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Asymmetric transfer hydrogenation of prochiral ketones catalyzed by aminosulfonamide-ruthenium complexes in ionic liquid

Research Article

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Abstract: Chiral aminosulfonamides containing imidazolium group were used as ligands for the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of prochiral ketones in ionic liquid, affording good to excellent conversions and enantiomeric excesses. The catalytic system could be easily recovered and reused several times.

Keywords: *Asymmetric transfer hydrogenation • Aminosulfonamide • Ionic liquid • Ketones*

1. Introduction

Asymmetric transfer hydrogenation (ATH) of prochiral ketones has emerged as a very valuable synthetic tool to obtain optically pure secondary alcohols because of its operational simplicity, the easy availability of hydrogen sources, lower cost and safety [1]. The ruthenium complexes containing arene and *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) ligand developed by Noyori and co-workers are efficient catalysts for the asymmetric transfer hydrogenation of ketones [2]. Recently, a number of researchers have shown that catalytic ATH of ketones can be carried out efficiently using monosulfonylated-1,2-diphenylethylenediamines as ligands with sodium formate as hydrogen source in aqueous solution, 2-propanol and a formic acid/triethylamine azeotrope as hydrogen donor as well as solvent [3-38]. However, to the best of our knowledge, there are only two reports using monosulfonylated-1,2-diphenylethylenediamines as ligands for the ATH with ionic liquids as solvents [39,40]. Ionic liquids have attracted increasing interest in recent years because of their properties of nonvolatility, nonflammability, thermal stability, controlled miscibility, low toxicity and reusability. The use of ionic liquids as a solvent is a more environmentally responsible strategy. The combination of the "green solvents" and the "recyclable catalytic system" would provide an ideal chemical process for environmentally friendly asymmetric synthesis. We recently communicated that the recyclable ruthenium catalysts prepared from ionic chiral aminosulfonamide ligands **1a** and **1b** (Fig. 1) with $[RuCl_2(p\text{-cymene})]_2$ were used in the asymmetric transfer hydrogenation of prochiral ketones in water [3]. As an extension of this work, herein we describe the recyclable catalytic system generated *in situ* from ruthenium complex and ionic chiral aminosulfonamide ligands **1** to catalyze the asymmetric transfer hydrogenation of ketones in ionic liquid.

2. Experimental Procedure

Melting points were determined on a melting point apparatus and were uncorrected. Specific rotations were recorded in a WZZ-3 digital polarimeter. IR spectra were obtained on a Nexus 470 FTIR spectrophotometer. ^1H NMR spectra were recorded on a Bruker Avance III 400 with TMS as internal standard. The conversions were measured by GC-MS on a Agilent 5973N (HP-5ms capillary column). The chemicals used in this work were

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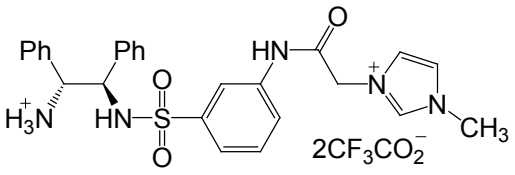
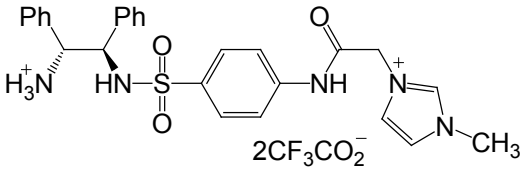


1a



1b

Figure 1. Chiral aminosulfonamides **1a** and **1b**

purchased from the Alfa Aesar and Sinopharm Chemcial Reagent Co., Ltd. Chiral aminosulfonamides **1a** and **1b** were prepared from (*R,R*)-1,2-diphenylethylenediamine by following the procedure we previously reported [3]. Ionic liquid [bmim][PF_6] was prepared according to literature procedures [41].

2.1. General procedure for asymmetric transfer hydrogenation in ionic liquid

(*R,R*)-**1** (0.012 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (3.1 mg, 0.005 mmol) were dissolved in [bmim][PF_6] (1 mL). The resulting solution was stirred at 40°C for 1 h under an argon atmosphere. Formic acid/triethylamine azeotrope (0.5 mL) and acetophenone (1.0 mmol) were then introduced. The mixture was stirred at 40°C for a certain period of time. After cooling to room temperature, the organic compounds were extracted with hexane-ether (1:1, v/v, 3×5 mL) using a syringe. The conversion was determined by GC-MS analysis. The enantiomeric excess was determined by GC (Agilent 6890N) equipped with a chiral column (Chirasil-Dex CP 7502). Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported [42,43]. Formic acid (1.0 mmol) and acetophenone (1.0 mmol) were added into the residual ionic liquid solution for a new reaction cycle.

2.2. Chiral GC analyses of chiral aromatic alcohols

(*R*)-1-Phenylethanol. The GC conditions were: inlet pressure 87 kPa, flow rate 1 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 120°C. t_R 8.67 min for (*R*), 9.73 min for (*S*).

(*R*)-1-Phenylpropanol. The GC conditions were: inlet pressure 58 kPa, flow rate 0.6 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 130°C. t_R 13.08 min for (*R*), 13.79 min for (*S*).

(*S*)-2-Chloro-1-phenylethanol. The GC conditions were: inlet pressure 96 kPa, flow rate 1 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 150°C. t_R 7.45 min for (*S*), 8.08 min for (*R*).

(*S*)-2-Chloro-1-(*p*-methylphenyl)ethanol. The GC conditions were: inlet pressure 96kPa, flow rate 1 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 150°C. t_R 9.78 min for (*S*), 10.83 min for (*R*).

(*R*)-1-(*p*-Chlorophenyl)ethanol. The GC conditions were: inlet pressure 62 kPa, flow rate 0.6 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 140°C. t_R 15.30 min for (*R*), 17.34 min for (*S*).

(*R*)-1-(*p*-Bromophenyl)ethanol. The GC conditions were: inlet pressure 93 kPa, flow rate 1 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 140°C. t_R 16.41 min for (*R*), 18.86 min for (*S*).

(*R*)-1-(*p*-Methylphenyl)ethanol. The GC conditions were: inlet pressure 58 kPa, flow rate 0.6 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 130°C. t_R 11.55 min for (*R*), 12.77 min for (*S*).

(*R*)-1-(*p*-Methoxyphenyl)ethanol. The GC conditions were: inlet pressure 96 kPa, flow rate 1 mL min^{-1}, injector temperature 250 °C, detector temperature 250°C, column temperature 150°C. t_R 6.8 min for (*R*), 7.1 min for (*S*).

(*S*)-2-Chloro-1-(*p*-chlorophenyl)ethanol. The GC conditions were: inlet pressure 110 kPa, flow rate 1.2 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 150°C. t_R 18.51 min for (*S*), 21.41 min for (*R*).

(*R*)-1-(*m*-Bromophenyl)ethanol. The GC conditions were: inlet pressure 96 kPa, flow rate 1 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 150°C. t_R 9.67 min for (*R*), 10.45 min for (*S*).

(*R*)-1-(*m*-Methoxyphenyl)ethanol. The GC conditions were: inlet pressure 81 kPa, flow rate 0.8 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 150°C. t_R 8.04 min for (*R*), 8.49 min for (*S*).

(*R*)-1-(*o*-Methylphenyl)ethanol. The GC conditions were: inlet pressure 60 kPa, flow rate 0.6 mL min^{-1}, injector temperature 250°C, detector temperature 250°C, column temperature 130°C. t_R 14.79 min for (*R*), 17.87 min for (*S*).

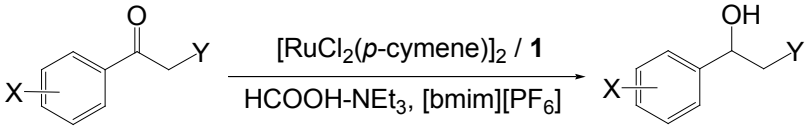
3. Results and Discussion

Ionic liquids are receiving growing attention as a means to immobilize catalysts. Catalysts that are soluble in ionic liquids may be recycled together with the ionic liquid, after extraction with the immiscible solvents used for product separation. Asymmetric transfer hydrogenation of various aromatic ketones has been examined using **1a** and **1b** as ligands in neat water using sodium formate as the hydrogen source [3]. Considering ionic chiral aminosulfonamides **1** are insoluble in most common organic solvents but are highly soluble in water and ionic liquids, the ATH of ketones was carried out in ionic liquid. On the basis of Ohta's work [39], ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] was chosen for the immobilization of the catalysts.

The ruthenium catalysts were prepared *in situ* by reacting aminosulfonamides (*R*,*R*)-**1** with [$RuCl_2$(*p*-cymene)]$_2$ in ionic liquids under argon atmosphere at 40°C for 1 h, and the reduction was started by introducing the formic acid/triethylamine azeotrope (molar ratio HCOOH/NEt_3=2.5:1) and acetophenone with a substrate/catalyst (S/C) ratio of 100:1. Acetophenone was converted into (*R*)-1- phenylethanol in 97% ee with 100% conversion in 8 h using [bmim][PF_6] as solvent when aminosulfonamide (*R*,*R*)-**1a** was used as the ligand (entry 1, Table 1). By using (*R*,*R*)-**1b**, (*R*)-1-phenylethanol was obtained in 100% conversion with 86% ee in 8 h (entry 2, Table 1).This is in stark contrast to the observation made with HCOONa in water, under which acetophenone was fully converted into (R)-1-phenylethanol in 2 h with comparable enantioselectivity [3]. ATH with HCOONa as the hydrogen source in water has shown faster rates than ATH with formic acid/triethylamine azeotrope as the hydrogen source in ionic liquid. The hydrogen source plays an important role [25]. The reaction rate was affected by pH values and HCOOH/NEt_3 molar ratios. For example, , lowering the HCOOH/NEt_3 molar ratios slightly lowered the reaction rate (entries 3 and 4, Table 1). The enantioselectivity varied with the pH value as well, lowering the HCOOH/NEt_3 molar ratios lowered the enantioselectivity dramatically from 98%ee to 84%ee (molar ratio HCOOH/NEt_3=1.2:1) and 81%ee (molar ratio HCOOH/NEt_3=0.7:1) when the reactions were complete.

Encouraged by the results mentioned above, the asymmetric transfer hydrogenation of various kinds of aromatic ketones using Ru-**1a** as a catalyst was investigated in [bmim][PF_6]. As shown in Table 1, the Ru-**1a** catalyst delivered high conversions for most of the ketones in 8 h reaction time and in most cases the

Table 1. Asymmetric transfer hydrogenation of prochiral ketones in [bmim][PF_6] [a]



Entry	X	Y	Ligand	Time (h)	Conversion (%)	ee (%)	Configuration
1	H	H	**1a**	8	100	97	R
2	H	H	**1b**	8	100	86	R
3[b]	H	H	**1a**	9	100	84	R
4[c]	H	H	**1a**	9	100	81	R
5	H	CH_3	**1a**	23	84	97	R
6	H	Cl	**1a**	8	100	86	S
7	*p*-CH_3	Cl	**1a**	8	100	96	S
8	*p*-Cl	H	**1a**	8	100	95	R
9	*p*-Br	H	**1a**	8	100	96	R
10	*p*-CH_3	H	**1a**	8	81	94	R
11	*p*-CH_3O	H	**1a**	48	91	74	R
12	*p*-Cl	Cl	**1a**	8	100	94	S
13	*m*-Br	H	**1a**	9	100	97	R
14	*m*-CH_3O	H	**1a**	9	100	97	R
15	*o*-CH_3	H	**1a**	48	54	81	R
16	*o*-CH_3	H	**1a**	70	77	83	R

[a] *Unless otherwise indicated, reactions were carried out using 1 mmol of ketone, 0.5 mL of formic acid/triethylamine azeotrope, and a S/C ratio of 100 in 1 mL of [bmim][PF_6] under argon atmosphere at 40°C.*
[b] *The HCOOH/NEt_3 molar ratio was 1.2:1.*
[c] *The HCOOH/NEt_3 molar ratio was 0.7:1.*

Table 2. Catalyst recycling in asymmetric transfer hydrogenation of acetophenone in [bmim][PF_6] [a]

Run	Ligand	Time (h)	Conversion (%)	ee (%)	Configuration
1	1a	8	100	97	R
2	1a	22	100	96	R
3	1a	80	100	94	R

[a] *Reactions were carried out using 1 mmol of acetophenone, 0.5 mL of formic acid/triethylamine azeotrope, and a S/C ratio of 100 in 1 mL of [bmim][PF_6] under argon atmosphere at 40 °C in the first run. Since the second run, formic acid (1.0 mmol) and acetophenone (1.0 mmol) were added in every recycling run.*

enantioselectivities were good to excellent, with ee values reaching up to 97%. Exceptions were encountered for aryl ketones bearing strongly electron-donating groups. The *p*-Me, *p*-OMe and *o*-Me substituted acetophenones were much less active. For instance, the reduction of *p*-methoxyacetophenone led to a 91% conversion in 74% ee in 48 h (entry 11, Table 1), the reduction of *o*-methylacetophenone led to a 77% conversion in 83% ee in 70h (entry 16, Table 1). Steric effects might have also contributed in the case of *o*-methylacetophenone. *m*-Methoxyacetophenone displayed faster rate than *p*-methoxyacetophenone. The results found in this study are consistent with those previously reported [8]. As for the asymmetric transfer hydrogenation of propiophenone, excellent enantioselectivity (97% *ee*) and good reactivity (84% conversion after 23 h) were observed (entry 5, Table 1). The present results reveal that ionic chiral aminosulfonamide **1a** and **1b** were efficient ligands for the ruthenium(II)- catalyzed asymmetric transfer hydrogenation of prochiral ketones in water [3] as well as ionic liquid.

From the viewpoint of green chemistry it is highly desirable that the catalyst can be recovered and reused. Recovery and reusability of the catalytic system were tested by carrying out consecutive cycles in [bmim][PF_6] using formic acid/triethylamine azeotrope as the hydrogen source and acetophenone as a standard substrate (Table 2). An attractive feature of the present catalytic system lies in the fact that the catalyst can be readily removed from the product by addition of a low polarity solvent. After the completion of the reaction, the catalytic system was easily recovered after extraction of the reduced products with ether. The residual solution containing the catalyst was recycled and reused for the next reaction by recharging formic acid and acetophenone under the same conditions. Although catalyst recycling led to a quick loss of catalytic activity, a very high conversion (100%) was obtained after a prolonged time of 80 h. The catalytic system could be easily recovered and reused three times with a slight loss of enantioselectivity. The activity of the catalyst showed a remarkable drop on the recycled application. The reason is probably due to some decomposition of the catalyst.

4. Conclusions

In summary, chiral aminosulfonamides containing an imidazolium group were used as ligands for the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of prochiral ketones in ionic liquid, affording good to excellent conversions and enantiomeric excesses. The catalytic system could be easily recovered and reused several times. Studies to further optimize the reaction conditions and to apply chiral aminosulfonamides **1** to other asymmetric catalytic reactions are underway.

Acknowledgements

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