Ruthenium catalyzed asymmetric hydrogenation of α- and β-keto esters in ionic liquids using chiral P-Phos ligand[1]

Kim Hung Lam, Lijin Xu, Lichun Feng, Jiwu Ruan, Qinghua Fan, and Albert S.C. Chan

Abstract: Chiral dipyridylphosphine ligand P-Phos was used in the Ru catalyzed asymmetric hydrogenation of α- and β-keto esters in room temperature ionic liquids (RTILs) with high conversions and good to excellent enantioselectivities. The catalyst was recycled by simple extraction and reused five times without loss of activity and enantioselectivity.

Key words: ruthenium, asymmetric hydrogenation, keto ester, ionic liquids, P-Phos.

Résumé : On a utilisé le ligand chiral dipyridylphosphine (P-Phos) dans l'hydrogénation asymétrique d'α- et de β-céto esters, catalysée par des complexes du ruthénium, à la température ambiante, dans des liquides ioniques, avec des degrés de conversion élevés et des énantiosélectivités allant de bonnes à excellentes. Le catalyseur peut être recyclé par simple extraction et peut être réutilisé jusqu'à cinq fois sans perte d'activité ou d'énantiosélectivité.

Mots clés : ruthénium, hydrogénation asymétrique, céto ester, liquides ioniques, P-Phos.

[Traduit par la Rédaction]

Introduction

Transition-metal-catalyzed asymmetric hydrogenation has become one of the most powerful tools for the preparation of optically active compounds in organic synthesis, and high activity and enantioselectivity have been observed using Rh, Ru, and Ir complexes with chiral phosphine, phosphite, or phosphoramidite as the ligand (1, 2). However, the industrial application of asymmetric hydrogenation has been hindered by the difficulty in the separation and recycling of the expensive chiral catalyst as well as the toxicity of the trace amounts of metal contaminants in the product. Immobilization of these catalysts offers an attractive solution to these problems (3). Recently, room temperature ionic liquids (RTILs) such as those based on imidazolium salts have attracted a great deal of interest because of their potential as a means to immobilize and to facilitate the recycling of transition-metal catalysts (4). A series of prochiral olefins, ketones, and imines have been successfully hydrogenated in ionic liquids, and the results were comparable to or even better than those obtained in common organic solvents (5–14). In most cases, the organic products could be easily separated via extraction with less polar solvents and the ionic liquid phase containing the active catalyst could be readily reused several times without significant loss of catalytic activity. However, recycling and reuse of the catalyst in ionic liquids has been problematic because of the leaching and (or) unstability of the catalyst. Recently, to overcome these obstacles, the attachment of the polar groups to the chiral phosphine ligands has been introduced (9–11). The synthesis of these modified ligands is tedious and much synthetic effort is required. It is highly desirable to develop efficient hydrogenation processes in ionic liquids with easily accessible ligands.

We have recently developed pyridyl-phosphine ligands, namely P-Phos and its derivatives, and have used them in transition-metal-catalyzed enantioselective hydrogenation of olefins and ketones to provide the desired products with high yields and excellent ees (15). In our pursuit of the immobilization and recycling of chiral catalysts in asymmetric hydrogenation (16), we have found that it is possible to replace the commonly used organic solvents with ionic liquids in the Ru-(P-Phos) catalyzed asymmetric hydrogenation of keto esters with retained enantioselectivity and catalytic activity. The use of ionic liquids allows easy isolation of the pure product and efficient recovery and reuse of the catalyst.

Results and discussion

The asymmetric catalytic hydrogenation of α-keto esters

Received 4 January 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 25 July 2005.

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[1]This article is part of a Special Issue dedicated to Professor Howard Alper.

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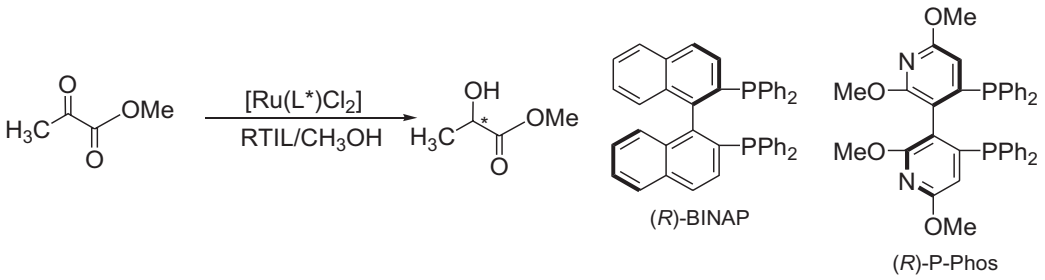
 doi: 10.1139/V05-102

Table 1. Asymmetric hydrogenation of methyl pyruvate in ionic liquids.[a]



L*	Solvent	ee (%)[b]	Conv. (%)[c]
(*R*)-P-Phos	[bmim][BF_4]–MeOH	83	95
(*R*)-P-Phos	[bmim][PF_6]–MeOH	86	73
(*R*)-P-Phos	MeOH	88	97
(*R*)-BINAP	[bmim][BF_4]–MeOH	55	98
(*R*)-BINAP	[bmim][PF_6]–MeOH	81	98
(*R*)-BINAP	MeOH	83	90

[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h.
[b]The ee values (%) were determined by GC on a Cyclosil-B (J & W Scientific) 30 m × 0.25 mm × 0.25 μm column.
[c]The conversions were determined by ^{1}H NMR analysis.

provides a convenient way to prepare chiral α-hydroxyl esters, and high enantioselectivities and conversions have been achieved in common organic solvents (1, 2). However, there is no report on the asymmetric hydrogenation of α-keto esters in ionic liquids. To determine whether the catalytic asymmetric hydrogenation of α-keto esters could occur in ionic liquids, we first examined the hydrogenation of methyl pyruvate in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) using [Ru((*R*)-P-Phos)Cl_2] as the catalyst. For comparison, we also tested the catalytic performance of the extensively used chiral ligand BINAP in ionic liquids. Our results indicated that the hydrogenation in pure ionic liquids was very sluggish with very low conversions (5% and 10% in [bmim][BF_4] and [bmim][PF_6], respectively) after 20 h. In view of the significant co-solvent effect of alcohol in asymmetric hydrogenation in ionic liquids (4), we used an equal volume of MeOH as a co-solvent. As shown in Table 1, high enantioselectivities could be obtained with Ru-P-Phos in both [bmim][BF_4] and [bmim][PF_6] and the results were comparable to the ee values achieved in MeOH. The enantioselectivity was insensitive to the nature of the ionic liquids. However, the reaction in [bmim][PF_6] was slower, and only 73% conversion was achieved after 20 h while nearly complete conversion was observed in [bmim][BF_4]. In contrast, lower enantioselectivities were observed in Ru-BINAP catalyzed hydrogenation, though nearly complete conversions were attained in both ionic liquids. With the BINAP ligand, the enantioselectivity was quite dependent on the nature of the ionic liquids. As shown in Table 1, 81% ee was obtained in [bmim][BF_4] while only 55% enantioselectivity was obtained in [bmim][PF_6]. It was notable that P-Phos performed better than BINAP in ionic liquids, which may be related to the dipyridyl backbone of P-Phos.

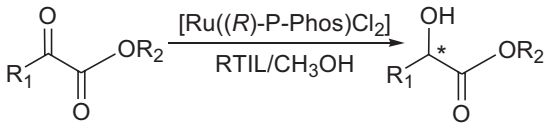
The hydrogenation was extended to other α-keto esters and low to high enantioselectivities were observed. Low enantioselectivities and conversions were observed in the hydrogenation of ketopantolactone in both ionic liquids (Table 2, entries 1 and 2). Moderate enantioselectivities and low conversions were obtained with ethyl 2-oxo-4-phenylbutyrate as a substrate (Table 2, entries 3 and 4). High ee values but low conversions were attained in the hydrogenation of methyl benzoylformate (Table 2, entries 5 and 6). The hydrogenation of ethyl benzoylformate only led to low conversions and low enantioselectivities (Table 2, entries 7 and 8).

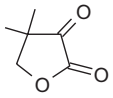
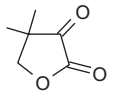
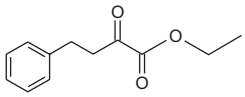
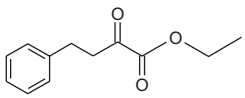
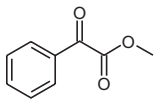
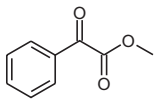
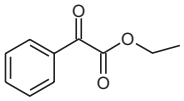
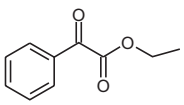
The asymmetric hydrogenation of β-keto esters has been previously studied in ionic liquids using modified BINAP ligands and the results are comparable to or better than those obtained in common organic solvents (9, 10). In this study, we examined the capability of [Ru((*R*)-P-Phos)Cl_2] in the asymmetric hydrogenation of β-keto esters in ionic liquids and the results are summarized in Table 3. The hydrogenation of methyl acetoacetate in a mixture of equal volumes of ionic liquid ([bmim][BF_4] or [bmim][PF_6]) and MeOH was first examined. After stirring at room temperature for 20 h, the reaction led to full conversion and higher than 99% ee. As shown in Table 3, the reaction was also conducted using (*R*)-BINAP as the ligand in both ionic liquids. Again, excellent conversions and enantioselectivites were achieved in both ionic liquids.

The results of the asymmetric hydrogenation of other β-keto esters are summarized in Table 4. High enantioselectivities (97%–99%) and high conversions (92% to >99%) were obtained for ethyl acetoacetate and *tert*-butyl acetoacetate (Table 4, entries 1–4). It should be pointed out that these results favorably compare with those obtained in common organic solvents. However, when R^1 was switched to other electronegative groups, both the enantioselectivity and the conversion declined (Table 4, entries 5–8). The Ru-P-Phos catalyst showed higher activity in [bmim][PF_6], but it gave better enantioselectivity in [bmim][BF_4].

The recyclability of the Ru-P-Phos catalyst in RTILs was explored using methyl acetoacetate as the model substrate.

Table 2. Asymmetric hydrogenation of α-keto esters in ionic liquids.[a]



Entry	Substrate	RTIL	ee (%)[b]	Conv. (%)[c]
1		[bmim][BF_4]	47	34
2		[bmim][PF_6]	60	46
3		[bmim][BF_4]	74	37
4		[bmim][PF_6]	76	63
5		[bmim][BF_4]	90	18
6		[bmim][PF_6]	93	65
7		[bmim][BF_4]	55	26
8		[bmim][PF_6]	38	20

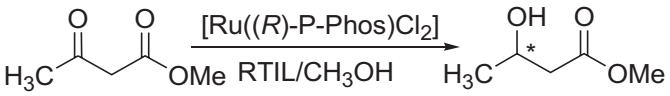
[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and methanol at room temperature for 20 h.

[b]The ee values (%) were determined by GC on a Cyclosil-B (J & W Scientific) 30 m × 0.25 mm × 0.25 μm column.

[c]The conversions were determined by ^{1}H NMR analysis.

Upon completion of the reaction, the methanol was evaporated in vacuo, and the product was extracted with degassed hexane. The RTIL phase was washed twice with hexane. The combined extracts were used for analysis. The RTIL phase was recharged with methyl acetoacetate and MeOH, and then subjected to hydrogenation again under the same conditions. As shown in Table 5, the Ru-P-Phos could be reused and recycled in both ionic liquids, but the results differ considerably. In [bmim][BF_4]–MeOH, the level of enantioselectivity could be reasonably maintained for nine runs, but the activity deteriorated from the second run, and the subsequent runs led to a significant drop in activity. However, in

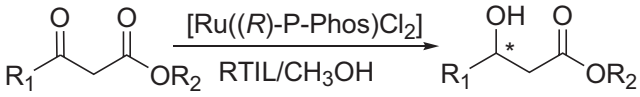
Table 3. Asymmetric hydrogenation of methyl acetoacetate in ionic liquids.[a]

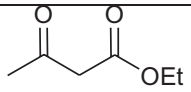
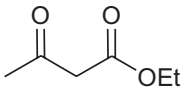
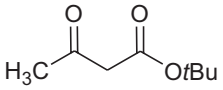
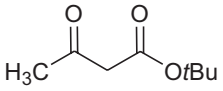
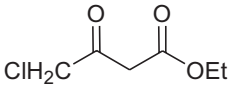
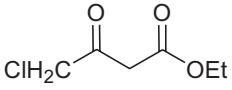
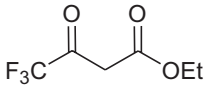
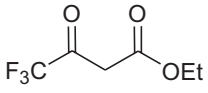


L*	RTIL	ee (%)[b]	Conv. (%)[c]
(*R*)-P-Phos	[bmim][BF_4]	>99	>99
(*R*)-P-Phos	[bmim][PF_6]	98	>99
(*R*)-BINAP	[bmim][BF_4]	>99	>99
(*R*)-BINAP	[bmim][PF_6]	>99	>99

[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h.
[b]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column.
[c]The conversions were determined by ^{1}H NMR analysis.

Table 4. Asymmetric hydrogenation of β-keto esters in ionic liquids.[a]



Entry	Substrate	RTIL	ee (%)[b]	Conv. (%)[c]
1		[bmim][BF_4]	>99	>99
2		[bmim][PF_6]	97	>99
3		[bmim][BF_4]	>99	86
4		[bmim][PF_6]	>99	92
5		[bmim][BF_4]	54	91
6		[bmim][PF_6]	58	93
7		[bmim][BF_4]	50	21
8		[bmim][PF_6]	21	78

[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h.
[b]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column.
[c]The conversions were determined by ^{1}H NMR analysis.

Table 5. Recycling and reuse of Ru-(*R*)-P-Phos catalyst for asymmetric hydrogenation of methyl actoacetate in ionic liquids.[a]

Entry	RTIL	Run	ee[b] (%)	Conv.[c] (%)
1	[bmim][BF_4]	1	>99	>99
2	[bmim][BF_4]	2	98	87
3	[bmim][BF_4]	3	97	78
4	[bmim][BF_4]	4	96	71
5	[bmim][BF_4]	5	95	62
6	[bmim][BF_4]	6	95	56
7	[bmim][BF_4]	7	93	52
8	[bmim][BF_4]	8	94	33
9	[bmim][BF_4]	9	94	39
10	[bmim][PF_6]	1	98	>99
11	[bmim][PF_6]	2	98	99
12	[bmim][PF_6]	3	97	96
13	[bmim][PF_6]	4	97	96
14	[bmim][PF_6]	5	96	93
15	[bmim][PF_6]	6	96	86
16	[bmim][PF_6]	7	96	78
17	[bmim][PF_6]	8	94	57
18	[bmim][PF_6]	9	94	49

[a]All the reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h.
[b]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column.
[c]The conversions were determined by ^{1}H NMR analysis.

the case of [bmim][PF_6], good activity and excellent enantioselectivity were retained in the first five runs of the hydrogenation reactions.

Conclusion

We have developed an efficient Ru-P-Phos catalyst for the asymmetric hydrogenation of α- and β-keto esters in RTILs with high conversions and ee values up to >99%. The catalyst was recycled and reused with the reasonable retention of activity and enantioselectivity.

Experimental

General information

All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-filled MBRAUN Lab Master 130 glovebox. The hydrogenation reactions were performed in a stainless-steel autoclave from the Parr company.[bmim][BF_4] and [bmim][PF_6] were prepared according to the literature method (17). Following vacuum drying at 80 °C for 8 h, the ionic liquid was stored under nitrogen at ambient temperature. Optically pure P-Phos and [Ru((*R*)-P-Phos)Cl_2] were synthesized based on our previous reports (14). Other chemicals were purchased and were used as received. The solvents were dried prior to use via standard procedures. The ^{1}H NMR spectra were recorded on a Varian AS 500 spectrometer in ppm with reference to the TMS internal standard in $CDCl_3$.

Typical procedure for asymmetric hydrogenation

A mixture of [bmim][BF_4] (0.5 mL) and MeOH (0.5 mL) was added into a glass-lined stainless-steel autoclave containing methyl acetoacetate (26.7 mg, 0.23 mmol) and [Ru((*R*)-P-Phos)Cl_2] (18.8 mg, 0.023 mmol) in a drybox under a nitrogen atmosphere. After purging the autoclave with hydrogen gas several times, the final pressure of the hydrogen was adjusted to 1000 psi (1 psi = 6.894 757 kPa), and the reaction mixture was stirred at room temperature. After 20 h, the hydrogen gas was released, and the product was extracted with hexane and passed through a small column of silica gel. The organic volatiles were removed under reduced pressure to obtain the desired product. The conversion was then assessed based on the ^{1}H NMR analysis, while the ee value was determined by GLC using a chiral column.

Acknowledgements

We thank the University Grants Committee Area of Excellence Scheme in Hong Kong (Project No. AoE/P-10/01), the Hong Kong Polytechnic University Area of Strategic Development Fund, and the National Natural Science Foundation of China (No. 20418002) for financial support.

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