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Short communication

Asymmetric transfer hydrogenation of ketones catalyzed by thermoregulated ionic liquid-regulating ruthenium complexes

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ABSTRACT

A sulfonated chiral diamine ligand anion-based functionalized ionic liquid has been synthesized. Then the new ionic liquid-regulating ruthenium complexes were prepared successfully and employed as efficient catalysts for the asymmetric transfer hydrogenation of various ketones. The catalysts were highly efficient for the hydrogenation of a wide range of substrates bearing different functional groups and could be separated easily from the reaction mixture by thermoregulated phase separation, which can be efficiently recycled five times without significant changes in catalytic activity and enantioselectivity.

1. Introduction

Asymmetric transfer hydrogenation (ATH) has been widely used as an efficient and practical method for preparation of optically pure secondary alcohols that are important key intermediates for the synthesis of a large number of pharmaceutical substances [1]. Catalytic asymmetric hydrogenation is a powerful method for the synthesis of enantiomerically pure compounds [2]. The design of organometallic complexes containing chiral ligand is the fundamental importance for asymmetric catalysis. One of the most attractive catalytic system was developed by Noyori [3], which was based on Ru-TsDPEN (TsDPEN = N-(p-tolylsulfonyl)-1,2-diphenylethylenediamine) complex catalysts with the successful use of HCOOH-NEt_3 azeotropic mixture as hydrogen donor for asymmetric transfer hydrogenation of ketones. In many cases, high activity and enantioselectivity can be achieved with this archetypal catalyst [4].

Ruthenium [5,6] rhodium [7] and iridium [8] complexes using chiral phosphines or amines as ligands exhibited excellent performance in the asymmetric homogeneous hydrogenation of prochiral ketones and other carbonyl compounds. Although numerous highly efficient homogeneous asymmetric catalysts have been developed for ATH in the past decades, the drawback of homogeneous asymmetric catalysis is obvious, such as difficulty in separating product and recycling of the catalyst. To date, only a few recyclable homogeneous catalysts have been reported in the ATH of ketones. For example, they could be separated and recycled through organometal silylated [9], fluorous-tagged and clathrate-enabled technologies [10,11], but the preparation of these catalysts is very complicated. Therefore, a universal method for recovering homogeneous catalysts is still a challenge for the ATH of ketones.

The thermoregulated phase-separation system provided an alternative approach to recycle homogeneous catalysts. This system combines the advantage of homogeneous catalysis with excellent activity and heterogeneous catalysis with the simple method of biphasic catalyst/product separation [12,13]. In this aspect, the thermoregulated phase-separable phosphine ruthenium complex catalyst has been used in catalytic hydrogenation [14], as well as hydroformylation of diisobutylene [15]. Recently, the cooperative effect regulated by a thermoregulated ionic liquid has been suggested by our group in catalytic hydrogenation and epoxidation of olefins [16,17]. However, to the best of our knowledge, the thermoregulated phase-separable catalysts have never been applied to the ATH of ketones up to now.

Here we report on the synthesis of thermoregulated ionic liquid catalysts consisting of poly(ethylene glycol) functionalized imidazolium cations and ruthenium complex anions. The cations of the ionic liquid can regulate the thermoregulated property while the anions play a pivotal role in offering the catalytic active center for the ATH of ketones. From the viewpoint of green catalysis, more attention needs to be paid to the use of environmentally benign media. The current catalyst showed excellent performance for thermoregulated phase-separation in low toxic ethyl acetate media. In a word, we report a new temperature-dependent catalytic system, affording high catalytic activities and good enantioselectivities for the ATH of ketones with HCOOH-Et_3N azeotrope as the hydrogen donor.

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2. Experimental section

The PEG chain-functionalized N-dodecylimidazolium dichlorides ([PEG-4000-C_8MIM] Cl_2) [18] and sulfonated N-(p-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPENDS, sodium salt) were prepared according to the previously reported procedure [19], and then the ionic liquid [PEG-4000-C_8MIM][TsDPENDS] was prepared conveniently by anion exchange in CH_2Cl_2. Thus the ionic liquid-regulating ruthenium complex [PEG-4000-C_8MIM][Ru-TsDPENDS] was obtained according to Scheme 1. The other catalysts [PEG-m-C_nMIM][Ru-TsDPENDS] were synthesized in a similar manner, where m represented the molecular weight of PEG and n alkyl chain length was tethered in imidazolium ring. All synthetic procedures and characterization of the ionic liquid-regulating ruthenium complexes have been afforded in the supporting information (Figs. 1S–15S).

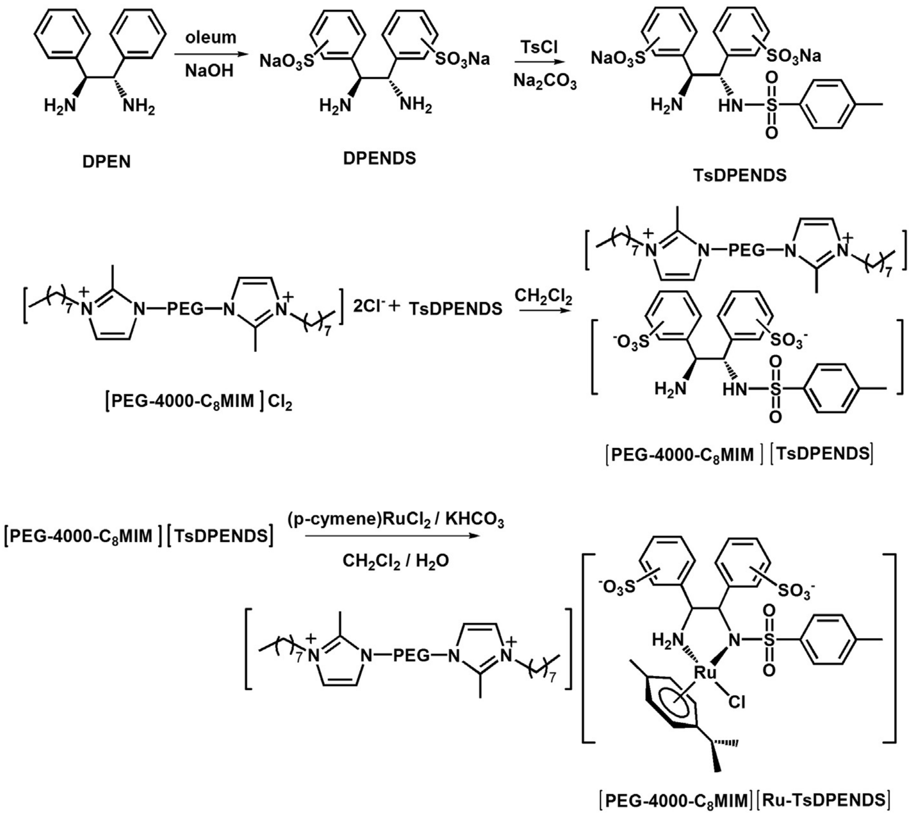
3. Results and discussion

3.1. Catalyst characterization

The ionic liquid-regulating ruthenium catalysts [PEG-m-C_nMIM][Ru-TsDPENDS] were characterized by ^{1}H NMR spectroscopy, ESI-MS, and elemental analysis (supporting information). The ^{1}H NMR spectra confirmed the formation of the proposed ruthenium arene complexes with sulfonated diamine ligand. In anion moiety, all proton resonances of the ethylenediamine, p-cymene and methyl groups of the isopropyl group were non-equivalent. The ESI-MS data of the catalysts were in agreement with the proposed structures and showed one group of peaks at 378.99 values corresponding to the molecular anion $\{[\text{Ru-TsDPENDS}]\text{-HCl}\}^{2-}$ (Figs. 3S, 5S and 7S). The results of ^{1}H NMR spectroscopy and ESI-MS on $\{(\text{p-cymene})RuCl_2\}_2$ part were similar to those of previously reported ruthenium complexes for the ATH of ketones in water [20]. In addition, the UV/vis spectra of [PEG-4000-C_8MIM][TsDPENDS], $\{(\text{p-cymene}) RuCl_2\}_2$ and [PEG-4000-C_8MIM][Ru-TsDPENDS] have been performed. As shown in Fig. 1a, the absorbance at 260–270 nm can be assigned to adsorption of imidazolium and aromatic rings in [PEG-4000-C_8MIM][TsDPENDS] (Fig. 1a). However, a peak at 410 nm was attributed to Cl p → Ru d transition (Fig. 1b), and it was moved to 565 nm after the diamine ligand was coordinated with Ru as shown in (Fig. 1c). The shift of adsorbing wavelength demonstrated that diamine ligand was coordinated with Ru complex. The similar shift was also found in the UV/vis spectra of [PEG-4000-C_4MIM][Ru-TsDPENDS] and [PEG-4000-C_1MIM][Ru-TsDPENDS] (Figs. 8S and 9S). Actually, the phenomenon has been observed in molecularly imprinted Ru-complex catalysts for the ATH in water media [21]. On the basis of the results of elemental analysis of C, H, N and ICP-AES analysis of Ru, the ionic liquid catalysts [PEG-m-C_nMIM][Ru-TsDPENDS] have been synthesized successfully. The thermal stability of the ionic liquid catalyst was examined by using the TGA method (Fig. 10S). The onset decomposing temperature was around 250 °C and almost decomposed completely at 600 °C.

3.2. Catalytic performance

From our previous work, it was known that poly(ethylene glycol)-2000 functionalized 1-alkylate-2-methylimidazolium chloride ([PEG-2000-C_{12}MIM]Cl_2), coupled with EtOAc as the solvent, exhibits a strong thermoregulated behavior [16]. Thus, in this work we first prepared poly(ethylene glycol) functionalized imidazolium chloride. To obtain high enantioselectivity, the mono-N-tosylated derivative TsDPENDS was chosen as anion of the ionic liquid. Therefore, the as-obtained ionic liquid was composed of poly(ethylene glycol)-functionalized alkylimidazolium cation and TsDPENDS anion. The cation of ionic liquid provided the thermoregulated property while the anion played a pivotal role in providing a chiral center for Ru coordination.



Scheme 1. Typical procedure for preparing the ionic liquid catalyst [PEG-4000-C_8MIM] [Ru-TsDPENDS].

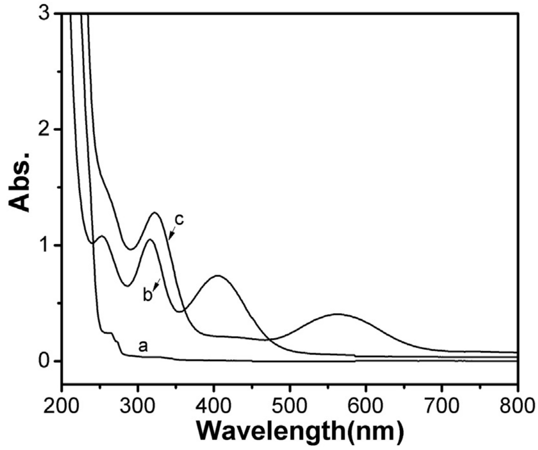


Fig. 1. UV–vis spectra of a) the [PEG-4000-C$_8$MIM][TsDPENDS] in water; b) the $\{(p\text{-cymene})RuCl_2\}_2$ in water; and c) the [PEG-4000-C$_8$MIM][Ru-TsDPENDS] in water.

The thermoregulated property of different catalysts [PEG-m-C$_n$MIM][Ru-TsDPENDS] in ethyl acetate was first screened, the transfer hydrogenation of acetophenone was chosen as the model reaction (Table 1). At first, three ionic liquid-regulating ruthenium complexes ([PEG-2000-C$_n$MIM][Ru-TsDPENDS], $n = 1$, 4 and 8, respectively) have been prepared. Unfortunately, these catalysts were all partially soluble in ethyl acetate at room temperature and cannot be precipitated from ethyl acetate even at 0 °C (Table 1, entries 1–3). However, when the chain length of PEG-2000 was replaced by that of PEG-4000, it was found that three ruthenium complexes ([PEG-4000-C$_n$MIM][Ru-TsDPENDS], $n = 1$, 4 and 8, respectively) exhibited excellent temperature-dependent behavior in ethyl acetate (Table 1, entries 4–6). Furthermore, the ionic liquid [PEG-4000-C$_8$MIM][Ru-TsDPENDS] with long alkyl chain ($n = 8$) proved to offer a better solubility in ethyl acetate during the reaction conditions and exhibited a higher conversion, in comparison with [PEG-4000-C$_1$MIM][Ru-TsDPENDS] (Table 1, entry 4 vs 6). An explanation is that the stronger hydrophobic interaction of the ionic liquid and substrate results in more accessibility of the substrate to catalytically active anion center. However, if the ionic liquid with longer alkyl chain ($n = 12$) was used, it resulted in a poor thermoregulated separation behavior. Especially, the absence of the ionic liquid cation could not promote the hydrogenation reaction due to the very poor solubility of sulfonated diamine ligand in ethyl acetate (Table 1, entry 7).

Next, the thermoregulated behavior of [PEG-4000-C$_8$MIM][Ru-TsDPENDS] was examined in the ATH of acetophenone. Before the reaction, the catalyst sank to the bottom of the flask (Fig. 3a). After adding azeotrope, acetophenone and increasing temperature to 40 °C, the resulting mixture became a homogeneous phase with a reddish brown color in ethyl acetate (Fig. 3b), and catalyst can catalyze smoothly and efficiently the reduction of acetophenone to the chiral 1-phenylethanol. As the reaction completed and temperature decreased, the catalyst was precipitated completely from the reaction system as solid and the ethyl acetate phase reverts to colorless (Fig. 3c). Therefore, this catalysis system showed the properties of thermoregulated phase-separation, which can offer an effective and convenient route to isolate the product and improve the recyclability of the catalyst.

Table 1
The catalytic activity, enantioselectivity and thermoregulated performance of different catalysts in ATH of acetophenone.

Entries	Catalysts	Con.%[a]	Ee.%[b]	Thermoregulated phase separation
1	[PEG-2000-C$_1$MIM][Ru-TsDPENDS]	67.8	95	No
2	[PEG-2000-C$_4$MIM][Ru-TsDPENDS]	77.6	96	No
3	[PEG-2000-C$_8$MIM][Ru-TsDPENDS]	99.5	96	No
4	[PEG-4000-C$_1$MIM][Ru-TsDPENDS]	64.5	94	Yes
5	[PEG-4000-C$_4$MIM][Ru-TsDPENDS]	94.8	96	Yes
6	[PEG-4000-C$_8$MIM][Ru-TsDPENDS]	97.5	95	Yes
7	[Ru-TsDPENDS]	25.9	51	No

[a] Reactions were carried out at 40 °C using 0.5 mmol of acetophenone and 0.005 mmol Ru(II) complex in 1 mL ethyl acetate and 0.2 mL HCOOH-NEt$_3$ azeotropic mixture for 10 h, 4 equivalents of HCOOH as hydrogen donor.

[b] GC analysis was performed with a β-DEX™120 capillary column (30 m × 0.25 mm, 0.25 μm film) and dodecane as internal standard.

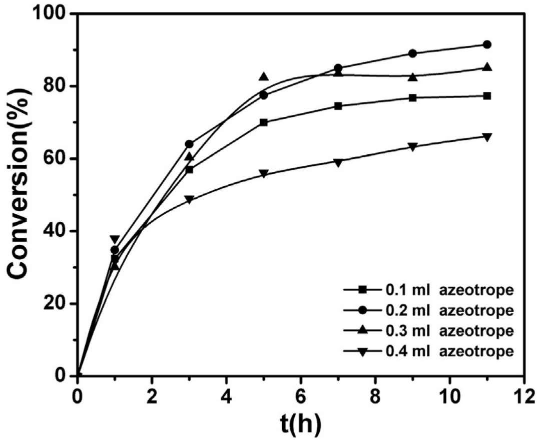


Fig. 2. Time profile of the reduction of acetophenone with different amounts of azeotrope.

Sequentially, the effects of the addition of HCOOH-NEt$_3$ azeotropic mixture on the reaction activity and phase separation behavior were examined over [PEG-4000-C$_8$MIM] [Ru-TsDPENDS] catalyst (Fig. 2). When the volume of azeotrope increased from 0.1 mL to 0.2 mL, the final conversion increased from 73% to 92%. However, when azeotrope increased to 0.3 mL, the final conversion reduced to 86%. By continuing the increase of the amount of azeotrope, the final conversion declined to 66%. The results indicated that more addition of the azeotrope was not favorable for the AHT reaction. With excessive formic acid, the reaction proceeded very slowly, probably because the protonation of the amino-group of the diamine ligand followed by its decoordination from the Ru atom [22,23]. Acid–base titration analysis indicated that a small amount of formic acid still remained after the reaction when the addition of the azeotrope was more than 0.2 mL. Besides, adding too much azeotrope (more than 0.2 mL in this case) led to the poor thermoregulated separation due to the good miscibility of [PEG-4000-C$_8$MIM][Ru-TsDPENDS] with the residual formic acid.

3.3. Substrate generality and reusability of the catalyst

Under the optimal conditions, we subsequently examined the substrate scope with a wide range of ketones. A variety of aromatic ketones were smoothly hydrogenated with high reactivities and enantioselectivities using a thermoregulated catalyst [PEG-4000-C$_8$MIM][Ru-TsDPENDS]. The reaction kinetic curves of the reactive substrates like acetophenone and p-bromoacetophenone, and less reactive substrate p-methyl-acetophenone were shown in Fig. 16S, indicating that the aromatic ketones with electron withdrawing group gave higher reactivity (Table 2, entries 1–4), while the aromatic ketones with electron donating group lowered reactivity (Table 2, entries 8, 9), which was in agreement with the previous report [24]. It was worth noting that the substituted groups had an obvious influence on the reaction rate, but not on the enantioselectivity (Table 2, entries 2–4, 8, 9). In the hydrogenation of the heteroatom aromatic ketones (Table 2, entries 5 and 6), chiral alcohol was obtained in high conversion and enantioselectivity. Good conversion and enantioselectivity were also observed in the reduction of 2-acetonaphthone (Table 2, entries 7).

Subsequently, the recyclability of the catalyst was examined by choosing the acetophenone as a model substrate in ethyl acetate. The

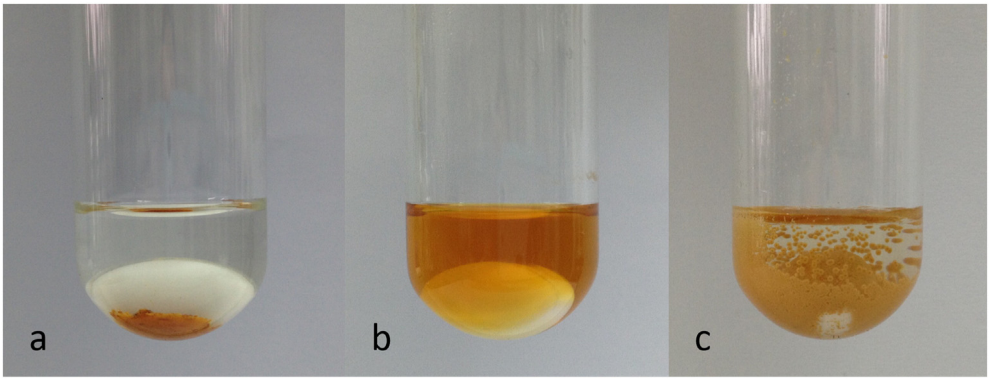
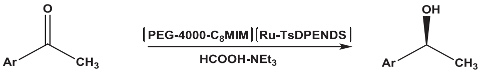


Fig. 3. The process of thermoregulated phase-separable catalysis via [PEG-4000-C_8MIM][Ru-TsDPENDS]: a) catalyst, ethyl acetate, HCOOH-NEt_3 and acetophenone at 0 °C; b) reaction at 45 °C; and c) complete phase-separation after cooling to 0 °C. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

catalyst could be reused by simple decantation of the products in the supernatant organic phase after reaction. The procedure was repeated five times and the results indicated that catalyst [PEG-4000-C_8MIM][Ru-TsDPENDS] could be recycled at least five times without much loss of the catalytic activity (Fig. 4). It was further found that the total amount of Ru(II) leaching into the organic phase was only 2.8 ppm by ICP-AES analysis in the whole four consecutive cycles, which confirmed that the clean separation can be achieved efficiently through the thermoregulated system.

Table 2

ATH of ketones with catalyst [PEG-4000-C_8MIM][Ru-TsDPENDS] in EtOAc.



Entry	Ar	Time (h)	Conv. (%)[a]	Ee (%)[b]
1	C_6H_5	10	97.5	95
2	4-BrC_6H_4	6.5	99.4	93
3	4-ClC_6H_4	6.5	99.5	92
4	4-$NO_2C_6H_4$	6.5	99.7	86
5	4-Thienyl	10	80.5	97
6	4-Furyl	10	96.5	97
7	2-Naphthyl	10	99.5	96
8	4-MeC_6H_4	16	66.3	95
9	4-MeOC_6H_4	16	55.0	92

[a] Reactions were carried out at 40 °C using 0.5 mmol of substrates and 0.005 mmol catalyst in 1 mL ethyl acetate and 0.2 mL HCOOH-NEt_3 azeotrope.

[b] GC analysis was performed with a β-DEX™120 capillary column (30 m × 0.25 mm, 0.25 μm film) and dodecane as internal standard.

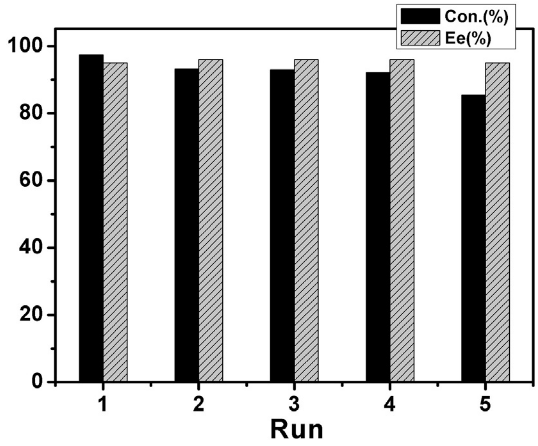


Fig. 4. Recyclability of catalyst [PEG-4000-C_8MIM][Ru-TsDPENDS] for ATH of acetophenone.

4. Conclusion

The functionalized ionic liquid-regulating ruthenium complex catalysts have been developed and employed successfully to ATH at the first time. The catalyst [PEG-4000-C_8MIM][Ru-TsDPENDS] displayed both excellent activity and enantioselectivity for the ATH of the aromatic ketone. Moreover, this type of catalytic system displayed excellent thermoregulated phase-separation behavior in ethyl acetate, resulting in highly clean separation and an effective recycling of the catalyst. It is believed that this catalytic system could be extended for the other reactions dealing with the separation of catalyst in homogeneous catalysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2015.04.013.

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