Asymmetric Catalysis

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Hydrogenation of Quinolines Using a Recyclable Phosphine-Free Chiral Cationic Ruthenium Catalyst: Enhancement of Catalyst Stability and Selectivity in an Ionic Liquid**

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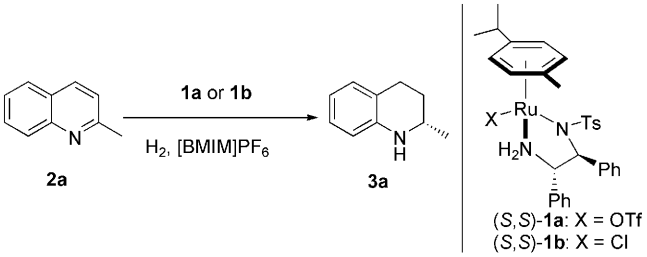
Dedicated to Professor Zhi-Tang Huang on the occasion of his 80th birthday

Room-temperature ionic liquids (RTILs) have recently received a great deal of attention as alternative reaction media.[1] Numerous catalytic reactions have proven feasible in a variety of ionic liquids, with many reactions displaying enhanced reactivities and selectivities, and some of which were not possible in common organic solvents.[2] Furthermore, RTILs have served as a promising means to immobilize a catalyst, therefore facilitating product isolation and offering an opportunity to reuse the catalyst. However, the use of RTILs in asymmetric catalytic reactions is still limited.[1f,g,2f,3] The recycling and reuse of chiral catalysts in ionic liquids have often been problematic because of the instability and/or leaching of the catalysts. From a practical standpoint, development of highly effective and recyclable catalysts in ionic liquids for use in asymmetric hydrogenation remains a challenge: in particular for heteroaromatic substrates which are difficult to hydrogenate.

Although a variety of chiral Rh, Ru, and Ir complexes have been efficient and enantioselective reagents for the hydrogenation of prochiral olefins, ketones, and imines,[4] most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[5] A few successful examples for the asymmetric hydrogenation of quinolines have recently been reported.[6] However, all catalysts for such reactions have at least one phosphine ligand around the metal center and are often air sensitive.[7] From the viewpoints of both scientific interest and practical application, it is highly desirable to develop recyclable and phosphine-free chiral catalysts for the highly enantioselective hydrogenation of quinolines. Few examples of phosphine-free homogeneous catalysts capable of activating molecular hydrogen have been reported.[8] Recently, Noyori and co-workers reported that chiral η^6-arene/*N*-tosylethylenediamine–Ru^{II} complexes (which are known as excellent catalysts for asymmetric transfer hydrogenation, for example Ru/Ts-dpen) can be used for the asymmetric hydrogenation of prochiral ketones under slightly acidic conditions.[9] Inspired by this important breakthrough and following our continued pursuit of developing effective and environmentally benign catalyst systems for asymmetric hydrogenations,[10] herein we report a practical and efficient catalyst system of Ru/Ts-dpen in $[BMIM]PF_6$ (BMIM = 1-*n*-butyl-3-methylimidazolium) for the enantioselective hydrogenation of quinolines (Scheme 1).



Scheme 1. Asymmetric hydrogenation of quinoline **2a** catalyzed by Ru/Ts-dpen catalysts. Ts-dpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine.

We have found that quinoline substrates could be efficiently hydrogenated to give 1,2,3,4-tetrahydroquinolines with excellent enantioselectivities (up to 99% *ee*) in neat ionic liquid without the need for additives. Furthermore, the catalyst, which was highly stable in ionic liquid and maintained the same activity even after exposure to air for 30 days, could be easily recycled.

Considering that methanol has been successfully used in the asymmetric hydrogenation of ketones by Noyori and coworkers,[9] we first examined the asymmetric hydrogenation

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of 2-methylquinoline (**2a**) catalyzed by (*S*,*S*)-**1a** in methanol. High enantioselectivity and conversion were obtained at room temperature under 50 atmospheres of hydrogen with a substrate/catalyst ratio of 100:1 (Table 1, entry 1). To our knowledge, this is the first example of a highly enantioselective hydrogenation of heteroaromatic compounds catalyzed by phosphine-free transition-metal complexes.

Table 1: Asymmetric hydrogenation of **2a** catalyzed by (*S*,*S*)-**1a** or (*S*,*S*)-**1b**.[a]

Entry	Cat.	Solvent	Reaction conditions H_2 [atm]	T [°C]	Conv. [%][b]	*ee* [%][c]
1	**1a**	MeOH	50	25	100(100)[d]	94(96)[d]
2	**1a**	[BMIM]PF_6	50	25	100 (30)[d]	99(−50)[d]
3	**1b**	[BMIM]PF_6	50	25	< 5	n.d.
4[e]	**1a**	[BMIM]PF_6	50	25	< 5	n.d.
5	**1a**	[BMIM]PF_6	20	25	54	98
6	**1a**	[BMIM]PF_6	80	25	100	99
7	**1a**	[BMIM]PF_6	50	50	100	98
8[f]	**1a**	[BMIM]PF_6	50	25	100	99

[a] Reaction conditions: **2a** (0.20 mmol) in [BMIM]PF_6 or MeOH (1.0 mL), (*S*,*S*)-**1** (1.0 mol%), 25 °C, 15–24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase. The predominant product has the *S* configuration. [d] Data in brackets were obtained by using acetophenone as the substrate under otherwise identical reaction conditions. [e] $BnMe_3N^+Cl^-$ (5.0 mol%) was added. [f] The catalyst was stored in [BMIM]PF_6 in air for 30 days after the first run and then used for the reaction. n.d. = not determined.

When methanol was replaced by neat [BMIM]PF_6, the hydrogenation of **2a** proceeded smoothly to give the partially reduced product **3a** in quantitative yield and with an even higher enantioselectivity (94% vs. 99% *ee*, compare Table 1, entry 1 vs. 2). This result was of particular interest because the hydrogenation of acetophenone was found to be sluggish in [BMIM]PF_6, and afforded the alcohol in a much lower enantioselectivity with the opposite configuration (96% vs. −50% *ee*, compare Table 1, entry 1 vs. 2).[11] Notably, catalysts (*S*,*S*)-**1b** (with chloride as the counterion) or (*S*,*S*)-**1a** (with $BnMe_3N^+Cl^-$ as the additive) showed no reactivity in [BMIM]PF_6 (Table 1, entries 3 and 4). The enantioselectivity of this reaction was insensitive to the H_2 pressure and the temperature (Table 1, entries 5–7). A low conversion was obtained under relatively lower pressure (Table 1, entry 5). Even after exposing the catalyst solution to air for 30 days, the reused catalyst gave almost the same activity and enantioselectivity (Table 1, entry 8).[12] However, under identical reaction conditions, catalyst (*S*,*S*)-**1a** in methanol decomposed within one week. The dramatic enhancement of the catalyst stability by an ionic liquid was probably a result of the solvation effect of [BMIM]PF_6 on the cationic Ru catalyst and the very low solubility of oxygen in the ionic liquid.[13,14]

The recyclability of the Ru catalyst (*S*,*S*)-**1a** in [BMIM]PF_6 was then examined by using **2a** as the model substrate. Upon completion of the reaction, the reduced product was easily separated by extraction with *n*-hexane. The ionic liquid phase was recharged with **2a** and again subjected to hydrogenation under the same reaction conditions. The Ru catalyst was reused eight times, with retention of reactivity and enantioselectivity both maintained up until the sixth run (Table 2, runs 1–6), and a slight decrease in reactivity was observed thereafter (Table 2, runs 7 and 8). No signals associated with the IL were detected in ^{1}H NMR spectra of the extracted crude product. Inductively coupled plasma (ICP) spectroscopy further showed that no significant leaching of Ru occurred during the extraction of organic products. From the ICP experiments, we estimated that less than 0.4% of the Ru catalyst had leached from the [BMIM]PF_6 into the hexane extract. These results further demonstrated the high stability of the Ru/Ts-dpen catalyst in an ionic liquid.

Table 2: Reuse of (*S*,*S*)-**1a** in the asymmetric hydrogenation of **2a**.[a]

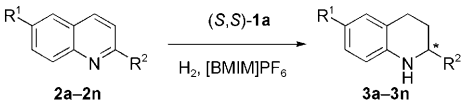
Run	Conversion [%][b]	Yield [%][c]	*ee* [%][d]
1	100	91	99
2	100	97	99
3	100	96	99
4	100	97	98
5	100	96	98
6	100	95	98
7	88	84	98
8	82	80	97

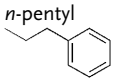
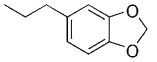
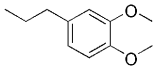
[a] Reaction conditions: see Table 1, entry 2. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase.

Next, we examined a variety of substituted quinoline derivatives in asymmetric hydrogenation reactions that were catalyzed by (*S*,*S*)-**1a** in [BMIM]PF_6 (Table 3). In general, all 2-alkyl-substituted quinolines were hydrogenated with good yields and remarkable enantioselectivities (up to 99% *ee*; Table 3, entries 1–13). The reaction was found to be insensitive to the length of the alkyl side chain as well as the existence of free hydroxy groups on the side chain (Table 3, entries 1–10). Substitution at the 6-position had no obvious effect on either yield or enantioselectivity (Table 3, entries 11–14). For example, the hydrogenation of **2k** proceeded smoothly in good yield and with much higher enantioselectivity than that obtained with the Ir/MeO-biphep catalyst (99% (Table 3, entry 11) vs. 84% *ee*; biphep = 2,2′-bis(phosphanyl)biphenyl).[6a] Interestingly, substrate **2n** bearing an acetyl group at the 6-position could be selectively hydrogenated to tetrahydroquinoline **3n** in good yield with 96% *ee* (Table 3, entry 14). Hydrogenation of **2n** under high pressure (100 atm) gave only slightly lower yield and enantioselectivity. These results indicated that the hydrogenation with (*S*,*S*)-**1a** in ionic liquid was selective for C=N (quinoline) over C=O bonds.[15] Significantly, the enantioselectivities for the hydrogenation of these substrates are among the highest reported to date.

To further investigate whether the catalytic pathway follows the same concerted mechanism proposed for the reduction of ketones,[9b] we carried out the hydrogenation of **2a** with a stoichiometric amount of hydride complex (*R*,*R*)-**4** (Table 4). To our surprise, no reaction between (*R*,*R*)-**4** and **2a** occurred, even with an excess of the hydride (5 equiv) after 12 h (Table 4, entry 1). Instead, the protonated species of **2a** reacted smoothly with the hydride (*R*,*R*)-**4** to give the reduced

Table 3: Enantioselective hydrogenation of quinoline derivatives using (*S*,*S*)-**1a**.[a]



Entry	Substrate	R^1	R^2	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	H	Me	**3a**	96	99 (99)[d]
2	**2b**	H	Et	**3b**	95	98 (98)[d]
3	**2c**	H	*n*Pr	**3c**	95	99 (98)[d]
4[e]	**2d**	H	*n*Bu	**3d**	95	98
5	**2e**	H	*n*-pentyl	**3e**	97	98
6	**2f**	H		**3f**	96	97
7	**2g**	H		**3g**	96	97
8	**2h**	H		**3h**	96	98
9	**2i**	H		**3i**	92	99
10	**2j**	H		**3j**	93	99
11	**2k**	MeO	Me	**3k**	91	99
12	**2l**	Me	Me	**3l**	94	99
13	**2m**	F	Me	**3m**	92	98
14[e]	**2n**	CH_3CO	Me	**3n**	87 (81)[f]	96 (95)[f]

[a] Reaction conditions: substrate (0.20 mmol) in [BMIM]PF_6 (1.0 mL), (*S*,*S*)-**1a** (1.0 mol%), H_2 (50 atm), 25°C, 15–24 h. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. Products **3a**–**c**, **3e**–**h**, and **3k**–**m** have the *S* configuration, whereas **3d**, **3i**,**j**, and **3n** have the *R* configuration. [d] Data in brackets were obtained by employing the reused catalyst which was stored in [BMIM]PF_6 in air for 30 days before the second run. [e] (*R*,*R*)-**1a** was used. [f] Data in bracket were obtained under 100 atmospheres of H_2.

Table 4: Stoichiometric reaction between **2a** and hydride complex (*R*,*R*)-**4** (where X = H) in [BMIM]PF_6.

Entry	Reactants	Additive	Product	Conv. [%][a]	*ee* [%][b]
1	**2a** + (*R*,*R*)-**4** (5 equiv)	none	no reaction	–	–
2	**2a**·TfOH + (*R*,*R*)-**4** (5 equiv)	none	**3a**	48	99
3	**2a**·TfOH + (*R*,*R*)-**4** (5 equiv)	**3e**·TfOH (1 equiv)	**3a**	95	99

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC on a chiral stationary phase.

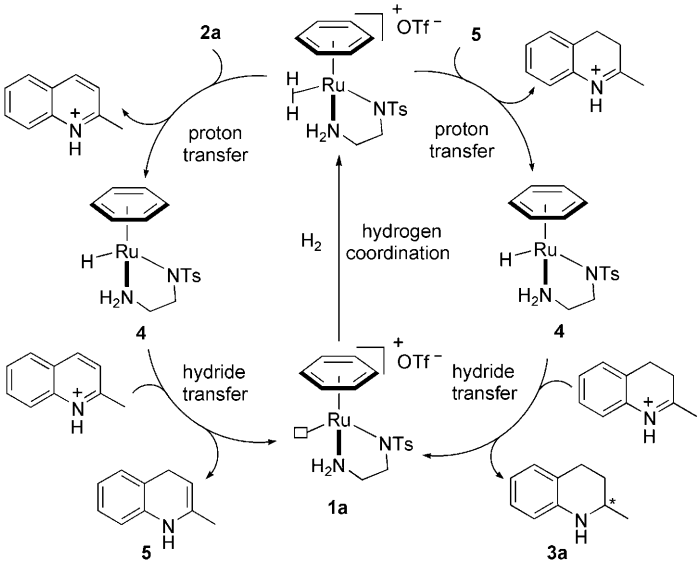
product in 48% yield with identical enantioselectivity to that of the catalytic reaction (Table 4, entry 2). The reaction mixture retained a yellow color throughout, indicating the absence of the 16-electron amide complex (purple). Furthermore, in the presence of a tetrahydroquinoline salt proton source (1 equiv; which was generated by mixing **3e** with TfOH), the protonated **2a** reacted with the hydride (*R*,*R*)-**4** to give the reduced product in 95% yield and 99% *ee* (Table 4, entry 3).

On the basis of these observations, we speculate that the hydrogenation of quinoline occurs by a different mechanism to that of the hydrogenation of ketone in methanol. A proposed ionic catalytic pathway is shown in Scheme 2. In this mechanism, dihydrogen is first coordinated to the cationic **1a** and the complex formed is then deprotonated by **2a** to generate the active monohydride complex **4** and the activated **2a**.[16] A subsequent 1,4-hydride transfer affords the enamine **5** and the regenerated catalyst **1a**. Similarly, **5** is activated by protonation to form an iminium cation,[17,18] which is susceptible to 1,2-hydride transfer, to give the final product **3a** and **1a**. Recently, Ru-catalyzed ionic hydrogenation[19] of iminium cations has been proposed by Norton and coworkers[8d] where the iminium ions were reduced through a stepwise H^+/H^- transfer process.

In conclusion, we have demonstrated the first phosphine-free cationic Ru/Ts-dpen catalyst to exhibit unprecedented reactivity and high enantioselectivity in the hydrogenation of quinolines in neat ionic liquid. The use of ionic liquid not only facilitates the recyclability, but also enhances the stability and selectivity of the catalyst. Detailed mechanistic study and further exploration of this catalyst for the hydrogenation of other heteroaromatic compounds are in progress.

Experimental Section

A typical procedure for the asymmetric hydrogenation of quinolines (Table 1, entry 2) and the catalyst recycling: A 50 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was



Scheme 2. Proposed mechanism for the hydrogenation of **2a** catalyzed by **1a** in an ionic liquid. The substituents on the arene and ethylenediamine ligands are omitted for clarity.

charged with Ru catalyst ((*S*,*S*)-**1a**, 1.5 mg, 0.002 mmol) and 2-methylquinoline (**2a**; 28.6 mg, 0.20 mmol) in $[BMIM]PF_6$ (1.0 mL). The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atmospheres after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for a predetermined period of time. After the autoclave was depressurized, the hydrogenated product was extracted with *n*-hexane or diethyl ether (6×1 mL) before being passed through a short column of silica gel. The residual ionic liquid phase containing the catalyst was recycled and reused for the next reaction by recharging of the substrates under the same reaction conditions. The conversion of the reaction was based on ^1H NMR spectra, and the *ee* value was determined by HPLC on a chiral stationary phase (91% yield, 99% *ee*).

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