 2-arylacrylic acids (aryl=Ph or 6-MeO-naphthyl) with enantioselectivities similar or higher than those obtained in homogeneous media. Moreover, the hydrogenated products can be quantitatively separated from the reaction mixture and the recovered ionic liquid catalyst solution can be reused several times without any significant changes in the catalytic activity or selectivity.
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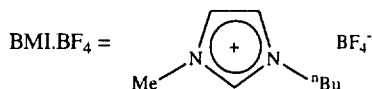
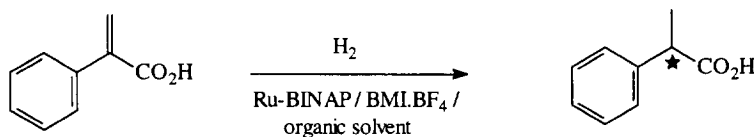
The asymmetric hydrogenation reaction of C=C bonds catalyzed by transition metal complexes is one of the most studied reactions of homogeneous catalysis.¹ For example, chiral ruthenium catalysts have been successfully used in the enantioselective synthesis of 2-arylpropionic acids², which represent an important class of anti-inflammatory³ and analgesic drugs. In this respect, (S)-Naproxen was readily obtained in 92% yield and 97% ee from the asymmetric hydrogenation of α -(methoxy-naphthyl)acrylic acid catalyzed by [(S)-BINAP]Ru(OAc)₂. However, in these homogeneous catalytic reactions, the recovery of the catalyst and the separation of the products from the reactants are still troublesome. One approach to solve this basic problem is the immobilization of water soluble organometallic complexes in a thin aqueous (SAPC=supported aqueous phase catalysis)⁴ or organic hydrophilic (SLP=supported liquid phase catalysis)⁵ film on a high-surface area hydrophilic support such as silica or controlled-pore glasses. The resulting catalyst is placed in contact with a water-immiscible liquid phase containing the substrate, however, this technique needs a ligand modification such as sulfonation of BINAP. We⁶ and others⁷ have recently introduced another approach to the immobilization of homogeneous catalysts by the use of room temperature molten salts. In most of the cases, the transition metal complexes are soluble in these ionic liquids and the organic substrates are immiscible. In this paper, we present results from the asymmetric hydrogenation of 2-arylacrylic acids in a system constituted of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate salt (BMI.BF₄) and isopropanol with the ruthenium catalyst precursor immobilized in an ionic liquid phase (Table 1). Moreover, the hydrogenated product can be quantitatively separated from the reaction mixture with enantioselectivities similar or higher than those obtained from a homogenous system.

* Corresponding author. Email: dupont@if.ufrgs.br

Table 1. Asymmetric hydrogenation of 2-phenylacrylic acid giving 2-phenylpropionic acid^{8*}

Entry	catalyst	cosolvents	Subs/Cat	P (atm)	Conv. (%)	% ee (conf.)
1	<i>in situ</i> Ru-(S)-BINAP	MeOH	40	35	100	62 (S)
2	[RuCl ₂ -(S)-BINAP] ₂ .NEt ₃	MeOH	80	25	100	83 (S)
3	[RuCl ₂ -(S)-BINAP] ₂ .NEt ₃	<i>i</i> -PrOH	80	25	100	64 (S)
4	<i>in situ</i> Ru-(R)-BINAP	MeOH / BMI.BF ₄	40	25	100	86 (R)
5	<i>in situ</i> Ru-(R)-BINAP	<i>i</i> -PrOH / BMI.BF ₄	80	35	99	69 (R)
6	recycle of entry 5	<i>i</i> -PrOH / BMI.BF ₄	80	22	99	72 (R)
7	recycle of entry 6	<i>i</i> -PrOH / BMI.BF ₄	80	25	99	77 (R)
8	recycle of entry 7	<i>i</i> -PrOH / BMI.BF ₄	80	25	99	70 (R)
9	[RuCl ₂ -(S)-BINAP] ₂ .NEt ₃	<i>i</i> -PrOH / BMI.BF ₄	20	50	100	78 (S)
10	recycle of entry 8	<i>i</i> -PrOH / BMI.BF ₄	20	75	100	84 (S)
11	recycle of entry 9	<i>i</i> -PrOH / BMI.BF ₄	20	25	90	79 (S)
12	recycle of entry 10	<i>i</i> -PrOH / BMI.BF ₄	20	100	95	67 (S)
13	[RuCl ₂ -(S)-BINAP] ₂ .NEt ₃	<i>i</i> -PrOH / BMI.BF ₄	400	25	100	72 (S)

* For reaction procedures and analysis see 8. Reaction conditions : [Ru]= 0.034 mmol; ROH= 30 mL; BMI.BF₄= 3 mL; time= 20 h.

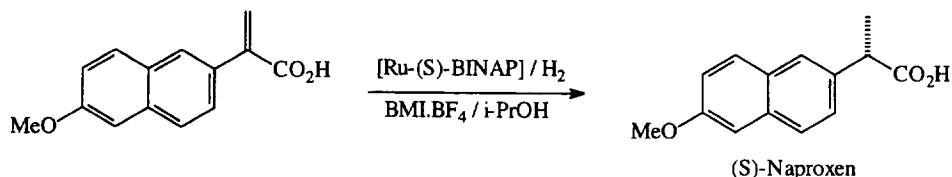


In order to obtain a simplified system, the hydrogenation reaction has been performed with an *in situ* formation of catalyst by mixing [Ru(COD)Cl₂], BINAP and NEt₃ in cosolvents under H₂ pressure⁹. Under these homogeneous conditions, the reaction in methanol affords (S)-2-phenylpropionic acid with 62% ee (entry 1). However, under the same reaction conditions, the preformed commercially available [RuCl₂-(S)-BINAP]₂.NEt₃ (Strem) in methanol gives the hydrogenated product with 83% ee (entry 2) and, in isopropanol, 64% ee (entry 3).

The mixture of methanol with BMI.BF₄ improves the enantioselectivity (86%, entry 4) but a homogeneous phase is formed at the end of the reaction. However, in isopropanol/BMI.BF₄ (entry 5) a two-phase mixture is obtained at the end of the reaction with similar enantioselectivities. Practically, all the hydrogenated products have been found in the isopropanol phase that was separated by simple decantation. Furthermore, the recovered ionic liquid phase containing the catalyst can be reused several times without any significant changes in the catalytic activity and enantioselectivity (entries 6–8).

The extent of asymmetric induction has often been found to depend on the hydrogen pressure or concentration in catalyst solution¹⁰. Under the conditions studied here, however, such effects were not observed (entries 9–12). In almost all cases, there are no significant differences in the catalytic activity and selectivity between *in situ* and preformed Ru-BINAP catalyst offering several practical and economical advantages.

This catalytic system was also successful applied to the hydrogenation reaction (75 atm, RT, 20 h) of 2-(6-methoxy-2-naphthyl)acrylic acid to give quantitatively (S)-Naproxen in 80% ee.



In summary, our results show that the asymmetric hydrogenation of 2-arylacrylic acids can be performed in presence of *in situ* or preformed Ru-BINAP catalyst precursors immobilized in an ionic liquid phase with similar or slightly increased optical yields in comparison with the homogeneous reaction. At the end of the reaction the hydrogenated 2-arylpropionic acid in isopropanol can be separated by simple decantation and the ionic catalyst solution can be recycled without significant changes in activity and selectivity. A detailed study about the optimization and the extension to hydrogenations of other prochiral unsaturated substrates are in progress.

Acknowledgements

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- (a) ***In situ* formation of the catalyst:** In a 100 mL-stainless steel autoclave under argon [Ru(COD)Cl₂]_n (0.035 mmol), BINAP (0.035 mmol), NEt₃ (0.175 mmol), *n*-butylmethylimidazolium tetrafluoroborate (3 mL), and isopropanol (30 mL) were placed. The reactor was pressurized with 25 atm of H₂ and the reaction mixture was stirred at room temperature for 4 h. (b) **Hydrogenation procedure:** After the *in situ* formation of the catalyst, the reactor was depressurized and a solution of 2-phenylpropionic acid in 5 mL of isopropanol was added. Repressurization with H₂ at the desired pressure was followed by stirring at room temperature for 20 h. The organic phase (upper phase) was separated and analyzed by gas chromatography and the ionic catalyst phase was reused. (c) **Quantitative analysis:** The mixture of hydrogenated and not hydrogenated acids are transformed into the methyl esters. The conversion and enantiomeric excess were determined on a Varian-CX-3400 GC equipped with a chiral column OV 1701 20heptakis(2,6-di-O-methyl-3-O-pentyl)- β -cyclodextrin. The absolute configuration was assigned by comparison with authentic samples of the esters of the (R)- and (S)-phenylpropionic acids.
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