

## Catalytic asymmetric hydrogenation of aromatic ketones in room temperature ionic liquids

Helen L. Ngo, Aiguo Hu and Wenbin Lin\*

Department of Chemistry, CB#3290, University of North Carolina, Chapel Hill, NC 27599, USA

Received 6 October 2004; revised 24 November 2004; accepted 29 November 2004

**Abstract**—Polar bisphosphonic acid-derived Ru(BINAP)(DPEN)Cl<sub>2</sub> precatalysts were synthesized and immobilized in room temperature ionic liquids (RTILs) for asymmetric hydrogenation of aromatic ketones with ee values of up to 98.7%. The performance of the Ru catalysts is highly dependent on the nature of imidazolium ILs. For the imidazolium ILs without acidic protons, both ILs and Ru catalysts were recycled by simple extraction and reused. Such a simple immobilization approach also prevented the leaching of Ru (and Ru catalysts) into the chiral secondary alcohol products, and should prove desirable for the production of pharmaceutical intermediates that are free from metal contaminants.  
© 2004 Elsevier Ltd. All rights reserved.

Catalytic asymmetric hydrogenation has been established as one of the most important methods for the synthesis of chiral molecules over the past three decades.<sup>1</sup> Elegant work by Noyori et al. has recently demonstrated the efficient synthesis of a variety of chiral secondary alcohols via the asymmetric hydrogenation of simple ketones by the Ru(XylBINAP)(DAIPEN)Cl<sub>2</sub> (XylBINAP is (*R*)-2,2'-bis[bis(3,5-dimethylphenyl)phosphino]-1,1'-binaphthalene and DAIPEN is (2*R*)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) precatalyst via an interesting catalytic pathway.<sup>2</sup> Compared to heterogeneous catalysts widely used for the production of commodity chemicals, homogeneous asymmetric catalysts are however often very expensive and difficult to recycle and reuse. Immobilization of homogeneous asymmetric catalysts on solid supports or liquid biphasic systems represents an interesting approach to catalyst recycle and reuse.<sup>3</sup> Room temperature ionic liquids (RTILs) have recently been explored as interesting alternatives to organic solvents as reaction media because they are environmentally benign and are easy to prepare and modify to impart desirable characteristics.<sup>4</sup> These features particularly make RTILs ideal solvents for the synthesis of high-value chiral organic compounds via catalytic processes. In ideal scenarios, not only high enantioselectivity can be obtained but also both ILs

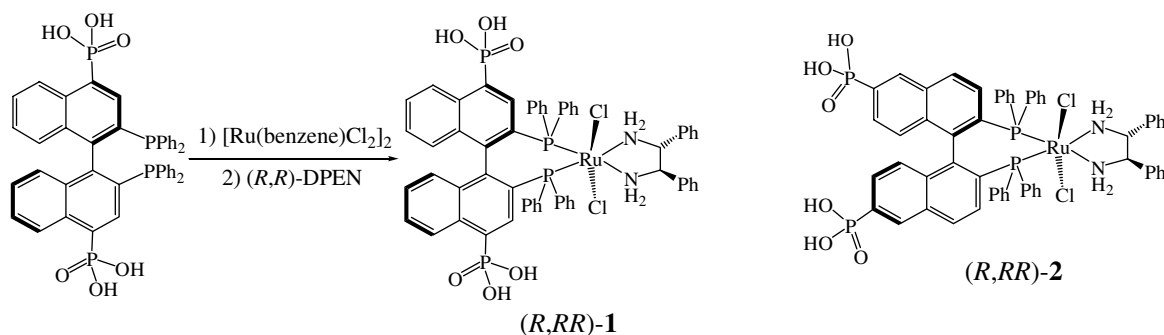
and asymmetric catalysts can be recycled and reused.<sup>5</sup> Herein we wish to report the immobilization of polar bisphosphonic acid-derived Ru(BINAP)(DPEN)Cl<sub>2</sub> precatalysts (DPEN is (*R,R*)-1,2-diphenylethylenediamine) in RTILs for enantioselective hydrogenation of aromatic ketones.

Two polar Ru precatalysts [((*R*)-L<sub>1</sub>)Ru((*R,R*)-DPEN)Cl<sub>2</sub>], (*R,RR*)-**1**, and [((*R*)-L<sub>2</sub>)Ru((*R,R*)-DPEN)Cl<sub>2</sub>], (*R,RR*)-**2**, were synthesized according to our recently reported procedures<sup>5d,6</sup> by first treating 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-4,4'-bisphosphonic acid (L<sub>1</sub>) or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-6,6'-bisphosphonic acid (L<sub>2</sub>) with [Ru(benzene)Cl<sub>2</sub>]<sub>2</sub> followed by the addition of (*R,R*)-DPEN, respectively (Scheme 1).<sup>5,7</sup> These polar precatalysts were used for the catalytic studies with the hope of facilitating the immobilization of the catalysts in the IL phase by taking advantage of their insolubility in the solvents used to extract the chiral alcohol products. Three different imidazolium RTILs, *n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF<sub>4</sub>), *n*-butyl-3-methylimidazolium hexafluorophosphate (BMImPF<sub>6</sub>), and *n*-propyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (DMPIIm) were first used for this study (Scheme 2).

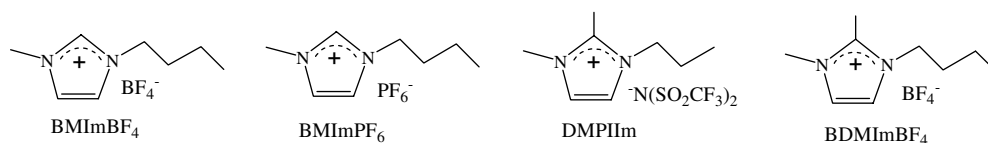
As shown in Table 1, a variety of aromatic ketones were hydrogenated with both (*R,RR*)-**1** and (*R,RR*)-**2** in a mixture of RTIL–isopropanol. Asymmetric hydrogenation reactions of aromatic ketones were carried out in

**Keywords:** Ionic liquid; Hydrogenation; Asymmetric catalysis.

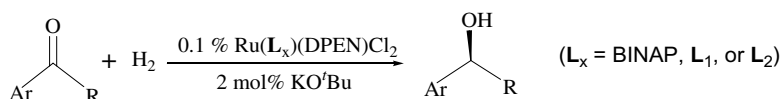
\* Corresponding author. Tel.: +1 919 962 6320; fax: +1 919 962 2388; e-mail: wlin@unc.edu



Scheme 1.



Scheme 2.

Table 1. Asymmetric hydrogenation of aromatic ketones<sup>a</sup>

Substrate	BINAP	L <sub>1</sub> ee% (conversion%)				L <sub>2</sub> ee% (conversion%)				L <sub>1</sub>
	IPA <sup>b</sup>	IPA <sup>b</sup>	BMImBF <sub>4</sub>	DMPIIm <sup>b</sup>	BMImPF <sub>6</sub>	IPA <sup>b</sup>	BMImPF <sub>4</sub>	DMPIIm <sup>b</sup>	BMImPF <sub>6</sub>	
Ar = 1-naphthyl, R = Me	96.7	99	98.5 (22)	98.5 98.3 <sup>c</sup>	93.9 (86)	96.6	94.3 (>99) 92.3 (5) <sup>c</sup>	97.3 96.7 <sup>c</sup>	97.9 (32)	92.9
Ar = 2-naphthyl, R = Me	68.9	97.9	96.3 (68)	96.7	80.5 (>99)	82.6	83.9 (>99)	80.1	—	—
Ar = Ph, R = Me	77.5	97.1	93.1 (49)	96.1	78.9 (97)	81.3	74.7 (77)	76.2	94.7 (66)	—
Ar = 4'-t-Bu-Ph, R = Me	83.9	99.1	98.7 (>99)	98.1	93.7 (>99)	91.6	94.1 (>99)	92.5	—	98.3
Ar = 4'-MeO-Ph, R = Me	52.3	95.4	96.7 (41)	93.3	75.9 (37)	80.7	81.9 (60)	78.7	46.1 (>99)	93.1
Ar = 4'-Cl-Ph, R = Me	54.5	95.8	93.3 (>99)	93.7	56.9 (93)	52.5	60.9 (>99)	53.4	92.9 (61)	89.2
Ar = 4'-Me-Ph, R = Me	72.9	97.4	95.9 (28)	96.5	64.7 (39)	78.1	81.1 (>99)	78.1	95.5 (45)	94.7
Ar = Ph, R = Et	83.3	94.2	91.7 (23)	92.9	82.7 (83)	83.0	82.1 (23)	83.8	86.9 (35)	—
Ar = Ph, R = cyclo-Pr	51.9	91	88.7 (11)	89.3	62.5 (44)	59.5	79.7 (23)	56.1	86.9 (15)	80.3

<sup>a</sup> The ee values were determined by chiral GC on a Supelco β-Dex 120 column. The absolute configurations of the products are identical to those obtained by the Ru[(R)-BINAP][(R,R)-DPEN]Cl<sub>2</sub> precatalyst.

<sup>b</sup> All the conversions were >99% unless indicated otherwise (inside the parentheses).

<sup>c</sup> 0.01 mol% Catalyst loading.

the presence of 0.1 mol% of precatalysts **1** and **2** in the presence of KO<sup>t</sup>Bu in both isopropanol and mixtures of RTIL–isopropanol.<sup>8</sup> Very high ee's (up to 98.7%) were obtained with precatalyst **1** in isopropanol and RTIL–isopropanol mixed solvents, and there is very small difference between ee's for the reactions in isopropanol alone and in RTIL–isopropanol. Precatalyst **2** afforded much lower ee's than **1**. The ee's afforded by **2** are comparable to those of the Ru(BINAP)-(DPEN)Cl<sub>2</sub> precatalyst. The greatly enhanced ee's observed for precatalyst **1** in RTIL–isopropanol mixed solvents are consistent with our earlier studies of homogeneous asymmetric hydrogenation of aromatic ketones by the catalysts derived from 4,4'-disubstituted BINAPs.<sup>6</sup> Our earlier single crystal X-ray diffraction studies indicated that the bulky substituents on the

4,4'-positions will have significant repulsive interactions with the aryl ring of the aromatic ketone in the disfavored transition state and thus lead to the enhancement of enantioselectivity.

The catalytic activities however vary greatly among the RTIL–isopropanol systems. Mixture solvents of BMImBF<sub>4</sub>/isopropanol or BMImPF<sub>6</sub>/isopropanol gave low activity for a number of substrates, while a mixture of DMPIIm and isopropanol gave high catalyst activity (complete conversions) for all the substrates studied. The low conversions observed for BMImBF<sub>4</sub> and BMImPF<sub>6</sub> could be a result of catalyst poisoning by BF<sub>4</sub><sup>-</sup> or PF<sub>6</sub><sup>-</sup> anions. Alternatively, the strong base co-catalyst can deprotonate the imidazolium ions to generate Arduengo carbenes, which can in turn poison the

catalyst. In contrast to  $\text{BMImBF}_4$  and  $\text{BMImPF}_6$ ,  $\text{DMPIIm}$  lacks acidic proton and  $\text{BF}_4^-$  and  $\text{PF}_6^-$  anions. To elucidate which mechanism is at work, we have carried out hydrogenation of aromatic ketones in a mixture of *n*-butyl-2,3-dimethylimidazolium tetrafluoroborate ( $\text{BDMImBF}_4$ ) and isopropanol. Interestingly, complete conversions were obtained for all the substrates tested under the same conditions (although with slightly lower ee's) (see the last column in Table 1). This control experiment supported the argument that the generation of Arduengo carbenes under catalytic conditions is responsible for the low catalytic activity observed for the reactions carried out in  $\text{BMImBF}_4$  and  $\text{BMImPF}_6$ . This work thus shows that the nature of RTILs can have a significant influence on their performance in catalytic reactions.

We have also demonstrated that both  $\text{DMPIIm}$  and catalyst **1** can be recycled and reused several times for asymmetric hydrogenation of 1-acetonaphthone in a mixture of  $\text{DMPIIm}$ /isopropanol.<sup>9</sup> With 0.1 mol% catalyst loading, 1-acetonaphthone was hydrogenated at 98.5% ee and 100% conversion, 98.1% ee and 100% conversion, 95.9% ee and 92% conversion, 94.5% ee and 40% conversion, 93.1% ee and 32% conversion, and 92.9% ee and 32% conversion, for six consecutive runs. Direct current plasma (DCP) spectroscopy further showed that no appreciable leaching of Ru occurred during the extraction of organic products. We estimated from DCP experiments that less than 0.01% of the Ru catalyst has leached into the chiral alcohol phase from the  $\text{DMPIIm}$  phase.

In summary, we have successfully applied polar phosphonic acid-derived Ru(BINAP)(DPEN) $\text{Cl}_2$  systems for asymmetric hydrogenation of aromatic ketones in RTILs with high ee's. Both RTIL and RTIL-immobilized catalysts were recycled and reused with no appreciable leaching of Ru into the chiral alcohol products. We believe that immobilization of homogeneous asymmetric catalysts in RTILs represents an interesting approach toward catalyst recycle and reuse and preventing the leaching of toxic metals into the organic products.

### Acknowledgements

We acknowledge financial support from NSF (CHE-0208930). We thank Dr. Allen F. Glazner for help with DCP experiments and Covalent Associates for supplying  $\text{DMPIIm}$ . W.L. is an Alfred P. Sloan Fellow, an Arnold and Mabel Beckman Young Investigator, a Cottrell Scholar of Research Corp, and a Camille Dreyfus Teacher-Scholar.

### References and notes

- (a) Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3–13; (b) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15–32; (c) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952; (d) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
- (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675; (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417; (c) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529; (d) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511; (e) Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508; (f) Doucet, H.; Okhuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703.
- (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (b) Fan, Q. H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385.
- (a) Wasscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (c) Dupont, J.; De Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
- (a) Ngo, H. L.; Hu, A.; Lin, W. *Chem. Commun.* **2003**, *15*, 1912; (b) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501; (c) Berthod, M.; Joerger, J.-M.; Mignani, G.; Vaultier, M.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2219; (d) Branco, L. C.; Afonso, C. A. M. *J. Org. Chem.* **2004**, *69*, 4381; (e) Cordova, A. *Tetrahedron Lett.* **2004**, *45*, 3949; (f) Lee, S. G.; Zhang, Y. J.; Piao, J. Y.; Yoon, H.; Song, C. E.; Choi, J. H.; Hong, J. *Chem. Commun.* **2003**, 2624; (g) Branco, L. C.; Afonso, C. A. M. *Chem. Commun.* **2002**, 3036; (h) Song, C. E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun.* **2000**, 1743.
- Hu, A.; Ngo, H. L.; Lin, W. *Org. Lett.* **2004**, *6*, 2937.
- A typical procedure for the synthesis of Ru precatalysts: a mixture of  $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$  (23 mg, 0.046 mmol) and  $\text{L}_1$  (78 mg, 0.1 mmol) in anhydrous DMF (4 mL) was heated at 100 °C under nitrogen for 1/2 h and was then cooled to rt for the addition of (*R,R*)-DPEN (21.5 mg, 0.1 mmol). With stirring, DPEN dissolved in ~15 min and the color of solution slowly changed from orange-red to yellow. After stirring at 80 °C for 2 h, solvent was removed under vacuum to give desired yellow solid of precatalyst, which was used for asymmetric hydrogenation reactions without further purification.
- A typical procedure for asymmetric hydrogenation of aromatic ketones: 3.3  $\mu\text{mol}$  of precatalyst was transferred into a vial inside a glove box. Under  $\text{N}_2$  gas flow, 2 mol%  $\text{KO}^t\text{Bu}$  in 0.5 mL of isopropanol was syringed into the vial, followed by the addition of 1-acetonaphthone (0.5 mL, 3.3 mmol) and  $\text{BMImBF}_4$  (0.5 mL). The reaction mixture was quickly transferred into a stainless steel autoclave and sealed. After purging with  $\text{H}_2$  for six times, final  $\text{H}_2$  pressure was adjusted to 700 psi. After 24 h, the autoclave was depressurized and the reaction mixture was washed with 3.1 mL of hexane–IPA (30/1; v/v) three times. The organic solvent was removed under reduced pressure and the residue was passed through a mini silica gel column using diethyl ether as the eluent. An aliquot was analyzed on GC to give conversion and ee values.
- For IL and catalyst recycle and reuse experiments, the reaction mixture was extracted with degassed distilled hexane–IPA three times under  $\text{N}_2$  gas flow. The organic layer was siphoned from the RTIL and the IL phase was dried under vacuum for 12 h before the addition of new ketone substrate,  $\text{KO}^t\text{Bu}$ , and IPA for another round of hydrogenation reaction.