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Asymmetric hydrogenation of aromatic ketones in ionic-liquid media catalyzed by Ru-TPPTS–(1*S*,2*S*)-DPENDS complexes

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Abstract—The catalytic performance of ruthenium phosphine complexes using (1*S*,2*S*)-DPENDS [(1*S*,2*S*)-1,2-diphenyl-1,2-ethylene diamine sulfonate disodium] as a chiral modifier in the asymmetric hydrogenation of aromatic ketones was examined in a series of hydrophilic ionic liquids $[RMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ (R = ethyl, butyl, octyl, dodecyl). The synergistic effect between (1*S*,2*S*)-DPENDS and KOH significantly accelerated the reaction and enhanced the enantioselectivity. An ee value of 84.8% was obtained in the asymmetric hydrogenation of acetophenone under the optimized conditions. The products were conveniently separated with cyclohexane extraction, and both the ruthenium catalyst and (1*S*,2*S*)-DPENDS were kept in the ionic liquid and could be reused.

1. Introduction

Catalytic asymmetric hydrogenation is a powerful method for the synthesis of enantiomerically pure compounds. A lot of catalysts contain rhodium and ruthenium complexes using chiral phosphines and amines as ligands display excellent performances in the asymmetric homogeneous hydrogenation of prochiral ketones and other carbonyl compounds.[1] However, their practical applications are often limited owing to the high cost of the chiral ligand and noble metal, as well as the difficulty in the separation of products from chiral catalyst. The immobilization of a homogeneous catalyst provides an efficient approach to resolve the problem. Recently room temperature ionic liquids (RTILs) have been used as an alternative reaction media in asymmetric hydrogenation of enamides,[2] arylacrylic acids,[3] imines,[4] aromatic ketones[5] and β-ketoesters.[6–8] These reports indicated that the products of hydrogenation could be easily separated from the catalyst by decantation or extraction with organic solvents while the chiral catalyst in ionic liquid (IL) could be reused several times without obvious decrease in the activity and enantioselectivity. However the chiral phosphines were expensive and too sensitive to air. In order to develop an inexpensive and stable chiral catalyst, as well as better combinations of ILs and metal complexes, we synthesized a series of ionic liquids $[RMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ and studied the catalytic performance of a novel catalyst system $[RuCl_2(TPPTS)_2]_2$–(1*S*,2*S*)-DPENDS–KOH [(TPPTS: $P(m\text{-}C_6H_4SO_3Na)_3$) in the asymmetric hydrogenation of aromatic ketones in the ionic liquids.

2. Results and discussion

2.1. Influence of ionic liquid properties and temperature

The data listed in Table 1 indicate that the activities of the catalyst system $[RuCl_2(TPPTS)_2]_2$–(1*S*,2*S*)-DPENDS–KOH were high in the ionic liquids containing the anionic group $[p\text{-}CH_3C_6H_4SO_3]^-$ and BF_4^-, but when butyl group in imidazole was substituted by another alkyl group, the enantioselectivities decreased gradually with an increase of alkyl chain length. The results suggest that increasing the hydrophobic chain length in imidazole could be unfavourable for the formation of the (*R*)-configuration in the transition state of hydrogenation of acetophenone. The activity of the catalyst system significantly decreased in $[BMIM]^+PF_6^-$. The conversion of acetophenone in $[BMIM]^+PF_6^-$ was only 5.6% for 1 h. As $[RuCl_2(TPPTS)_2]_2$ is a strong hydrophilic complex and its solubility in hydrophobic

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Table 1. Influence of different ionic liquid media on asymmetric hydrogenation

Ionic liquid	Conv. (%)	ee (%)	Configuration
$[EMIM]^+[p\text{-}CH_3C_6H_4SO_3^-]$	100	75.2	*R*
$[BMIM]^+[p\text{-}CH_3C_6H_4SO_3^-]$	100	79.2	*R*
$[OMIM]^+[p\text{-}CH_3C_6H_4SO_3^-]$	100	66.5	*R*
$[DoMIM]^+[p\text{-}CH_3C_6H_4SO_3^-]$	100	59.4	*R*
$[BMIM]^+BF_4^-$[a]	98.5	67.1	*R*
$[BMIM]^+PF_6^-$[a]	5.6	52.9	*R*

Reaction conditions: acetophenone: 0.85 mmol, Ru complex/acetophenone/(1*S*,2*S*)-DPENDS = 1:112:6 (mole ratio), [KOH] = 0.36 mol/L, ionic liquid: 1.0 mL, P_{H2} = 5 MPa, Temp: 50 °C, reaction time: 0.5 h.
[a] Reaction time: 1.0 h.

$[BMIM]^+PF_6^-$ is very low, the catalyst can not fully exert its function. The matching property between metal complexes and ionic liquids not only influences the solubility of metal complexes in ionic liquids, but also influences the catalytic activity. When both are matching, the catalyst system will display high activity, in addition to the character being favourable for the separation of metal complex catalyst from products.

The results listed in Table 2 suggested that the enantioselectivity increased with a decrease of reaction temperature with an ee value of 84.8% being obtained at 5 °C.

Table 2. Effect of reaction temperature on asymmetric hydrogenation

Temperature (°C)	Reaction time (h)	Conv. (%)	ee (%)	Configuration
5	2.0	31.8	84.8	*R*
15	2.0	48.5	83.0	*R*
20	2.0	100	81.3	*R*
50	0.5	100	79.2	*R*

The reaction conditions in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ media are the same as in Table 1, except for a change in temperature.

2.2. Influence of (1*S*,2*S*)-DPENDS and KOH concentration

The influence of (1*S*,2*S*)-DPENDS and KOH concentration on the asymmetric hydrogenation of acetophenone is very significant as shown in Tables 3 and 4. The conversion of acetophenone was only 1.1% with an ee value of zero in the absence of (1*S*,2*S*)-DPENDS. The addition of both (1*S*,2*S*)-DPENDS and KOH greatly enhanced the catalytic activity and enantioselectivity. When the concentrations of (1*S*,2*S*)-DPENDS and KOH were 4.8×10^{-2} mol/L and 0.36 mol/L, the conversion and ee value could reach 100% and 79.2%, respectively. However, if there was no addition of KOH into the reaction solution, the conversion was only 0.6%. The results suggest that the combination of chiral diamine and KOH is an essential factor for the formation of a chiral induction and the active catalytic species. This synergistic effect between the chiral diamine and KOH was also found in our research on the asymmetric hydrogenation of acetophenone using γ-Al_2O_3 supported ruthenium nanocluster catalyst.[17] The important role of KOH is to neutralize HCl formed in the activation process and promotes the catalyst precursor $[RuCl_2(TPPTS)_2]_2$ to convert into active species $[RuHCl(TPPTS)_2$–DPENDS] as described.[1] However, the enhancement role of KOH for the enantioselectivity and the synergistic effect was not observed in homogeneous catalysis. This suggests that the catalytic mechanism is different from that reported by Noyori et al.[1,18] and is currently being studied.

Table 3. Influence of KOH concentration on asymmetric hydrogenation

$[KOH] \times 10^{-2}$ mol/L	Conv. (%)	ee (%)
0.0	0.60	44.2
4.5	97.0	72.5
9.0	99.0	73.8
18.0	99.8	75.6
36.0	100	79.2
39.0	100	77.7

The reaction conditions in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ media are the same as in Table 1.

Table 4. Influence of (1*S*,2*S*)-DPENDS concentration on asymmetric hydrogenation

$[(1S,2S)\text{-DPENDS}] \times 10^{-2}$ mol/L	Conv. (%)	ee (%)
0.0	1.1	0.0
0.48	23.3	60.1
1.9	48.9	61.3
2.4	62.9	71.3
3.8	82.6	76.1
4.8	100	79.2
6.0	100	78.9

The reaction conditions in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ media are the same as in Table 1.

2.3. Influence of different ruthenium complexes

The activities and enantioselectivities of different ruthenium complexes in the asymmetric hydrogenation of acetophenone were investigated in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ solution with the results summarized in Table 5. The data showed that the $[RuCl_2(TPPTS)_2]_2$ was the most efficient catalyst precursor. The conversion of acetophenone and the ee value of the products were 100% and 79.2% for 0.5 h, respectively. When phosphine ligand TPPTS was used instead of other water-soluble diphosphine ligand BISBIS, the activities and enantioselectivities obviously decreased, because the stability and steric effect of chelate ruthenium complex, which was formed by BISBIS coordination with Ru, would influence the catalytic activity and chiral modification of

Table 5. Influence of different ruthenium complexes

Ruthenium complex	Conv. (%)	ee (%)
$[RuCl_2(TPPTS)_2]_2$	100	79.2
$RuCl_2(BISBIS)_2$	39.2	58.6
$RuCl_3$–2TPPTS	3.0	53.1
$RuCl_2(COD)$–2TPPTS	6.8	33.3

The reaction conditions are the same as in Table 1, except the ionic liquid is $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$.

(1*S*,2*S*)-DPENDS. When the catalyst precursor was $RuCl_3$, the ruthenium must be reduced to a low oxidation state and coordinated with TPPTS, in order for the ruthenium complex to become an active catalyst. COD in $RuCl_2(COD)$ would be exchanged with TPPTS in the solution according to the reaction:

$$RuCl_2(COD) + 2TPPTS \rightarrow RuCl_2(TPPTS)_2 + COD$$

then the ruthenium complex was able to dissolve in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$. Therefore, when both catalyst precursors $RuCl_3$ and $RuCl_2(COD)$ were used in the reaction, there was a long induction period for forming catalytic active species, causing the very low catalytic activities observed.

2.4. Hydrogenation of different aromatic ketones

Asymmetric hydrogenation of different aromatic ketones in $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ were carried out under the same reaction conditions with the results summarized in Table 6. Acetophenone and propiophenone exhibited the highest reactivities, and ee values of their hydrogenation products also were higher than those of other ketones. The substituent in the phenyl ring, whether it was an electron-withdrawing group or electron-donating group, had an obvious influence on the reactivity of aromatic ketones. The decrease in reaction rates and ee values can be mainly attributed to the steric effect, which influences the reactant–modifier interaction. The major product in the hydrogenation of 2-methoxy-acetophenone was (*S*)-2-methoxy-α-phenyl ethanol. The change in configuration is agreement with that observed in the literature.[19]

Table 6. Hydrogenation of different aromatic ketones

Substrate	Conv. (%)	ee (%)	*R*/*S*
Acetophenone	100	79.2	*R*
Propiophenone	100	80.6	*R*
2-Fluoroacetophenone	98.2	46.4	*R*
2-Chloroacetophenone	96.4	63.7	*R*
2-Bromoacetophenone	86.5	66.3	*R*
2-(Trifluoromethyl)acetophenone	88.6	57.3	*R*
4-(Trifluoromethyl)acetophenone	78.3	51.8	*R*
2-Methoxyacetophenone	68.0	40.0	*S*
4-Methoxyacetophenone	83.0	64.7	*R*

The reaction conditions are the same as in Table 1.

2.5. Catalyst recycling

We have demonstrated that the products could be separated by extraction with cyclohexane and the ionic liquid phase containing the active catalyst while the chiral ligand could be reused several times in the asymmetric hydrogenation of acetophenone. The results are listed in Table 7. Although the activities of the catalyst system $[RuCl_2(TPPTS)_2]_2$–(1*S*,2*S*)-DPENDS–KOH decreased in runs 6 and 7, the ee values could still be maintained at about 70%. When 1.8×10^{-4} mol KOH was supplied into the ionic liquid solution, the conversion rose from 68.7% (run 7) to 94.0% (run 8). These results further confirm the important effect of KOH on the reaction.

Table 7. Recycling and reuse of $[RuCl_2(TPPTS)_2]_2$ catalyst in ionic liquid $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$

Run	Conv. (%)	ee (%)
1	100	79.2
2	100	74.2
3	96.4	71.6
4	98.1	70.3
5	97.4	70.3
6	88.0	69.3
7	68.7	70.8
8[a]	94.0	72.6
9	91.2	69.1

The reaction conditions are the same as in Table 1.
[a] 1.8×10^{-4} mol of KOH is added in the eighth run.

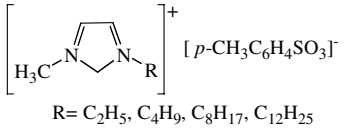
3. Conclusions

$[RuCl_2(TPPTS)_2]_2$–(1*S*,2*S*)-DPENDS–KOH catalyst system in ionic liquid $[BMIM]^+[p\text{-}CH_3C_6H_4SO_3]^-$ exhibits excellent catalytic properties for asymmetric hydrogenation of acetophenone. A synergistic effect between (1*S*,2*S*)-DPENDS and KOH in ionic liquid solution significantly accelerates the reaction and enhances the enantioselectivity. The ionic liquid phase containing the active catalyst and chiral ligand can be reused for several times without significant decrease in activity and ee value.

4. Experimental

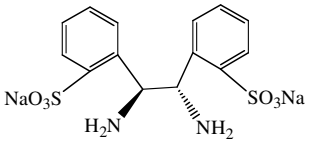
4.1. Materials and methods

1-Methylimidazole (Fluka, >99%) and 1-butanebromide (Lancaster, >99%) were distilled before use. Aromatic ketones (≥98% Acros) $RuCl_2(COD)$ [dichloro(1,5-cyclooctadiene)ruthenium(II), 99%] (Strem Chemical Co.) and hydrogen (99.99%) were used as received. Hexafluorophosphoric acid (Acros, 60 wt % solution in water), *p*-toluene sulfonic acid, $RuCl_3{\cdot}3H_2O$ and other reagents are analytical grade. TPPTS, BISBIS (sodium of sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl) and a series of ionic liquids $[RMIM]^+[p\text{-}CH_3C_6H_4SO_3^-]$ (R = ethyl, butyl, octyl, dodecyl) (Scheme 1) were synthesized according to known methods in our laboratory.[9–14] $[RuCl_2(TPPTS)_2]_2$

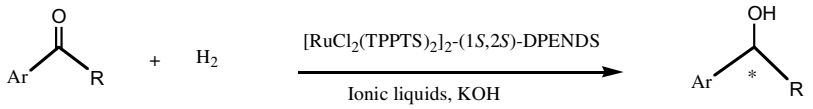


R= C_2H_5, C_4H_9, C_8H_{17}, $C_{12}H_{25}$

Scheme 1. Ionic liquids.



Scheme 2. (1*S*,2*S*)-DPENDS.



Ar = C_6H_5, *o*-FC_6H_4, *o*-ClC_6H_4, *o*-BrC_6H_4, *o*-$CF_3C_6H_4$, *o*-$CH_3OC_6H_4$, *p*-$CF_3C_6H_4$, *p*-$CH_3OC_6H_4$, R = CH_3
Ar = C_6H_5, R = C_2H_5

Scheme 3. The asymmetric hydrogenation of aromatic ketones.

and $RuCl_2(BISBIS)_2$ were prepared by a ligand exchange method.[15] (1*S*,2*S*)-DPENDS (Scheme 2) was prepared by means of sulfonation of (1*S*,2*S*)-DPEN (Chengdu LiKai Chiral Tech Co., >99%).[9,16]

4.2. Hydrogenation of aromatic ketones

The reaction was performed in a 60 mL stainless autoclave with a glass linear and magnetic stirrer. A typical procedure for an asymmetric hydrogenation of aromatic ketones (Scheme 3) is as follows: the ruthenium complexes, (1*S*,2*S*)-DPENDS, KOH, ionic liquid and reactant were added to autoclave, followed by a purge with hydrogen, three times. Hydrogen was introduced to the desired hydrogen pressure. The products were extracted by cyclohexane and analyzed by GC-960 with FID detector and β-DEX™120 capillary column (30 m × 0.25 mm, 0.25 μm film) at 115 °C. The enantiomeric excess (ee value) was calculated from the equation: ee (%) = $100 \times (R - S)/(R + S)$.

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