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Highly Enantioselective Synthesis of Chiral Tetrahydroquinolines and Tetrahydroisoquinolines by Ruthenium-Catalyzed Asymmetric Hydrogenation in Ionic Liquid

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Abstract: Asymmetric hydrogenation reactions of quinolines and 3,4-dihydroisoquinolines using the chiral cationic ruthenium complex Ru(TsDPEN) [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] as catalyst in neat imidazolium ionic liquids have been investigated. The catalytic performance was influenced by the anion of the ionic liquids for both substrate classes. A range of 2-alkyl-substituted 1,2,3,4-tetrahydroquinolines and 1-alkyl-substituted 1,2,3,4-tetrahydroisoquinolines was obtained in high yields with up to >99% *ee*. Interestingly, the hydrogenation of quinoline derivatives bearing a carbonyl group was selective for the C=N (quinoline) over the C=O (ketone) bonds, while such a unique chemoselectivity was not observed in methanol. Furthermore, the ruthenium catalysts could be easily recycled at least 5 times in the asymmetric hydrogenation of 3,4-dihydroisoquinoline by solvent extraction. To further facilitate the recovery of catalyst and reduce the use of organic solvent, a thin film of ionic liquid containing Ru(TsDPEN) was supported on silica gels. This supported ionic liquid-phase catalyst was effective in the asymmetric hydrogenation of quinoline, and could be recycled at least 6 times by simple filtration.

Keywords: asymmetric hydrogenation; catalyst recycling; ionic liquids; tetrahydroisoquinolines; tetrahydroquinolines

Introduction

Optically active tetrahydroquinolines and tetrahydroisoquinolines are two kinds of important structural units in a large number of natural and synthetic products with a wide variety of biological activities.[1] For example (Figure 1), (*S*)-flumequine,[1b] which belongs to the quinoline family, is an important antibacterial agent. Solifenacin is a prescription drug for the treatment of overactive bladder.[1c] Chiral torcetrapib[1d] has recently attracted much attention for the treatment of low high-density lipoprotein cholesterol and atherosclerosis. In addition, many naturally occurring alkaloids contain tetrahydroquinoline or tetrahydroisoquinoline units, including carnegine,[1e,f] angustureine,[1g] cuspareine,[1h] and galipinine.[1h] Therefore, it is not surprising that the development of efficient methods for the preparation of such enantiomerically enriched heterocycles has been an appealing goal in both academia and industry for many years.

Among various methods available for the synthesis of chiral 1,2,3,4-tetrahydroquinolines[1a,2a] and 1,2,3,4-tetrahydroisoquinolines,[2b] asymmetric homogeneous hydrogenation of the corresponding unsaturated compounds using inexpensive molecular hydrogen and a small amount of chiral transition metal catalyst is perhaps the most straightforward, efficient and atom-economic method. Indeed, considerable progress has been made in this field over the past decade.[3] A variety of chiral metal catalysts, including Ir, Ru, Ti, Rh and Pd complexes, has been successfully employed in the asymmetric hydrogenation of readily available quinolines,[4] isoquinolines[5] as well as isoquinoline-type imines,[6] affording the chiral 1,2,3,4-tetrahydro-

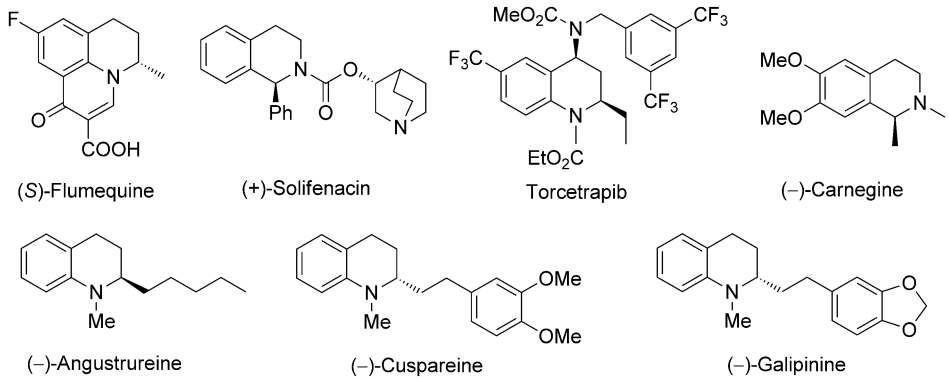


Figure 1. Structures of selected bioactive compounds and alkaloids derived from chiral 1,2,3,4-tetrahydroquinoline or 1,2,3,4-tetrahydroisoquinoline derivatives.

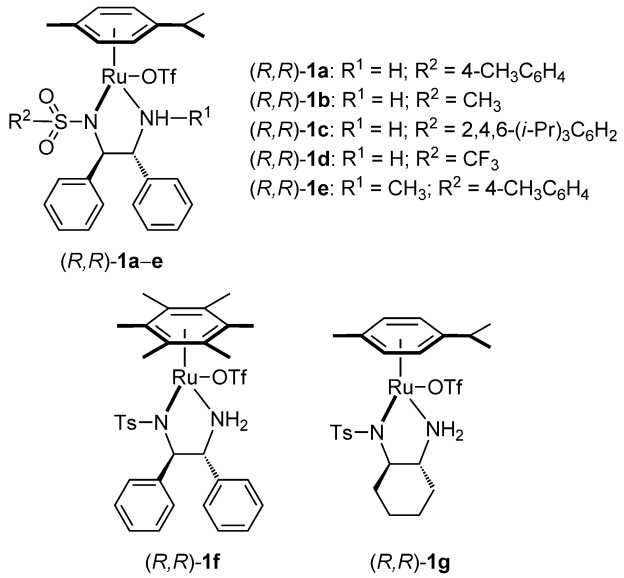
quinolines and 1,2,3,4-tetrahydroisoquinolines with good to excellent enantioselectivities. However, in comparison with the relative maturity of asymmetric hydrogenation of prochiral olefins and ketones, enantioselective hydrogenation of nitrogen-containing heterocyclic compounds, including heteroaromatic compounds and cyclic imines, is still suffering from some drawbacks. First, asymmetric hydrogenation of heteroaromatic compounds under mild conditions might be difficult due to their high resonance stability. Second, the nitrogen-containing substrates and/or products may poison and/or deactivate the metallic catalysts, and thus high catalyst loading (1.0 mol% in most cases) is often required.[7] In addition, recycling of the homogeneous catalysts is still a big challenge. From the viewpoints of both fundamental research and industrial applications, more efficient, stable and recyclable catalyst systems are desirable.

On the other hand, room-temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations have emerged as environmentally benign alternative reaction media for a number of catalytic reactions.[8] Many catalytic reactions displayed enhanced reactivities and selectivities in RTILs, even the ones which could not occur in common organic solvents.[9] Furthermore, the widely tunable features of RTILs can be adapted to a specific catalytic reaction and their advantages as reusable homogeneous supports offer an opportunity to reuse the catalyst. Most recently, we demonstrated that the phosphine-free chiral cationic Ru(TsDPEN) complex [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] was an efficient catalyst for the enantioselective hydrogenation of quinoline derivatives in neat [Bmim]PF_6 (Bmim = 1-*n*-butyl-3-methylimidazolium).[4d] It was found that the use of ionic liquid not only facilitated the recycling of catalyst, but also enhanced the stability and selectivity of the catalyst. Encouraged by these preliminary observations, we then performed a systematic and detailed study on the asymmetric hydrogenation of quinolines and 3,4-dihydroisoquinolines in imidazolium ionic liquids. It was found that a range of 2-substituted quinoline and 1-alkyl-3,4-dihydroisoquinoline derivatives could be efficiently hydrogenated to give the chiral 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinolines with unprecedented reactivity, chemoselectivity and excellent enantioselectivity. In addition, the ruthenium catalysts in ionic liquid are more stable and could be recycled by simple solvent extraction. The hydrogenation and catalyst recycling were also realized by using the ruthenium catalyst immobilized in a supported ionic liquid-phase.

Results and Discussion

Asymmetric Hydrogenation of Quinoline Derivatives Catalyzed by Cationic Ruthenium Catalysts in Ionic Liquids

The pioneer works on asymmetric hydrogenation of quinolines were started by Zhou and co-workers.[4a] They first reported that an Ir/MeO-BIPHEP/I_2 system could produce chiral tetrahydroquinolines with up to 96% *ee*. After that, numerous Ir complexes containing chiral phosphorus ligands have been developed for the hydrogenation of a wide range of quinoline derivatives with good to excellent enantioselectivities.[3b] In most cases, good results could only be obtained at a low substrate/catalyst ratio of 100. Additionally, almost all the reactions were carried out in aprotic organic solvents, such as toluene and THF. The hydrogenation of 2-methylquinoline in ionic liquid resulted in poor *ee*s and conversions.[4c] In contrast, the Ru complexes containing chiral diamines[10] were found to be highly effective catalysts for the asymmetric hydrogenation of quinolines in neat ionic liquid.[4d] In addition, such transformation could also be carried out under solvent-free conditions by using the same Ru-TsDPEN catalyst.[4e] Both catalytic systems catalyzed the reaction under homogeneous conditions

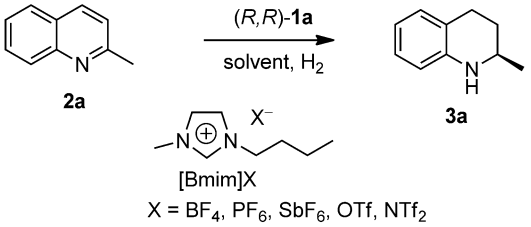


Scheme 1. Chiral diamine-containing ruthenium catalysts used in this study.

with high reactivity. However, in the latter case, the ruthenium catalyst could not be recycled. To develop a more efficient and recyclable catalytic system for the asymmetric hydrogenation of quinolines, we thus started to investigate the effects of IL anions and catalyst structures on catalytic performance. Two series of ruthenium complexes containing chiral *N*-sulfonylated 1,2-diphenylethylenediamine (DPEN) and 1,2-cyclohexanediamine (CYDN) were prepared accordingly (Scheme 1).

In our initial study, we investigated the asymmetric hydrogenation of 2-methylquinoline (**2a**) with Ru-diamine catalyst (*R,R*)-**1a** in neat [Bmim]PF_6. To our great delight, the reaction proceeded smoothly with high reactivity and excellent enantioselectivity, even better than those obtained with common organic solvents under the same reaction conditions (Table 1, entry 1 *vs.* entry 2). Encouraged by this result and based on our previous finding about the significant anion effect of this catalytic system,[11] we further examined a series of imidazolium ionic liquids with different weakly coordinating anions ([Bmim]X, X = SbF_6, BF_4, NTf_2, OTf). The results are summarized in Table 1. It was found that all of these ionic liquids gave complete conversions with excellent enantioselectivities. Notably, both the reactivity and enantioselectivity were influenced by the nature of the anion. When [Bmim]PF_6, [Bmim]SbF_6 and [Bmim]NTf_2 were used, almost optically pure product **3a** (99% *ee*) was obtained, and [Bmim]SbF_6 gave the highest reactivity. However, the use of more coordinating anions, such as OTf and BF_4, significantly reduced the reactivity and slightly lowered the enantioselectivity (95% and 98% *ee*, respectively). Thus, [Bmim]SbF_6 was selected

Table 1. Anion effect of ionic liquids on the asymmetric hydrogenation of **2a**.[a]



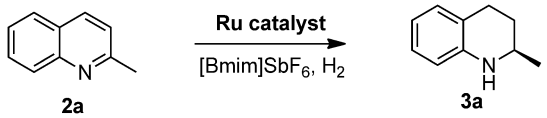
Entry	Solvent	Time [h]	Conv. [%][b,c]	*ee* [%][d]
1	[Bmim]PF_6	1.5	>99 (56)	99
2	MeOH	3	>99 (52)	96
3	[Bmim]SbF_6	24	>99 (94)	>99
4	[Bmim]BF_4	24	>99 (25)	98
5	[Bmim]OTf	24	>99 (26)	95
6	[Bmim]NTf_2	24	>99 (51)	>99

[a] *Reaction conditions:* 0.2 mmol **2a** in 1 mL solvent, 1.0 mol% (*R,R*)-**1a**, 50 atm H_2, 25 °C.
[b] Determined by ^{1}H NMR analysis.
[c] Data in brackets were obtained when the reaction time was 40 min.
[d] Determined by chiral HPLC analysis.

as the best choice of reaction media for the asymmetric hydrogenation of quinolines.

Next, we screened all the ruthenium catalysts described in Scheme 1, and the results are listed in Table 2. Generally, the catalytic performance was significantly affected by both the substituents of the η^6-arene ligand and the *N*-monosulfonylated diamine ligand (entries 1–7). The steric effects of the *N*-sulfonate substituents were also manifest. It was found that catalyst (*R,R*)-**1a** having a *p*-tolyl group as the *N*-sulfonate substituent gave the highest *ee* value and conversion (entry 1), while the catalysts bearing the less steric methyl group or the more steric 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ group gave much lower reactivities and slightly lower enantioselectivities (entries 2 and 3). Catalyst (*R,R*)-**1d** with an electron-withdrawing *N*-sulfonate substituent resulted in much lower conversion and *ee* value (entry 4). In addition, introducing a methyl group to the other N atom of the diamine ligand or replacement of the *p*-cymene ligand with the sterically demanding η^6-arene gave much lower conversion without any loss of enantioselectivity (entries 5 and 6). Catalyst (*R,R*)-**1g** bearing the diamine ligand TsCYDN [TsCYDN = *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine] showed much lower enantioselectivity and reactivity (entry 7). Having the optimized catalyst structure in hand (entry 1), we further examined the effects of hydrogen pressure and temperature on the catalytic performance. It was found that the enantioselectivity was insensitive to hydrogen pressure and temperature (entries 8–13). Notably, when the catalyst loading of (*R,R*)-**1a** was decreased

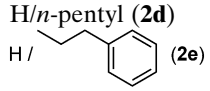
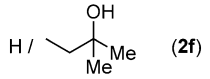
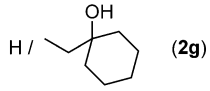
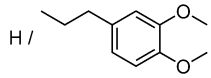
Table 2. Optimization of the reaction conditions for the asymmetric hydrogenation of **2a**.[a]



Entry	Catalyst	H_2 [atm]; Temp. [°C]	Time [h]	Conv. [%][b]	*ee* [%][c]
1	(*R,R*)-**1a**	50; 25	1	>99	>99
2	(*R,R*)-**1b**	50; 25	1	76	98
3	(*R,R*)-**1c**	50; 25	1	9	98
4	(*R,R*)-**1d**	50; 25	1	17	78
5	(*R,R*)-**1e**	50; 25	1	14	>99
6	(*R,R*)-**1f**	50; 25	1	5	>99
7	(*R,R*)-**1g**	50; 25	1	70	90
8	(*R,R*)-**1a**	50; 0	7	>99	>99
9	(*R,R*)-**1a**	50; 50	40 min	>99	99
10	(*R,R*)-**1a**	50; 80	40 min	>99	98
11	(*R,R*)-**1a**	1; 25	18	60	>99
12	(*R,R*)-**1a**	20; 25	40 min	88	>99
13	(*R,R*)-**1a**	80; 25	40 min	>99	>99
14[d]	(*R,R*)-**1a**	50; 25	24	>99	99
15[e]	(*R,R*)-**1a**	50; 25	24	>99	99
16[f]	(*R,R*)-**1a**	50; 25	24	32	96

[a] *Reaction conditions:* 0.2 mmol **2a** in 1 mL [Bmim]SbF_6, 1.0 mol% (*R,R*)-**1**, 25 °C.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] Substrate/catalyst = 500.
[e] Substrate/catalyst = 1000.
[f] Substrate/catalyst = 2000.

Table 3. Asymmetric hydrogenation of 2-alkyl-quinoline derivatives catalyzed by (*R,R*)-**1a** in [Bmim]SbF_6.[a]

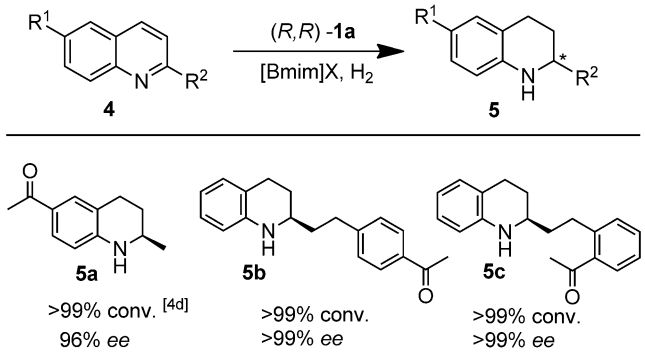
Entry	R^1/R^2	Conv. [%][b]	*ee* [%][c]
1	H/Me (**2a**)	>99	99
2	H/Et (**2b**)	>99	99
3	H/*n*-Pr (**2c**)	>99	99
4	H/*n*-pentyl (**2d**)	>99	98
5	 (**2e**)	>99	98
6	 (**2f**)	>99	99
7	 (**2g**)	>99	99
8	 (**2h**)	>99	99
9	MeO/Me (**2i**)	>99	99
10	Me/Me (**2j**)	>99	98
11	F/Me (**2k**)	>99	99
12	H/Ph (**2l**)	>99	50

[a] *Reaction conditions:* 0.2 mmol substrate in 1 mL [Bmim]SbF_6, 0.2 mol% (*R,R*)-**1a**, 50 atm H_2, 25 °C, 24–60 h.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.

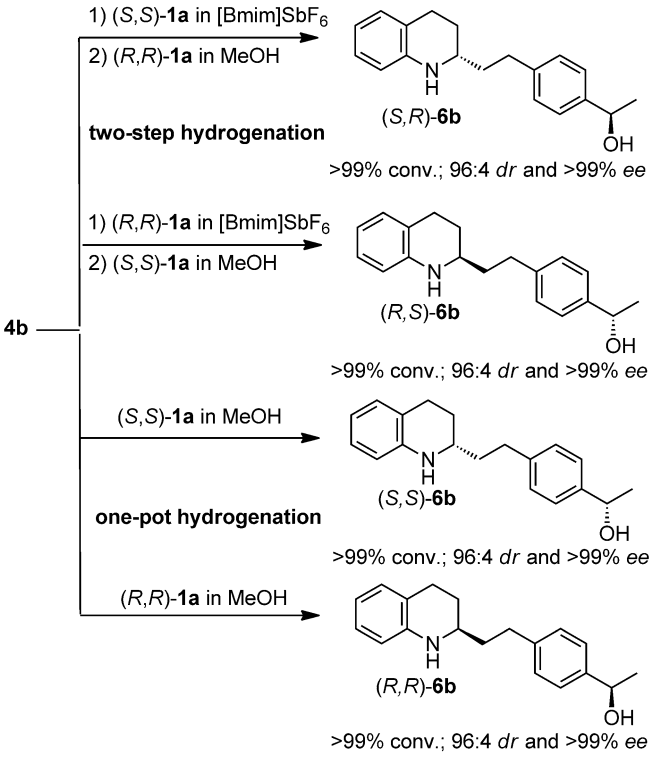
to 0.2 mol% and 0.1 mol%, full conversions and excellent enantioselectivities (99% *ee*) were still observed within 24 h (entries 14 and 15). Even with 0.05 mol% catalyst, the reaction still led to excellent enantioselectivity, albeit with quite lower conversion (entry 16).

Under the optimized conditions (entry 1 in Table 2), we further explored the substrate scope of the Ru-catalyzed asymmetric hydrogenation of 2-alkyl-substituted quinolines in [Bmim]SbF_6. As shown in Table 3, all reactions proceeded smoothly to give full conversions and excellent enantioselectivities (94% to 99% *ee*) with 0.2 mol% catalyst loading. The reaction was found to be insensitive to the length of the alkyl side chain (entries 1–4) as well as the existence of phenyl groups or free hydroxy groups on the side chain (entries 5–8). Substitution at the 6-position had no obvious effect on either conversion or enantioselectivity (entries 9–11). Notably, remarkably higher reactivities and comparable or better enantioselectivities for the hydrogenation of all these substrates were observed as compared with those obtained in [Bmim]PF_6 and under solvent-free conditions.[4d,e] Also, we studied the asymmetric hydrogenation of 2-phenylquinoline. The reaction proceeded smoothly, albeit only with medium enantioselectivity (51% *ee*, entry 12).

To further extend the substrate scope, we investigated the asymmetric hydrogenation of some quinoline derivatives bearing a carbonyl group. In previous studies, we have found that substrate **4a** bearing an acetyl group at the 6-position could be selectively hydrogenated to tetrahydroquinoline **5a** in good yield with 96% *ee* (Scheme 2).[4d] This result indicated that the hydrogenation with Ru-diamine catalyst in ionic liquid was more selective for C=N (quinoline) over C=O (ketone) bonds. We futher found that the hydrogenations of substrates **4b** and **4c** bearing the C=O group at different positions on the phenyl ring of the side chain afforded the corresponding 1,2,3,4-tetrahydroquinoline derivatives in high yields and excellent enantioselectivities with the C=O bonds being retained. In contrast, both unsaturated bonds were reduced in MeOH under otherwise the same reaction conditions. This solvent-induced different chemoselectivity of the ruthenium catalyst probably results from different mechanisms for the hydrogenation of ketones[10c] and imines.[4f] On the basis of this unique chemoselectivity in different solvents, all four enantiomers of the fully reduced product of **4b** could be



Scheme 2. Asymmetric hydrogenation of quinoline derivatives bearing a C=O functional group in $[Bmim]PF_6$ (**4a**) and $[Bmim]SbF_6$ (**4b** and **4c**). *Reaction conditions:* 0.2 mmol substrate in 1 mL ionic liquid, 1 mol% (*R,R*)-**1a**, 50 atm H_2, 25 °C, 15 h.



Scheme 3. Synthesis of all four enantiomers of **6b** through asymmetric hydrogenation of **4b**. *Reaction conditions:* 0.2 mmol substrate in 1 mL solvent, 1.0 mol% catalyst, 50 atm H_2, 25 °C, 12 h.

easily obtained through two-step or one-pot asymmetric hydrogenation catalyzed by (*S,S*)- and/or (*R,R*)-**1a**, respectively (Scheme 3). Some of these optically pure compounds are difficult to access with other methods.

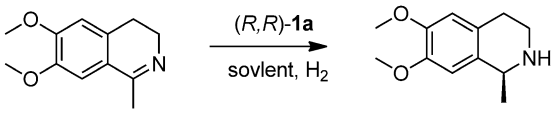
Asymmetric Hydrogenation of 3,4-Dihydroisoquinoline Derivatives Catalyzed by Cationic Ruthenium Catalysts in Ionic Liquids

The first asymmetric hydrogenation of isoquinoline-type imines was reported by Buchwald and co-workers in 1993.[6a] They used a chiral titanocene catalyst for the hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline with 98% *ee*. Since then, a number of chiral transition metal catalysts was applied to such types of transformation.[3a,6] More recently, Xiao and co-workers found that a cationic Cp*Rh(TsDPEN) complex was an efficient catalyst for this type of cyclic imines in the presence of $AgSbF_6$.[6d]

Encouraged by the excellent results obtained in the asymmetric hydrogenation of quinolines in ionic liquids, and based on our recent reports on the asymmetric hydrogenation of other acyclic and cyclic *N*-alkylimines with this catalytic system,[11] we thus expand the imine substrate range to 3,4-dihydroisoquinoline derivatives.

We first chose the hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**7a**) in the presence of 2.0 mol% (*R,R*)-**1a** in $[Bmim]PF_6$ as a standard reaction. To our great delight, the reaction proceeded smoothly to afford the 1,2,3,4-tetrahydroisoquinoline in full conversion with 96% *ee* (Table 4, entry 1). Then we investigated the anion effect of ionic liquids in this reaction. Generally, all the ionic liquids tested gave full conversions with excellent enantioselectivities. Similar to the asymmetric hydrogenation of quinolines, the catalytic performance was also affected by the anions. It was found that hydrogenation of **7a**

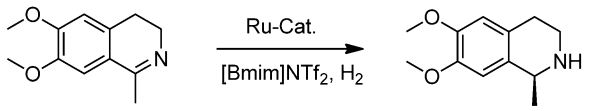
Table 4. Anion effect of ionic liquids on the asymmetric hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **7a**.[a]



Entry	Solvent	Conv. [%][b,c]	*ee* [%][d]
1	$[Bmim]PF_6$	>99 (38)	96
2	$[Bmim]SbF_6$	>99 (98)	95
3	$[Bmim]BF_4$	>99 (48)	97
4	[Bmim]OTf	>99 (30)	96
5	$[Bmim]NTf_2$	>99 (60)	98
6	MeOH	>99 (60)	96

[a] *Reaction conditions:* 0.2 mmol substrate in 1 mL solvent, 1.0 mol% (*R,R*)-**1a**, 50 atm H_2, 25 °C, 24 h.
[b] Determined by ^1H NMR analysis.
[c] Data in brackets were obtained when the reaction time was 2.5 h.
[d] Determined by chiral HPLC analysis.

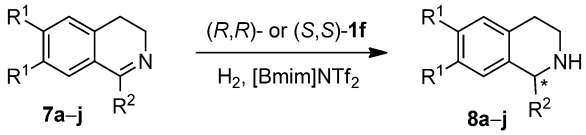
Table 5. Optimization of the reaction conditions for the asymmetric hydrogenation of **7a**.[a]



Entry	Catalyst	H_2 [atm]; Temp. [°C]	Time [h]	Conv. [%][b]	*ee* [%][c]
1	(*R,R*)-**1a**	50; 25	3.5	84	98
2	(*R,R*)-**1b**	50; 25	3.5	64	96
3	(*R,R*)-**1c**	50; 25	44	28	73
4	(*R,R*)-**1d**	50; 25	44	15	49
5	(*R,R*)-**1e**	50; 25	44	38	86
6	(*R,R*)-**1f**	50; 25	3.5	>99	99
7	(*R,R*)-**1g**	50; 25	3.5	78	75
8	(*R,R*)-**1f**	50; 0	10	70	>99
9	(*R,R*)-**1f**	50; 50	3.5	>99	98
10	(*R,R*)-**1f**	20; 25	3.5	83	99
11	(*R,R*)-**1f**	80; 25	3.5	>99	98
12[d]	(*R,R*)-**1 f**	50; 25	14	75	97

[a] *Reaction conditions:* 0.2 mmol substrate with 2.0 mol% catalyst in 1 mL [Bmim]NTf_2.
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] With 1.0 mol% (*R,R*)-**1f**.

Table 6. Asymmetric hydrogenation of 3,4-dihydroisoquinoline derivatives catalyzed by catalyst (*R,R*)- or (*S,S*)-**1f** in [Bmim]NTf_2.[a]



Entry	R^1/R^2	Yield [%][b]	*ee* [%][c]
1	MeO/Me (**7a**)	92	99
2	MeO/Et (**7b**)	93	97
3[d]	MeO/*i*-Pr (**7c**)	94	93
4[d]	MeO/*n*-pentyl (**7d**)	95	98
5	MeO/cyclohexyl (**7e**)	91	97
6[d]	H/Me (**7f**)	91	99
7	H/Et (**7g**)	92	96
8	H/*n*-pentyl (**7h**)	93	98
9[d]	H/cyclohexyl (**7 i**)	93	94

[a] *Reaction conditions:* 0.2 mmol substrate in 1 mL [Bmim]NTf_2, 2.0 mol% (*R,R*)-**1f**, 50 atm H_2, 25 °C, 10–20 h.
[b] Isolated yield (complete conversion in all cases).
[c] Determined by chiral HPLC analysis.
[d] With 2.0 mol% (*S,S*)-**1 f**, and the corresponding products have the *R* configuration.

in [Bmim]SbF_6 showed the highest reactivity with 95% *ee* (entry 2). The highest enantioselectivity was observed in [Bmim]NTf_2 (98% *ee*, entry 5), which was better than that in methanol (96% *ee*, entry 6). In terms of both reactivity and enantioselectivity, [Bmim]NTf_2 was selected as the best choice of media for the asymmetric hydrogenation of dihydroisoquinolines.

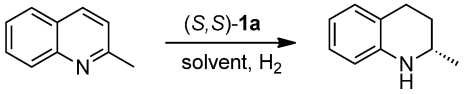
Next, all catalysts described in Scheme 1 were screened and the results are listed in Table 5. It was found that steric and electronic effects of the diamine ligand were manifested (entries 1–7), and the TsDPEN ligand gave the best catalytic performance (entries 1 and 6). Catalyst bearing TsCYDN showed much lower enantioselectivity and reactivity (entry 7). Gratefully, replacement of the *p*-cymene ligand with the sterically demanding hexamethylbenzene ligand led to an increase in both enantioselectivity and reactivity (entry 6). Thus, the ruthenium complex (*R,R*)-**1f** was the best choice of catalyst for such transformations. In addition, it was found that the enantioselectivity was insensitive to the hydrogen pressure and reaction temperature (entries 8–11); and lower conversions were observed when the reactions were carried out under low temperature or low hydrogen pressure (entries 8 and 10). Decreasing catalyst loading (1.0 mol%) resulted in lower conversion and enantioselectivity (entry 12).

Under the optimized reaction conditions (entry 6 in Table 5), a variety of 1-alkyl-substituted 3,4-dihydroisoquinolines was hydrogenated in [Bmim]NTf_2. As shown in Table 6, all substrates were completely reduced to afford 1,2,3,4-tetrahydroisoquinolines with excellent enantioselectivities (93–99% *ee*), which are better than those obtained with the rhodium catalytic system in organic solvent.[6d] In comparison with **7a**, substrates bearing longer (ethyl, pentyl) or more steric (isopropyl, cyclohexyl) alkyl side chains gave only slightly lower enantioselectivities (entries 2–5). Notably, hydrogenation of substrates without methoxy substitutions at the 6,7-positions also gave very good yields with excellent enantioselectivities (entries 6–9). Unfortunately, the hydrogenation of the 1-phenyl-substituted substrate did not occur in neat ionic liquid or methanol.

Stabilization of Catalyst in Ionic Liquid

Immobilization of a transition metal catalyst in ionic liquids often gives enhanced catalyst stability.[9] To investigate the stabilization of catalyst (*S,S*)-**1a** in [Bmim]PF_6, we chose the hydrogenation of **2a** as the model reaction, and all manipulations were conducted in air. The catalyst solutions in organic solvents (MeOH, CH_2Cl_2) or ionic liquid ([Bmim]PF_6) were stirred under an air atmosphere for 20 h before use. Then, substrate **2a** was added for hydrogenation after

Table 7. Asymmetric hydrogenation of **2a** with (*S,S*)-**1a**: catalyst stability.[a]

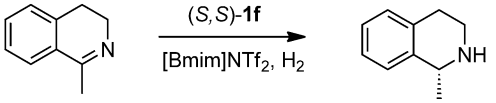


2a **3a**

Entry	Solvent	Conv. [%][b]	*ee* [%][c,d]
1	[Bmim]PF_6	98	98 (99)
2	MeOH	6	85 (94)
3	CH_2Cl_2	16	92 (97)
4[e]	[Bmim]PF_6	>99	99 (99)

[a] *Reaction conditions:* (*S,S*)-**1a** (1.0 mol%) in 1 mL solvent, which was stirred in air for 20 h before **2a** (0.2 mmol) was added, 50 atm H_2, 25 °C, 24 h.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] Data in brackets were obtained in degassed solvents under an N_2 atmosphere.
[e] The catalyst in [Bmim]PF_6 was stored in air for a month before use.

Table 8. Reuse of (*S,S*)-**1f** in the asymmetric hydrogenation of **7g** in ionic liquid.[a]



7g **8g**

Run	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	>99	84	99
2	91	88	99
3	>99	96	98
4	>99	93	96
5	>99	95	96
6	94	90	90

[a] *Reaction conditions:* **7g** (0.2 mmol) in 1 mL [Bmim]NTf_2, 2.0 mol% (*S,S*)-**1f**, 50 atm H_2, 25 °C, 10 h (entries 1 and 2) and 24 h (entries 3–6).
[b] Determined by ^{1}H NMR spectroscopy.
[c] Isolated yields.
[d] Determined by HPLC analysis.

purging the autoclave with hydrogen gas several times. As shown in Table 7, almost identical enantioselectivity was observed with 98% conversion in [Bmim]PF_6 (entry 1), while a significant decrease in conversions and enantioselectivities was observed in MeOH and CH_2Cl_2 (entries 2 and 3). Notably, it was found that the catalyst in [Bmim]PF_6 could catalyze the hydrogenation smoothly in full conversion with 99% *ee*, even after air exposure for a month (entry 4). These results indicated that the ruthenium catalyst in the ionic liquid medium was highly stable.

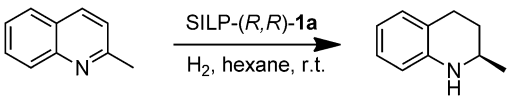
Catalyst Recycling

Another advantage of ionic liquids as environmentally friendly reaction media is the facile catalyst recycling *via* solvent extraction. In our study, the cationic Ru(diamine) complexes, which have a strong affinity to the highly polar ionic liquids, hardly dissolved in non-polar solvents like hexane. In contrast, the less polar products show good solubility in hexane. Such distinct solubility differences between the catalyst and the product can facilitate catalyst separation and product isolation.

In our previous work, we have demonstrated that the ruthenium catalyst (*S,S*)-**1a** could be easily recycled at least 7 times for quinoline hydrogenation in [Bmim]PF_6 by solvent extraction.[4d] Then, we also investigated the recyclability of catalyst (*S,S*)-**1f** in the asymmetric hydrogenation of **7g** (Table 8). In a similar way, the catalyst immobilized in [Bmim]NTf_2 could be recycled no less than five times, maintaining excellent enantioselectivity (96% *ee*) but at the expense of gradually decreasing reactivity. In the sixth run, an obviously decreased enantioselectivity was also observed.

To further facilitate the recovery of catalyst and reduce the use of organic solvents, we next attempted to immobilize the catalyst (*R,R*)-**1a** in a thin film of ionic liquid which was supported on 200–300 M silca gels. This supported ionic liquid-phase (SILP) catalytic system[12] was applied to the asymmetric hydrogenation of **2a** in hexane. It was found that the reaction could proceed smoothly in full conversion with 99% *ee* (Table 9, entry 1). Furthermore, this heterogenized

Table 9. Reuse of the heterogenized (*R,R*)-**1a** in the asymmetric hydrogenation of **2a**.[a]



2a **3a**

Run	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	>99	94	99
2	>99	92	98
3	>99	96	98
4	>99	96	97
5	>99	94	98
6	>99	93	98
7[e]	84	64	99
8[e]	37	20	98

[a] *Reaction conditions:* 0.2 mmol **2a** in 1 mL hexane, 50 atm H_2, 25 °C, 1.0 mol% SILP-(*R,R*)-**1a**, 24 h.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Isolated yields.
[d] Determined by HPLC analysis.
[e] For 48 h.

ruthenium catalyst could be easily separated by simple filtration and reused five times without obvious loss of reactivity and enantioselectivity (entries 2–6). Notably, a decrease of reactivity was observed in the seventh and eighth runs, even though identical *ee* values were retained.

Conclusions

In conclusion, we have demonstrated that chiral cationic phosphine-free Ru(diamine) complexes exhibited unprecedented reactivity and excellent enantioselectivity (up to >99% *ee*) in the hydrogenation of quinolines and 3,4-dihydroisoquinolines in neat ionic liquids. It was found that the catalytic performance was influenced by the anion of the ionic liquids in both cases. Interestingly, the hydrogenation of quinoline derivatives bearing a carbonyl group was selective for C=N (quinoline) over C=O (ketone) bonds, while such a chemoselectivity was not observed in methanol. Importantly, the use of ionic liquid could stabilize the ruthenium catalyst and thus facilitate its recycling. This catalytic protocol thus provides a greener and practical access to a variety of optically active 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline derivatives.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of Quinolines in Ionic Liquids

A 50-mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with Ru catalyst [(*S,S*)-**1a** or (*R,R*)-**1a**] and 2-substituted quinoline in [Bmim]X (1.0 mL, X = BF_4, PF_6, SbF_6, OTf or NTf_2) under a nitrogen atmosphere in a glove box. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm 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 had been carefully depressurized, the reduced product was extracted with *n*-hexane (6×1 mL). The combined hexane layer was concentrated under vacuum to give the tetrahydroquinoline product. The conversions were determined by ^{1}H NMR, and the *ee* values were determined by HPLC on a chiral stationary phase.

Typical Procedure for the Two-Step Asymmetric Hydrogenation of 4b

In the first step, a 50-mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with Ru catalyst [(*S,S*)-**1a**, 1.5 mg, 0.002 mmol] and substrate **4b** (0.20 mmol) in 1 mL [Bmim]SbF_6 under a nitrogen atmosphere in a glove box. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for 12 h. After the autoclave was depressurized, the reduced product was extracted with *n*-hexane (6×1 mL). The combined hexane layer was concentrated under vacuum to give the partially hydrogenated product (*S*)-**5b**. In the second step, (*S*)-**5b** was further hydrogenated with (*R,R*)-**1a** (1.5 mg, 0.002 mmol**)** in 1 mL MeOH, affording the fully reduced product (*S,R*)-**6b.** The conversion was determined by ^{1}H NMR, and the diastereoselectivity (94/6 *dr*) and enantioselectivity (99% *ee*) were determined by HPLC on a chiral stationary phase.

General Procedure for the Asymmetric Hydrogenation of 3,4-Dihydroisoquinolines in Ionic Liquids and Catalyst Recycling

A 50-mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with Ru catalyst [(*S,S*)-**1f** or (*R,R*)-**1f**, 1.6 mg, 0.002 mmol] and 1-alkyl-3,4-dihydroisoquinoline (0.20 mmol) in [Bmim]X (1.0 mL, X = BF_4, PF_6, SbF_6, OTf or NTf_2) under a nitrogen atmosphere in a glove box. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm 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 had been depressurized, the reduced product was extracted with *n*-hexane (6×2 mL). After vacuum drying, the ionic liquid phase containing the catalyst was reused for the next run by recharging of substrate under the same reaction conditions. The combined hexane layer was concentrated under vacuum to give the tetrahydroisoquinoline product. The conversions were determined by ^{1}H NMR, and the *ee* values were determined by HPLC on a chiral stationary phase.

General Procedure for the Preparation and Reuse of the Supported Ionic Liquid-Phase Catalyst

The preparation of the immobilized Ru catalyst was carried out under an inert gas atmosphere. First, the ruthenium complex (*R,R*)-**1a** (150 mg, 0.2 mmol, 3 wt%) and the ionic liquid [Bmim]PF_6 (1.25 g, 4.4 mmol, 25 wt%) were dissolved in 25 mL acetone to give a clear orange solution. After the addition of silica gel (200–300 M, 3.75 g, 75 wt%), the volatile component of the mixture was removed under reduced pressure. The resulting material was dried under vacuum at room temperature for 12 h to give the supported ionic liquid-phase catalyst as an orange solid.

Then, a 50-mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with the above formed immobilized catalyst [1.0 mol% SILP-(*R,R*)-**1a**], and 2-methylquinoline **2a** (50 mg, 0.20 mmol) in 1.0 mL hexane under a nitrogen atmosphere in a glove box. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm 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 had been depressurized, the heterogenized catalyst was separated by simple filtration, and then reused in the next run under the same reaction conditions. The hexane layer was concentrated under vacuum to give

the tetrahydroquinoline product. The conversions were determined by ^{1}H NMR, and the *ee* values were determined by HPLC on a chiral stationary phase.

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