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Highly enantioselective catalytic asymmetric hydrogenation of β-keto esters in room temperature ionic liquids†

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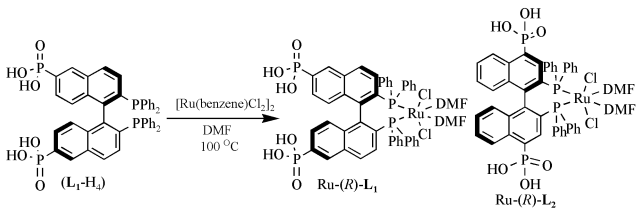
Polar phosphonic acid-derived Ru-BINAP systems were used to catalyze asymmetric hydrogenation of β-keto esters in room temperature ionic liquids (RTILs) with complete conversions and ee values higher than those obtained from homogeneous reactions in MeOH (up to 99.3%), and were recycled by simple extraction and used for four times without the loss of activity and enantioselectivity.

Catalytic asymmetric hydrogenation reactions have been established as one of the most versatile and powerful methods for the synthesis of optically pure organic compounds.[1] Ru and Rh complexes of 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) have been shown to be particularly effective asymmetric catalysts for the hydrogenation of prochiral olefins, ketones and other carbonyl compounds.[2] High costs of both the BINAP ligand and group 8 metals as well as the toxicity of trace metal contaminants in the organic products have hindered their industrial applications. Immobilization of such homogeneous asymmetric catalysts presents an interesting solution to these obstacles.[3]

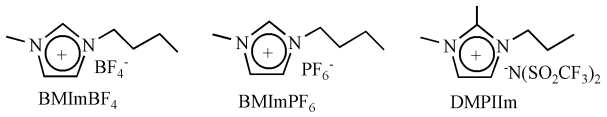
Room temperature ionic liquids (RTILs) have recently received a great deal of attention as alternative reaction media.[4] RTILs have been used as alternative solvents for asymmetric hydrogenation of arylacrylic acids to generate anti-inflammatory drugs Ibuprofen and Naproxen[5] and asymmetric hydrogenation of enamides to give α-amino acids.[6] The organic products from these reactions were separated by extraction with nonpolar solvents or supercritical CO_2 while the IL phase containing active catalysts could be reused several times without significant deterioration of activity and enantioselectivity. RTILs thus represent an effective means for the immobilization of expensive asymmetric catalysts.

To facilitate the separation of active catalysts from the organic products, we have designed two polar derivatives of Ru-BINAP precatalysts. Herein we wish to report their application in highly enantioselective asymmetric hydrogenation of β-keto esters in RTILs. These polar asymmetric catalysts immobilized in the IL phase can be readily recycled and reused.



Scheme 1 Synthesis of precatalysts Ru-$\mathbf{L_1}$ and Ru-$\mathbf{L_2}$.

2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl-6,6′-bis(phosphonic acid), $\mathbf{L_1}$–$\mathbf{H_4}$ (Scheme 1), was synthesized in 3 steps starting from previously reported 2,2′-dihydroxy-1,1′-binaphthyl-6,6′-bis(diethylphosphonate),[7] while 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-4,4′-bis(phosphonic acid), $\mathbf{L_2}$–$\mathbf{H_4}$, was synthesized according to a literature procedure.[8] Ru($\mathbf{L_1}$–$\mathbf{H_4}$)$(DMF)_2Cl_2$ and Ru($\mathbf{L_2}$–$\mathbf{H_4}$)$(DMF)_2Cl_2$ precatalysts were synthesized by treating $\mathbf{L_1}$–$\mathbf{H_4}$ and $\mathbf{L_2}$–$\mathbf{H_4}$ with 0.46 equiv of $[Ru(benzene)Cl_2]_2$ in DMF at 100 °C, respectively.



We have examined the utility of Ru–(*R*)–$\mathbf{L_1}$ and Ru–(*R*)–$\mathbf{L_2}$ for asymmetric hydrogenation of β-keto esters in RTILs butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$), butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$), and propyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (DMPIIm).‡ We first attempted to hydrogenate methyl acetoacetate with 1 mol% precatalyst Ru–(*R*)–$\mathbf{L_1}$ in a DMPIIm/H_2O (1 : 1 v/v) biphasic system. After 36 h of reaction at 1500 psi of H_2 pressure, 3-hydroxybutyrate was obtained at a reasonable conversion of 76%, but a modest ee of 33%. When the hydrogenation reaction was carried out in pure DMPIIm with 0.5 equiv of MeOH (relative to methyl acetoacetate) for 24 h, 3-hydroxybutyrate was obtained in 38% yield and 50% ee. The use of increased amount of MeOH has drastically improved the catalytic activity and enantioselectivity. Hydrogenation of methyl acetoacetate with 1 mol% precatalyst Ru–(*R*)–$\mathbf{L_1}$ in a homogeneous mixture of DMPIIm–MeOH (1 : 1 v/v) for 22 h afforded 3-hydroxybutyrate in quantitative yield and 93% ee. All the subsequent reactions were carried out in an equal volume homogeneous mixture of RTIL and MeOH.

As shown in Table 1, Ru–(*R*)–$\mathbf{L_1}$ and Ru–(*R*)–$\mathbf{L_2}$ are highly active for catalytic asymmetric hydrogenation of a wide range of β-keto esters in the homogeneous RTIL–MeOH systems. Although complete conversions have been achieved with three different RTILs for all the β-keto esters, the enantioselectivity is quite sensitive to the nature of RTILs. For Ru–(*R*)–$\mathbf{L_1}$ precatalyst, $BMImBF_4$ is the best choice of RTIL and afforded ee values comparable to those obtained from homogeneous reactions in MeOH (with the exception of methyl 2,2-dimethylacetoacetate). Ru–(*R*)–$\mathbf{L_1}$ performed poorly with methyl 2,2-dimethylacetoacetate in all of the three RTILs. Complete conversions and comparable ee's were also achieved with lower precatalyst loadings. In fact, methyl acetoacetate was hydrogenated to give 3-hydroxybutyrate with 0.1 mol% Ru–(*R*)–$\mathbf{L_1}$ in quantitative yield and 99% ee in 22 h.

Interestingly, Ru–(*R*)–$\mathbf{L_2}$catalyzed highly enantioselective hydrogenation of β-keto esters in all three RTILs, with ee values higher than those obtained from homogeneous reactions in MeOH. All the β-keto esters in Table 1 were hydrogenated in the homogeneous RTIL–MeOH systems to give β-hydroxy esters in quantitative yields and ee values ranging from 94.9% to 99.3%. As shown in Table 1, these ee values compare favorably with those obtained with Ru-BINAP catalyst in the homogeneous DMPIIm–MeOH system (1:1 v/v).

We have also demonstrated that both the RTILs and catalysts can be recycled and reused several times for asymmetric hydrogenation of methyl acetoacetate. At the end of each hydrogenation run, 3-hydroxybutyrate was readily extracted with degassed hexanes. The IL phase was washed two more

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b302637j/

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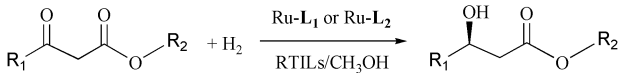
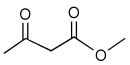
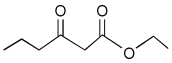
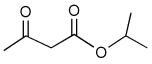
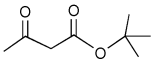
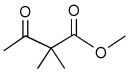
Table 1 Ee values for asymmetric hydrogenation of β-keto esters in RTILs[a]



	Ru–(R)–$\mathbf{L_1}$				Ru–(R)–$\mathbf{L_2}$				Ru-BINAP
Substrate	MeOH	DMPIIm	$BMImBF_4$	$BMImPF_6$	MeOH	DMPIIm	$BMImBF_4$	$BMImPF_6$	DMPIIm
	98.9	93	98.3	93.9	98.3	99.0	98.9	99.3	98.9
	98.7[b]	98.5[b]	98.9[b]	98.7[b]	98.6[b]	99.3[b]	99.1[b]	99.1[b]	99.1[b]
	98.3	93	97.5	93.5	94.2	98.1	98.9	98.9	98.1
	99.1	92.5	96.1	89.5	96.7	97.5	98.5	97.5	96.9
	95.5	79	77	47.3	91.7	95.1	96.3	94.9	98.1

[a] All the reactions were carried out with 1 mol% precatalyst in a H_2 pressure of 1500 psi at a 50 : 50 mixture of RTIL and MeOH at rt for 22 h and have complete conversions. The ee values (%) were determined by GC on a Supelco γ-Dex 225 column. [b] The ee values (%) were determined by GC on a Superco β-Dex 120 column. The absolute configurations of the products are identical to those obtained by the Ru–(R)-BINAP catalyst. The conversions were determined by the integrations of ^{1}H NMR spectra.

times with degassed hexanes. After being dried under vacuum, the RTIL phase was simply recharged with methyl acetoacetate and MeOH and then subjected to the hydrogenation conditions. As shown in Table 2, both Ru–(*R*)–$\mathbf{L_1}$ and Ru–(*R*)–$\mathbf{L_2}$ catalytic systems were recycled and reused in all three RTILs. The first three runs of hydrogenation reactions with Ru–(*R*)–$\mathbf{L_1}$ in $BMImBF_4$–MeOH gave the same level of activity and enantioselectivity. Subsequent runs led to only a slight deterioration of enantioselectivity but a significant drop in activity. We have also successfully recycled and reused the Ru–(*R*)–$\mathbf{L_2}$ catalytic system in both $BMImPF_6$ and DMPIIm. In particular, the Ru–(*R*)–$\mathbf{L_2}$ catalytic system immobilized in DMPIIm retained both activity and enantioselectivity for four 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 0.02%, 0.04%, and 0.01% of the Ru catalyst has leached into the hexane extract from the $BMImBF_4$, $BMImPF_6$, and DMPIIm phase, respectively.

In summary, polar phosphonic acid-derived Ru-BINAP systems were designed and used to catalyze asymmetric hydrogenation of β-keto esters in RTILs with complete conversions and ee values of up to 99.3%. These RTIL-immobilized catalysts were recycled by simple extraction and used for four times without any deterioration of activity and enantioselectivity. Such a simple immobilization approach also promises to prevent the leaching of toxic group 8 metals into the organic products, and should be highly desirable for the production of pharmaceutical intermediates that are free from metal contaminants.

Table 2 Recycling and reuse of Ru–$\mathbf{L_1}$ and Ru–$\mathbf{L_2}$ catalysts for hydrogenation of methyl acetoacetate in RTILs[a]

Run	Ru–$\mathbf{L_1}$/$BMImBF_4$		Ru–$\mathbf{L_2}$/$BMImPF_6$		Ru–$\mathbf{L_2}$/DMPIIm	
	Ee (%)	Conversion (%)	Ee (%)	Conversion (%)	Ee (%)	Conversion (%)
1	97.4	> 99	99.3	> 99	98.5	> 99
2	97.6	97	97.3	98	98.9	> 99
3	97.1	94	95.2	89	98.3	> 99
4	95.1	75	89.7	84	97.5	> 99
5	94.7	45	74.9	62	95.9	77
6	91.0	30	66.7	50	81.9	44

[a] All the reactions were carried out with 1 mol% catalyst under 1500 psi of H_2 for 22 h.

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Notes and references

‡ **General procedure for catalysis**: To a vial containing a mixture of $BMImBF_4$ (0.5 mL) and MeOH (0.5 mL) was added methyl acetoacetate (0.05 mL, 0.46 mmol) and ($Ru(\mathbf{L_1}–H_4)(DMF)_2Cl_2$) (5.0 mg, 4.5 μmol). The vial was then placed inside a 300 mL stainless steel autoclave, which was pressurized with 1500 psi of H_2 and stirred at rt. After 22 h, the reactor was depressurized and hexane was added to extract the product. The organic layer was decanted and evaporated dry under reduced pressure to afford the desired 3-hydroxybutyrate product. The conversions were assessed based on the integration of ^{1}H NMR peaks of the products and starting materials, while the ee values were determined using chiral GC.

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