Personal Account

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Asymmetric Hydrogenation of Quinoline Derivatives Catalyzed by Cationic Transition Metal Complexes of Chiral Diamine Ligands: Scope, Mechanism and Catalyst Recycling

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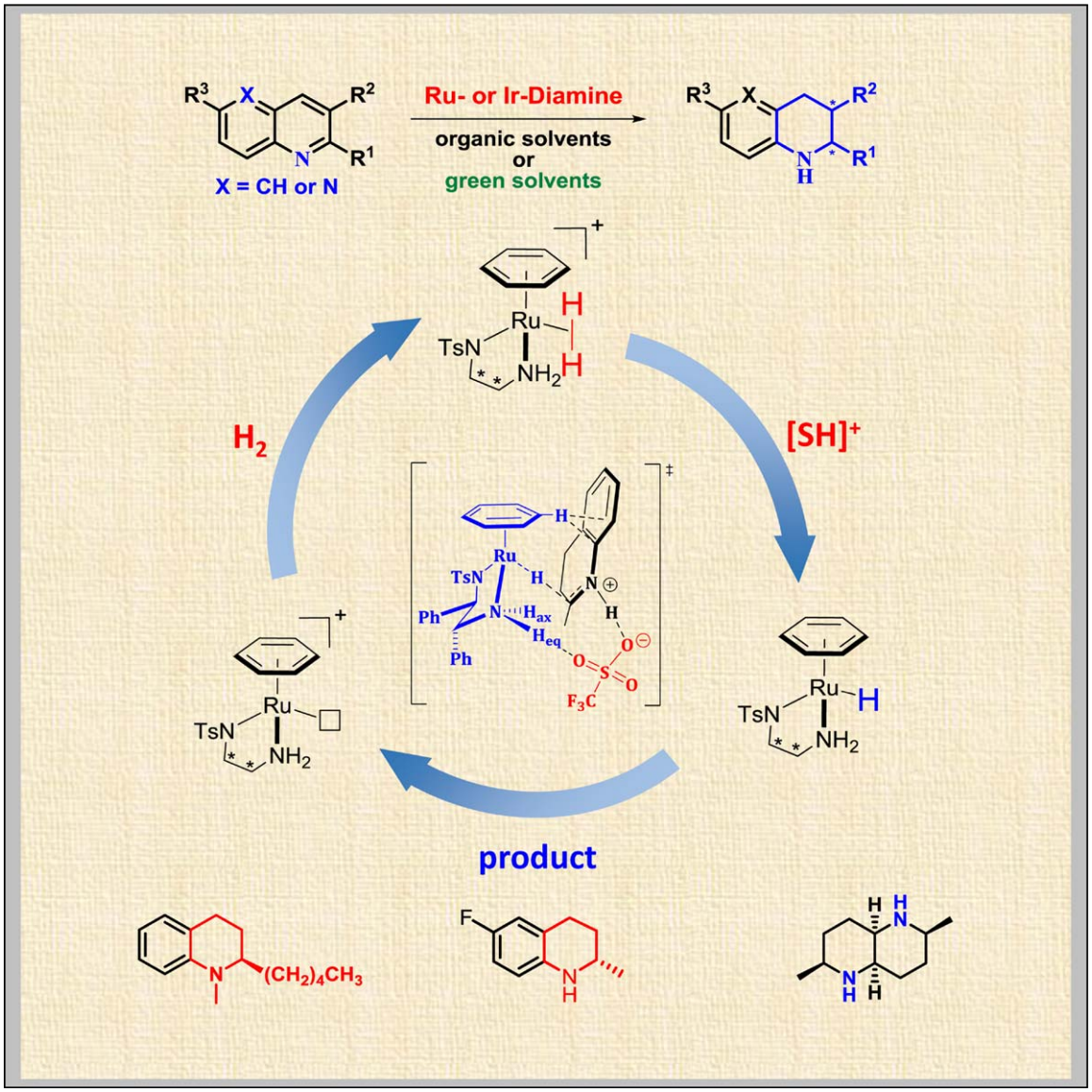

ABSTRACT: This personal account is focused on the asymmetric hydrogenation of quinolines and their analogues recently developed by using phosphorus-free chiral cationic ruthenium(II)/η^6-arene-*N*-monosulfonylated diamine complexes. In our initial study, the chiral Ru-diamine complexes were found to be highly effective catalysts for the asymmetric hydrogenation of difficult quinoline substrates in room temperature ionic liquids (RTILs) with unprecedentedly excellent enantioselectivity. Our further systematic study revealed that a wide range of quinoline derivatives could be efficiently hydrogenated in alcoholic solvents, or under solvent-free and concentrated conditions with good to excellent stereoselectivity. Complexes of iridium analogues could also efficiently catalyze the asymmetric hydrogenation of quinolines in undegassed solvent. Asymmetric tandem reduction of various 2-(aroylmethyl)quinolines was achieved in high yield with excellent enantioselectivity and good diastereoselectivity. More challenging substrates, alkyl- and aryl-substituted 1,5- and 1,8-naphthyridine derivatives were successfully hydrogenated with these chiral ruthenium catalysts to give 1,2,3,4-tetrahydronaphthyridines with good to excellent enantioselectivity. Unlike the asymmetric hydrogenation of ketones, quinoline is reduced *via* a stepwise H^+/H^- transfer process outside the coordination sphere rather than a concerted mechanism. The enantioselectivity originates from the CH/π attraction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of dihydroquinoline *via* a 10-membered ring transition state with the participation of TfO^- anion. In addition, the Ru-catalyzed asymmetric hydrogenation of quinolines could be carried out in some environmentally benign reaction media, such as undegassed water, RTILs and oligo(ethylene glycol)s (OEGs). In the latter two cases, unique chemoselectivity and/or reactivity were observed. Catalyst recycling could also be realized by using [BMIM]PF_6 and OEGs as solvents, as well as *via* magnetic nanoparticles. Applications of this catalytic protocol were also exemplified by the employments of the reduced products for the syntheses of some important natural alkaloids, pharmaceutical intermediates, as well as chiral diamine ligands.

Keywords: asymmetric hydrogenation, quinoline derivatives, chiral diamine, transition metal, catalyst recycling

1. Introduction

Optically active 1,2,3,4-tetrahydroquinoline derivatives are important building blocks for the preparation of pharmaceutically and agrochemically important compounds, and have been found as basic units in many natural products.[1] Among various methodologies for the synthesis of such chiral heterocyclic compounds, the asymmetric reduction of the corresponding unsaturated quinolines with hydrogen gas or other hydrogen sources represents the most straightforward and effective way.[2] Although homogeneous asymmetric reduction of quinolines has been considered a challenging task due to the high resonance stability and the possible catalyst poisoning and/or deactivation by quinoline substrates and/or reduced products,[3] a breakthrough has been made in 2003 by Zhou and co-workers. The asymmetric hydrogenation of 2-substituted quinolines using Ir/(*R*)-MeO-BIPHEP catalyst has been successfully achieved by adding iodine.[4a] Following this significant discovery, a variety of iridium complexes of chiral phosphorus-containing ligands have been proved to realize the highly enantioselective hydrogenation of a wide range of 2-alkyl-substituted quinoline derivatives (Scheme 1).[4b-h] Meanwhile, substrate activation strategies have been developed[5] instead of catalyst activation, and palladium[4i] and rhodium[4j] complexes were also demonstrated to be effective for this transformation. In addition to the phosphorus-containing transition metal catalytic systems, transfer hydrogenation with either chiral Brønsted acid[6] or Rh/diamine as catalyst[7] has also been built up. Very recently, metal free catalytic hydrogenation based on Frustrated Lewis Pair (FLP) chemistry has shown its unique advantages on polysubstituted bulky quinoline substrates,[8] the control of diastereoselectivity and enantioselectivity has reached a high level with FLP catalysis (Scheme 1).

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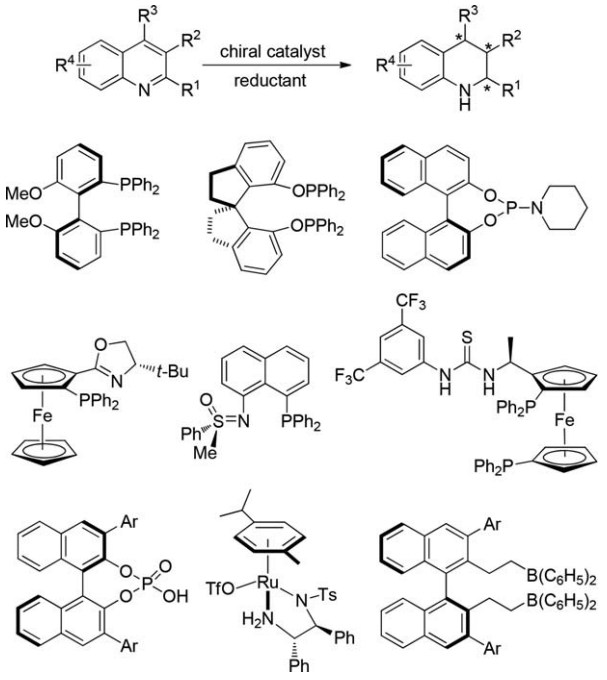
Dedicated to Professor Noyori on the occasion of the 15TH anniversary of his Noble Prize



Scheme 1. Representative chiral ligands and catalysts used for asymmetric reduction of quinolines.

In comparison with chiral phosphorus ligands, phosphorus-free chiral diamine ligands are more stable, easily tunable, and readily available from merchandise.[9] Early in 1995, Noyori and co-workers reported the most successful application of chiral diamine ligand TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) in the ruthenium-catalyzed asymmetric transfer hydrogenation of simple aromatic ketones.[10] Thereafter, chiral TsDPEN also found itself powerful ligand in the transfer hydrogenation of imines too.[10e] Recently, Noyori and co-workers described the asymmetric hydrogenation of ketones under slightly acidic conditions by using chiral cationic Ru(II)/η^6-arene-*N*-monotosylated diamine complexes.[11] Inspired by this discovery, in 2008, we found that this chiral cationic TsDPEN/Ru(II) complex was highly effective and enantioselective in the asymmetric hydrogenation of quinoline derivatives in an imidazolium ionic liquid.[12] Later on, systematic studies on this catalytic system have been performed, including the investigation of various factors affecting the hydrogenation, extension of catalyst and substrate scopes, revealing the reaction pathway and the origin of enantioselectivity, and realizing catalyst recycling and reuse.

In this present account, a thorough and detailed introduction of our works on the asymmetric hydrogenation of quinoline derivatives by utilizing chiral cationic transition-metal complexes of chiral diamine ligands will be included.

2. Asymmetric Hydrogenation of Quinolines and Their Analogues

2.1. Ru-Catalyzed Asymmetric Hydrogenation of Quinolines

The first example of chiral cationic Ru(II)/TsDPEN catalyzed asymmetric hydrogenation of quinolines was set up in 2008

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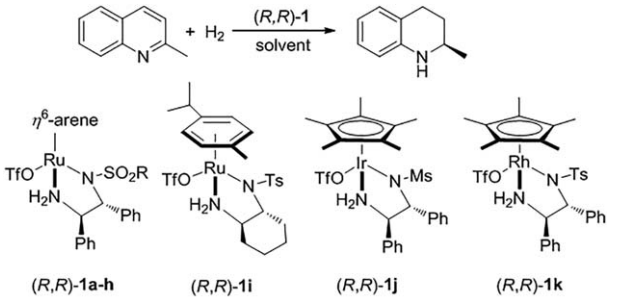
Table 1. Optimization for the asymmetric hydrogenation of 2-methylquinoline.

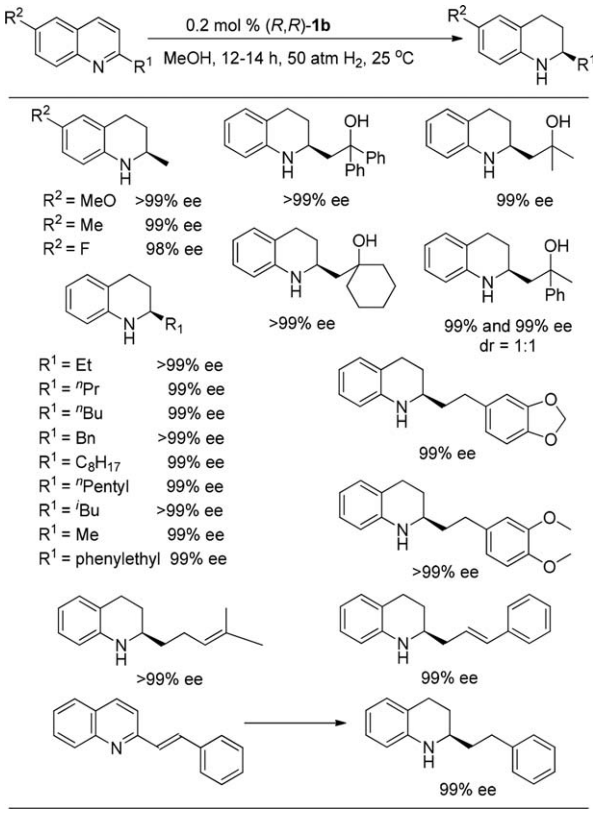


(*R*,*R*)-**1a**: R = 4-$CH_3C_6H_4$, η^6-arene = *p*-cymene
(*R*,*R*)-**1b**: R = 4-$CH_3C_6H_4$, η^6-arene = hexamethylbenzene
(*R*,*R*)-**1c**: R = 4-$CH_3C_6H_4$, η^6-arene = benzene
(*R*,*R*)-**1d**: R = CH_3, η^6-arene = *p*-cymene
(*R*,*R*)-**1e**: R = 2,4,6-triisopropylbenzene, η^6-arene = *p*-cymene
(*R*,*R*)-**1f**: R = 4-$CF_3C_6H_4$, η^6-arene = *p*-cymene
(*R*,*R*)-**1g**: R = CF_3, η^6-arene = *p*-cymene
(*R*,*R*)-**1h** R = CH_3, η^6-arene = hexamethylbenzene

entry	catalyst	solvent	temp. (°C)	H_2 (atm)	time (h)	conv. (%)	ee (%)
1	(*R*,*R*)-**1a**	MeOH	15	20	6	100	96
2	(*R*,*R*)-**1a**	EtOH	15	20	6	100	96
3	(*R*,*R*)-**1a**	^{i}PrOH	15	20	6	84	97
4	(*R*,*R*)-**1a**	acetone	15	20	6	78	96
5	(*R*,*R*)-**1a**	CH_2Cl_2	15	20	6	54	98
6	(*R*,*R*)-**1a**	THF	15	20	6	40	92
7	(*R*,*R*)-**1a**	toluene	15	20	6	38	92
8	(*R*,*R*)-**1a**	H_2O	15	20	6	31	94
9	(*R*,*R*)-**1a**	MeOH	25	50	1	33	96
10	(*R*,*R*)-**1b**	MeOH	25	50	1	40	>99
11	(*R*,*R*)-**1c**	MeOH	25	50	1	23	89
12	(*R*,*R*)-**1d**	MeOH	25	50	1	74	94
13	(*R*,*R*)-**1e**	MeOH	25	50	1	17	95
14	(*R*,*R*)-**1f**	MeOH	25	50	1	19	96
15	(*R*,*R*)-**1g**	MeOH	25	50	1	22	94
16	(*R*,*R*)-**1i**	MeOH	25	50	1	15	81
17	(*R*,*R*)-**1j**	MeOH	25	50	1	48	96
18	(*R*,*R*)-**1k**	MeOH	25	50	1	27	>99

with an ionic liquid [BMIM]PF_6 as reaction medium.[12] Without any additives, a series of 2-alkyl-substituted quinolines were hydrogenated smoothly, affording 1,2,3,4-tetrahydroquinolines with high isolated yields and unprecedentedly excellent enantioselectivities (95∼99% ee).

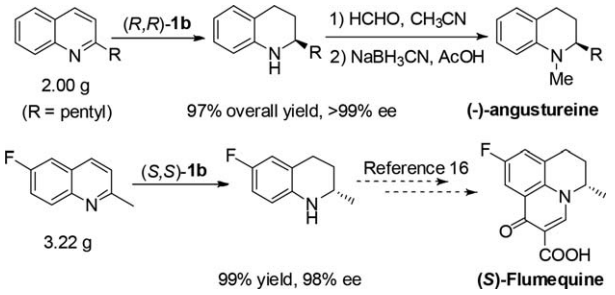
To further uncover the scope of this hydrogenation, a variety of chiral cationic transition metal/η-arene-*N*-monosulfonylated diamine complexes were synthesized to study the structure-property relationship of catalyst.[13] First, we investigated the effect of solvent on catalyst performance. By



Scheme 2. Asymmetric hydrogenation of 2-alkyl-substituted and 2-functionalized quinolines.

choosing the hydrogenation of 2-methylquinoline as the standard reaction, various conventional organic solvents were tested (Table 1). Unlike asymmetric hydrogenation of ketones, excellent enantioselectivity was achieved not only in protic solvents, but also in aprotic solvents, such as acetone and dichloromethane (DCM). Further screening of various catalysts in methanol showed that the catalytic activity varied extremely with the enantioselectivity ranging from 81% to >99% ee. Complex **1b** with hexamethylbenzene as η^6-arene ligand was found to give the highest ee value. It was noted that both the iridium and rhodium complexes also exhibited excellent enantioselectivity. Unlike asymmetric hydrogenation of functionalized olefins with chiral rhodium or ruthenium diphosphine complexes,[14] the enantioselectivity was found to be insensitive to hydrogen pressure and temperature. By using **1b** as catalyst, the substrate/catalyst (S/C) molar ratio could be increased to 5000 without compromised enantioselectivity.

Under the optimal reaction conditions, a variety of 2-alkyl-substituted and 2-functionalized quinolines were subjected to hydrogenation (Scheme 2), full conversions and excellent ee values from 98% to >99% were achieved. The quinoline substrates bearing free hydroxyl group on the side chain could be efficiently hydrogenated in full conversion with

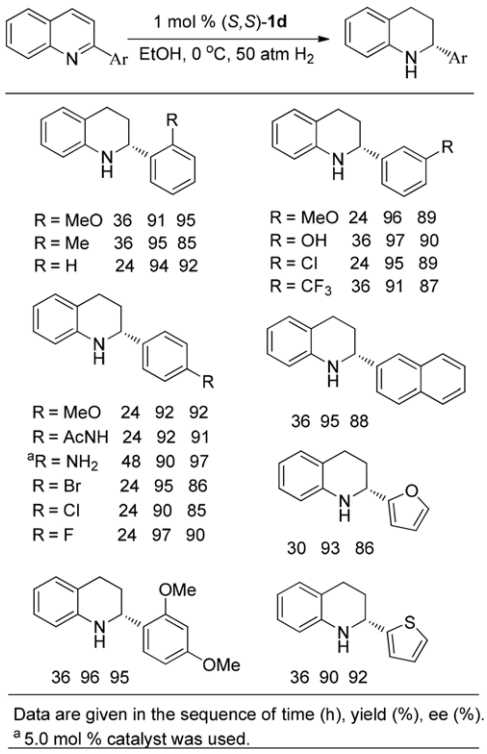


Scheme 3. Gram-scale syntheses of biologically important *N*-heterocylic compounds.

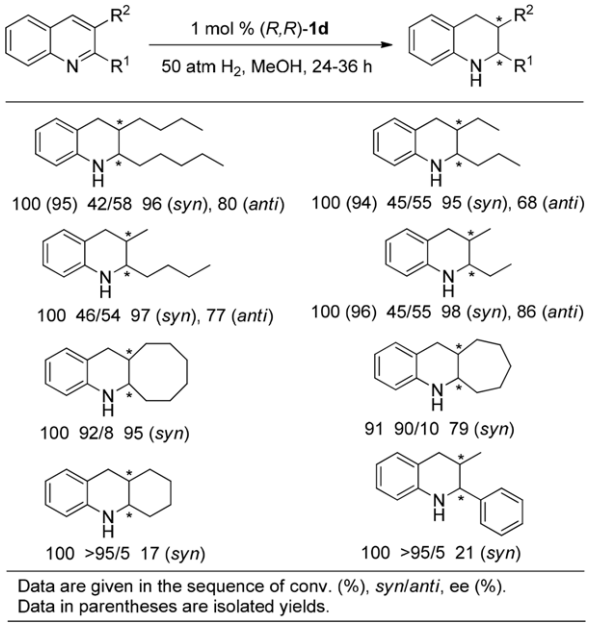
99% ee. Interestingly, the conjugated double bond was also hydrogenated, while the system could tolerate isolated double bond. Quinolines having a carboxylic acid or ester substituents were inactive in this reaction. With our protocol, gram-scale syntheses of biologically active 1,2,3,4-tetrahydroquinoline alkaloid, angustureine,[15] and a key intermediate for the synthesis of antibacterial agent (*S*)-flumequine, 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline,[16] were successfully achieved (Scheme 3).

Comparing with the 2-alkyl-substituted quinolines, the asymmetric hydrogenation of 2-aryl-substituted quinolines is far from satisfactory from both viewpoints of catalytic reactivity and enantioselectivity. Mashima and co-workers described a highly enantioselective hydrogenation of 2-aryl-substituted quinolinium salts by using cationic dinuclear Ir(III)/diphosphine complexes.[4f] Ee values up to 95% were obtained which were much better than those reported of the corresponding 2-arylquinolines. Rueping and co-workers developed a Brønsted acid-catalyzed cascade transfer hydrogenation of 2-arylquinolines, providing excellent enantioselectivities ranging from 87∼>99% ee.[6] Upon the successful asymmetric hydrogenation of 2-alkyl-substituted quinolines, we explored the hydrogenation of 2-aryl-substituted quinolines of a wide substrate scope by the chiral cationic Ru(II)/diamine system (Scheme 4).[13] In all cases, good to excellent enantioselectivities (85∼97% ee) were obtained. It was observed that both steric and electronic properties of the substituents on 2-phenyl group had a great impact on enantioselectivity and reactivity. Notably, when a coordinating group such as thiozyl as the 2-substituent, the hydrogenation still proceeded smoothly with good enantioselectivity.

Multi-substituted quinolines are more challenging substrates for asymmetric hydrogenation to afford heterocycles bearing more than one chiral carbon centers. To the best of our knowledge, there are only few catalytic systems that could successfully realize such a transformation.[8,17] We explored the asymmetric hydrogenation of 2,3-disubstituted quinolines with the ruthenium catalyst **1d** (Scheme 5).[13] Excellent ee values of the *syn*-products were acquired for the dialkyl-



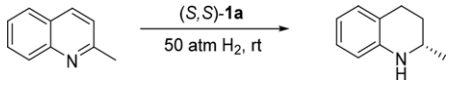
Scheme 4. Asymmetric hydrogenation of 2-aryl-substituted quinolines.



Scheme 5. Asymmetric hydrogenation of 2,3-disubstituted quinolines.

substituted acyclic compounds, while the diastereoselectivity is quite low. On the contrary, excellent diastereoselectivities were observed for the alkyl-substituted cyclic substrates and

Table 2. Comparison of the asymmetric hydrogenation of 2-methylquinoline in methanol and under solvent-free conditions.



entry	S/C	solvent	time (h)	conv. (%)	ee (%)
1	200	MeOH (0.2 M)	4	29	95
2	500	MeOH (0.2 M)	12	12	94
3	1000	MeOH (0.2 M)	24	<5	—
4	1000	MeOH (2.0 M)	24	38	95
5	1000	solvent free	24	95	96
6[a]	5000	solvent free	24	57	93

[a] 0.1 mol % TfOH was used as an additive.

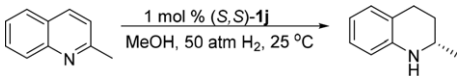
2-pheny-3-methylquinoline. The enantioselectivity of the *syn*-products was affected by the ring size of the cyclic substituent, varying extremely from 95% ee to 17% ee upon decreasing from 8-membered to 6-membered ring.

There are still substrate limitations for this chiral Ru-diamine complexes catalyzed asymmetric hydrogenation, for example, the quinoline substrates bearing a substituent at 4-position are inert to this catalytic system, and only racemic products could be obtained with 3-substituted quinolines. Most recently, Du and co-workers have realized the asymmetric hydrogenation of multi-substituted quinoline derivatives bearing a phenyl substituent at the 4-position with chiral FLP catalysts generated *in situ* from chiral dienes.[8] High isolated yields and enantioselectivities up to 99% ee were obtained. But the substrate scope is still limited to the 2-aryl-4-phenyl substituted quinolines.

2.2. Asymmetric Hydrogenation under Solvent-Free Conditions

It's still a big challenge to develop highly enantioselective solvent-free catalytic reactions,[18] especially for the asymmetric hydrogenation of heteroaromatic compounds because of the potential poisoning of catalyst by substrates and/or products. As shown above, the solvent selection influences the outcome of the asymmetric hydrogenation of quinolines. Meanwhile, the amount of the solvent used, which means the concentrations of substrate and catalyst, will also affect the reaction. Unexpectedly, the asymmetric hydrogenation of 2-substituted quinolines catalyzed by chiral Ru-diamine complexes proceeded smoothly under solvent-free or concentrated conditions (up to 99% yield and 97% ee).[19] More importantly, the reactivity and enantioselectivity were obviously increased with comparison to those obtained in methanol, and the catalyst loading could be cut down to 0.02-0.1 mol % (Table 2). In the cases of solid substrates, a little amount of 2-propanol and 0.1 mol % TfOH were needed to accelerate the hydrogenation process.

Table 3. Asymmetric hydrogenation of 2-methylquinoline: effects of oxygen and acid.



entry	conditions	time (h)	TFA (mol %)	conv. (%)	ee (%)
1	A	2	0	71	94
2	B	2	0	69	94
3	B	1	10	95	96
4	B	1	25	>95	94
5	C	1	10	58	94
6[a]	C	24	10	10	93

[a]Catalyst Ru(OTf)(*p*-cymene)(TsDPEN) was used. Condition A: with degassed solvent under nitrogen atmosphere; Condition B: with undegassed solvent but purging the autoclave with H_2 before reaction; Condition C: with undegassed solvent without purging the autoclave with H_2 before reaction.

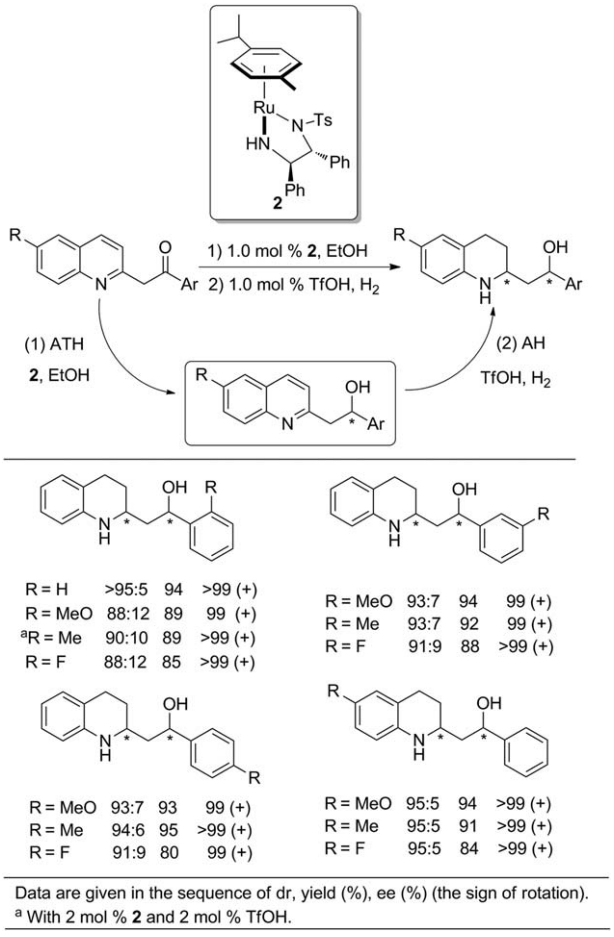
2.3. Ir-Catalyzed Asymmetric Hydrogenation of Quinolines in Air

Many metal complexes that are reactive toward hydrogen are known to be easily oxidized upon treatment with oxygen. For most chiral diphosphine-containing catalysts, hydrogenation must be performed under extremely oxygen-free conditions.

Recently, Rauchfuss and Ikariya independently reported that the iridium hydride complex Cp*IrH(TsDPEN) could efficiently catalyze the hydrogenation of oxygen in the presence of a Brønsted acid.[20] Inspired by this finding, we explored the hydrogenation of 2-methylquinoline catalyzed by iridium diamine complexes in undegassed methanol (Table 3).[21a] It was found that the hydrogenation proceeded smoothly in undegassed methanol without using a glovebox. The addition of CF_3COOH (TFA) remarkably elevated the conversion while the enantioselectivity retained. Even when the reaction was carried out in the presence of air, similar enantioselectivity was achieved. In contrast, the Ru-diamine catalyst was almost inactive under otherwise identical reaction conditions. A variety of 2-alkyl-substituted quinolines were successfully hydrogenated in nearly 100% isolated yields with excellent enantioselectivities (94∼99% ee). More importantly, this air tolerant method provides a more efficient and practical tool for the gram-scale synthesis of optically active 1,2,3,4-tetrahydroquinoline derivatives.[21b]

2.4. Asymmetric Tandem Reduction of 2-(Aroylmethyl)quinolines

2-(Aroylmethyl)quinolines bearing C=N and C=O functional groups present ketoimine and enaminone tautomers in



Scheme 6. Asymmetric tandem reduction of 2-(aroylmethyl)quinolines.

solution.[22] The selective and/or full hydrogenation of both functionalities will provide new kinds of optically pure quinoline and/or 1,2,3,4-tetrahydroquinoline derivatives. Most recently, Zhou and co-workers reported the first selective asymmetric hydrogenation of such quinoline derivatives with their Ir/diphosphine/I_2 catalyst system, in which only the fused pyridine ring was reduced.[17a]

2-(Aroylmethyl)quinolines are suitable substrates for investigating the chemoselective property of our Ru-diamine catalytic system.[23] The initial hydrogenation of 2-(benzoylmethyl)quinoline with (*R,R*)-**1a** as catalyst only gave a mixture of a partially reduced product and a fully reduced product. The fully reduced product, 2-(1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanol, was observed with high enantioselectivity, but the major product was found to be an enamine, (*Z*)-2-(3,4-dihydroquinolin-2(1*H*)-ylidene)-1-phenylethanone. This is different from the hydrogenation using Ir-diphosphine complexes, in which only the quinoline unit was reduced with the ketone untouched.[17a] To obtain the fully reduced product in high yield, we have to develop a new strategy to meet this requirement. Considering the fact that the amido complex **2** is effective catalyst for asymmetric transfer hydrogenation of aromatic ketones, and is easily to be conversed to the cationic triflate complex (*R,R*)-**1a** by adding one equivalent of TfOH,[11b] a tandem asymmetric transfer hydrogenation/asymmetric hydrogenation of 2-(aroylmethyl)-quinolines were designed and tested (Scheme 6). High yields with excellent enantioselectivities and good diastereoselectivities were achieved for all substrates studied (Scheme 6).

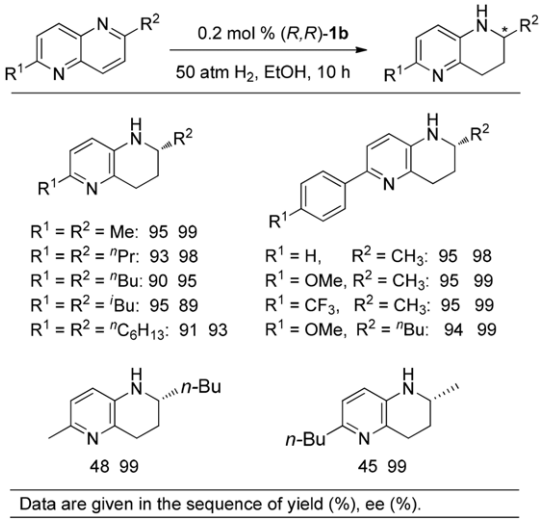
2.5. Ru-catalyzed Asymmetric Hydrogenation of Naphthyridines

Naphthyridines have similar chemical structures to quinolines. Asymmetric reduction of 1,5- and 1,8-naphthyridine derivatives can provide optically active 1,2,3,4-tetrahydronaphthyridines, which is an important structural unit in many biologically active compounds and have shown great potential for pharmaceutical development.[24] However, there are only a few reports describing the asymmetric synthesis of 1,2,3,4-tetrahydronaphthyridines,[25] and the asymmetric hydrogenation of 2,6-disubstituted 1,5-naphthyridines and 2,7-disubstituted 1,8-naphthyridines is still a big challenge.

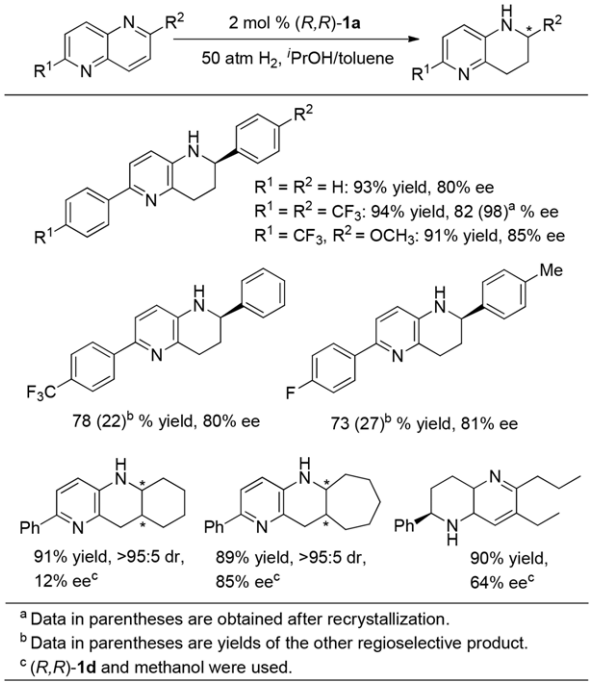
On the basis of the success gained in the asymmetric hydrogenation of a large variety of quinoline substrates, we explored the asymmetric hydrogenation of 2,6-disubstituted 1,5-naphthyridine derivatives by using the chiral cationic transition metal/diamine catalysts. It was found that various 2,6-disubstituted 1,5-naphthyridines could be hydrogenated smoothly.[26a] For the 2,6-disubstituted substrates bearing at least one alkyl substituent (Scheme 7), excellent enantioselectivities were obtained (93∼99% ee). No regioselectivity was observed when the substrates bear two different alkyl groups at the 2- and 6-positons. Interestingly, only the pyridyl ring bearing an alkyl group was hydrogenated for the 2-alkyl-6-aryl-disubstituted naphthyridines. In the cases of diaryl-substituted naphthyridines, full conversion and good enantioselectivity (80∼85% ee) could be obtained with high catalyst loading (Scheme 8). High regioselectivity was observed for the unsymmetric diaryl-substituted substrates, and the pyridyl rings bearing more electron-rich substituents were found to be more easily reduced. Other trisubstituted substrates were also tested, and good results were obtained (Scheme 8).

One of the reduced 1,2,3,4-tetrahydronaphthyridine product was applied for further heterogeneous platinum-catalyzed diastereoselective hydrogenation, affording the perhydrogenated product, (2*S*,6*S*,9*R*,10*R*)-2,6-dimethyl-1,5-diaza-*cis*-decalin in total 80% isolated yield without observation of other diastereomers (Scheme 9).

Comparing with 1,5-naphthyridines, 1,8-naphthyridines are more challenging substrates for asymmetric hydrogenation due to the two adjacent *N*-coordinating groups. Both

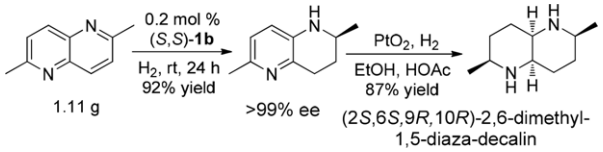


Scheme 7. Asymmetric hydrogenation of alkyl-substituted 1,5-naphthyridines.

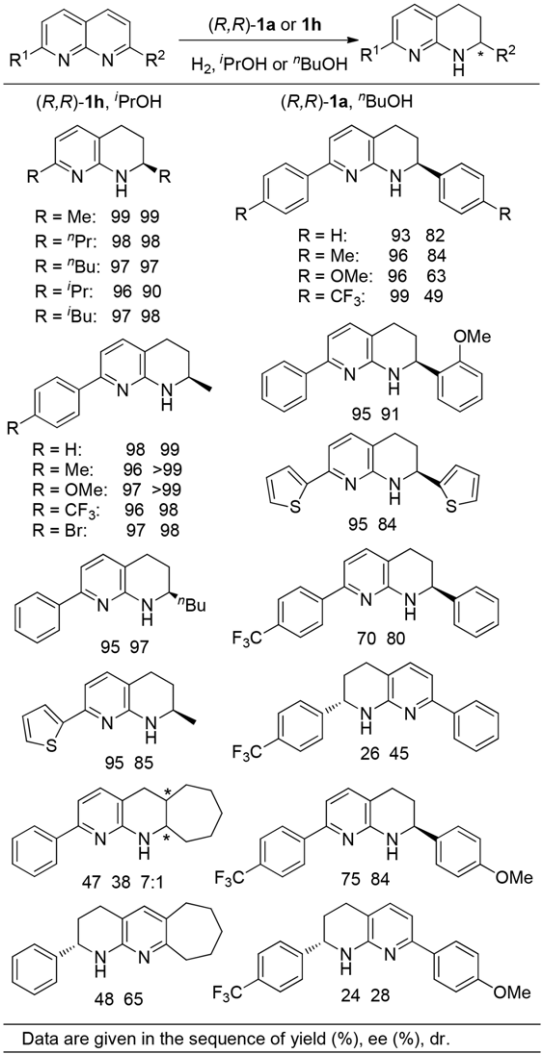


Scheme 8. Asymmetric hydrogenation of aryl-substituted 1,5-naphthyridines.

substituents at the 2- and 7-positions were found to be critical for achieving complete conversion. By utilizing the chiral Ru-diamine complexes, most recently, we have realized the first highly efficient asymmetric hydrogenation of a range of 2,7-substituted 1,8-naphthyridines with good to excellent enantioselectivities (Scheme 10).[26b]



Scheme 9. Synthesis of chiral 2,6-dimethyl-1,5-diaza-*cis*-decalin.



Scheme 10. Asymmetric hydrogenation of 2,7-substituted 1,8-naphthyridines.

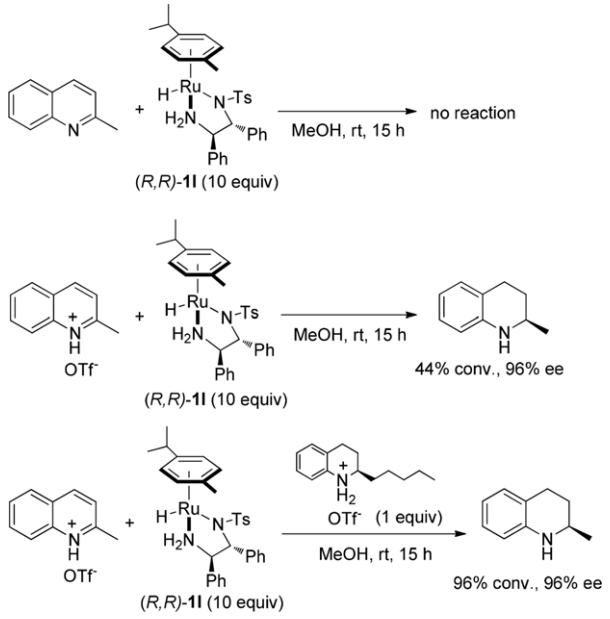
3. Mechanistic Study

In general, the reduction of quinolines includes a hydrogenation sequence of C=C and C=N double bonds. The early mechanistic study of quinoline hydrogenation catalyzed by achiral transition metal complexes proposed an inner-sphere 1,2- and 3,4-hydrogen sequential addition process.[27] After the first highly enantioselective hydrogenation of quinolines

was reported in 2003,[4a] Zhou and co-workers carried out mechanistic studies of this Ir/diphosphine/I_2 catalytic system.[17a] A combination of experimental and theoretical studies suggested that a cascade reaction of 1,4-hydride addition, enamine-imine isomerization, and 1,2-hydride addition involving a conventional inner-sphere mechanism was proposed.

After our initial publication on the asymmetric hydrogenation of quinolines in ionic liquid and an unusual outer-sphere mechanism proposed,[12] we began to do thorough and detailed mechanistic studies to support our proposal. Systematic investigations were carried out by using a combination of stoichiometric reaction, intermediate characterization and isotope labeling patterns together with DFT (density functional theory) calculation.[13] Solid evidences were obtained to confirm the reaction pathway and the origins of enantioselectivity.

Unlike the reaction of ketone with ruthenium hydride complex,[28] no conversion was observed in the stoichiometric reaction of 2-methylquinoline (Scheme 11). By using quinolinium salt as substrate, reaction took place but with no more than 50% conversion. After adding 1 equiv. of tetrahydroquinolinium salt into the reaction, full conversion could be achieved. These results suggest that quinoline must first be activated by protonation before reduction. In addition, the existence of



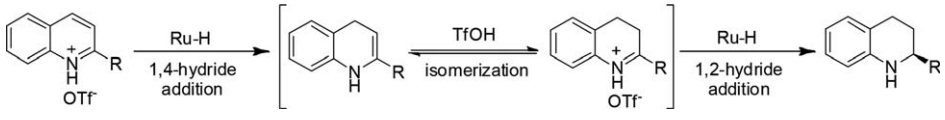
Scheme 11. Stoichiometric reduction of quinoline with isolated ruthenium hydride complex.

imine intermediate from ^{1}H NMR (nuclear magnetic resonance) and ESI-MS (electrospray ionization-mass spectrometry) characterization confirmed that the hydrogenation of quinoline proceeded through an ionic and cascade reaction pathway including 1,4-dihydrogen addition, tautomerization, and then 1,2-dihydrogen addition process (Scheme 12).

This reaction pathway was further demonstrated by the results of deuteration study (Scheme 13). It is clearly shown that the deuterium at C2- and C4-positions in the product come from D_2, and the deuterium at C1- and C3-positions are from the CD_3OD solvent. Transfer hydrogenation process was excluded by using $(CH_3)_2CDOH$ as the reaction medium. Meanwhile, a reversible aromatization of the imine intermediate could also happen in the hydrogenation process which was demonstrated by deuterium scrambling into the recovered 2-phenyl quinoline at the C4-position, and 1,2,3,4-tetrahydroquinoline at the C2- and C4- positions.

To further understand the mechanism and the origins of enantioselectivity, theoretical calculations were carried out to study the hydrogenation process of the protonated imine intermediate with ruthenium hydride complex. The computational results indicated that the final 1,2-hydride addition proceeded through an ionic pathway involving a 10-membered ring transition state with the participation of TfO^- anion (Scheme 14). Similar to the ketone reduction reported by Noyori and coworkers,[29] the enantioselectivity originates from the CH/π attraction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of dihydroquinoline. This proposed transition state will shed light on the mechanism of other imine reduction involved reactions with similar ruthenium catalysts.

Unlike the asymmetric reduction of ketones,[11b,29] the hydrogenation of quinolines underwent a stepwise H^+/H^- transfer process outside the coordination sphere rather than a concerted mechanism, which involving 1,4-dihydrogen addition, tautomerization, and 1,2-dihydrogen addition. A possible catalytic cycle was proposed on the basis of the experimental and theoretical calculation results described above (Scheme 14).The ionized ruthenium complex **3** reversibly coordinates a dihydrogen molecule to form complex **4**. Deprotonation of the dihydrogen by quinoline generates both the active species **5** and the activated substrate. A subsequent 1,4-hydride transfer affords the enamine intermediate and regenerates complex **3**. Similarly, the enamine or imine serves as a base to deprotonate the dihydrogen ligand, resulting in species **5** and iminium cation. Then, the irreversible 1,2-



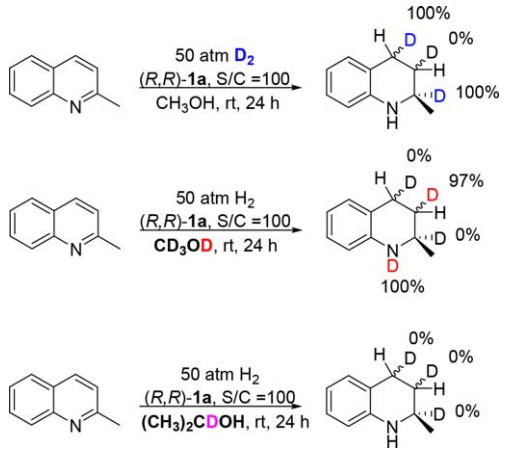
Scheme 12. The possible reaction pathway of quinoline hydrogenation catalyzed by ruthenium/diamine complexes.

hydride transfer gives the complex **3** and the final product, 1,2,3,4-tetrahydroquinoline.

In 2011, Crabtree and co-workers developed a new homogeneous achiral iridium catalyst for the hydrogenation of quinolines under mild conditions.[30] Based on the experimental and theoretical results, a similar ionic and cascade reaction pathway and a stepwise outer-sphere mechanism were proposed. Most recently, Zhang and co-workers realized rhodium-catalyzed asymmetric hydrogenation of quinolines and isoquinolines by using a new ferrocene-thiourea chiral diphosphine ligand.[4j] A plausible outer-sphere mechanism was also proposed.

4. Asymmetric Hydrogenation in Alternative Reaction Media and Catalyst Recycling

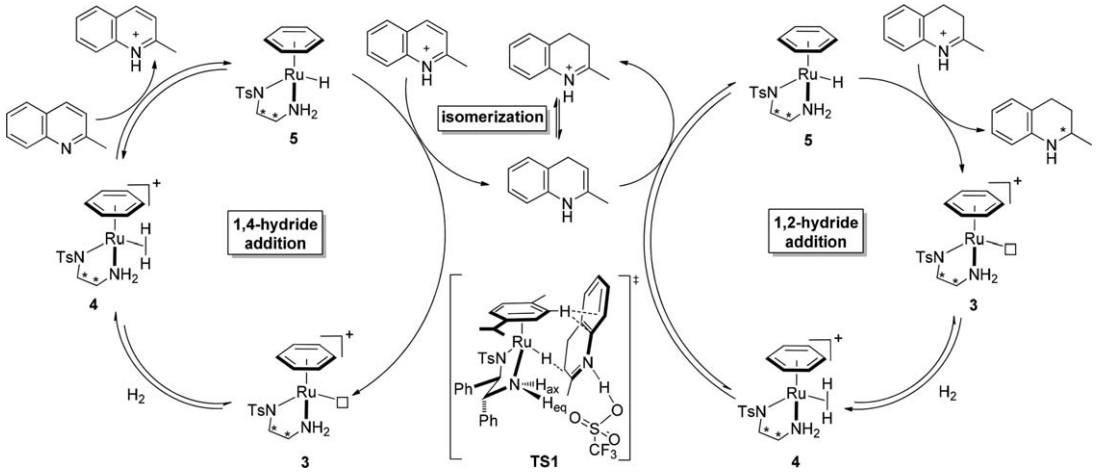
Over the past decades, seeking environmentally benign reaction media is one of the major goals of green chemistry, and has been attracting great attention.[31] The use of alternative solvents in catalytic reactions is not just a simple solvent replacement, it may bring fascinating characteristics such as enhancements in catalytic performance as well as uncovering new reactions. In addition, some of these new reaction media can be also severed as a vehicle to facilitate the recycling of homogeneous catalysts. The very first successful example of asymmetric hydrogenation of quinolines with chiral Ru-diamine complexes was realized in [BMIM]PF_6.[12] So, we explored this asymmetric hydrogenation in several alternative solvents frequently used, such as imidazolium ionic liquids, oligo(ethylene glycol)s, and water. Distinct features were observed respectively, and catalyst recycling and reuse were achieved with the catalytic systems other than water.



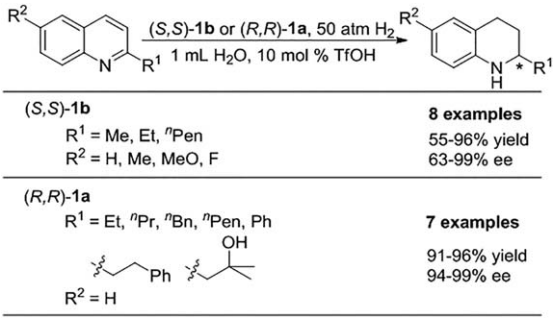
Scheme 13. Deuterium-labeling studies.

4.1. Asymmetric Hydrogenation in Water

Water has been considered as the most preferred green reaction medium for catalytic reactions.[32] Due to its unique physical and chemical properties, enhancement in reactivity and/or selectivity was observed for some catalytic reactions in water. To date, great progress has been made in this field, however, only limited success was achieved in the highly effective asymmetric hydrogenation in neat water.[33] Recently, the ruthenium and rhodium complexes of chiral monotosylated diamines have proven to be effective for asymmetric transfer hydrogenation of ketones and quinolines in water.[33] On the basis of our success in the asymmetric hydrogenation of quinolines in organic solvents, we explored the hydrogenation of quinolines catalyzed by the chiral cationic Ru-diamine complexes in undegassed neat water (Scheme 15).[34] It was found that the hydrogenation proceeded smoothly with the addition of 10 mol % HOTf. Particularly, all manipulations could be conducted in air. A range of 2-substituted quinolines was hydrogenated in water, providing the optically active 1,2,3,4-



Scheme 14. Catalytic cycle proposed for the asymmetric hydrogenation of quinolines.



Scheme 15. Asymmetric hydrogenation of quinolines in undegassed deionized water.

tetrahydroquinoline derivatives in high yields with excellent enantioselectivities.

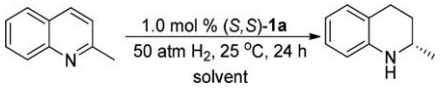
4.2. Asymmetric Hydrogenation in Ionic Liquids

Room-temperature ionic liquids (RTILs), especially those containing 1,3-dialkylimidazolium cations, have emerged as environmentally benign alternative reaction media for catalytic reactions. Furthermore, RTILs have served as a promising means for catalyst immobilization to facilitate product isolation, catalyst recycling and reuse.[35] In 2008, we first used chiral cationic Ru/TsDPEN catalyst for the asymmetric hydrogenation of quinolines.[12] It was found that the reaction proceeded smoothly in neat [BMIM]PF_6. Unlike the Ir/diphosphine catalytic system which gave poor results in ionic liquid,[4c] a variety of 2-alkyl-substituted quinolines were hydrogenated smoothly to 1,2,3,4-tetrahydroquinolines in high yields (87∼97%) with excellent enantioselectivities (96∼99% ee), which are similar to or better than those obtained in methanol.

In our following systematic study,[36] the catalyst was found to be highly stable in ionic liquid, and its activity was influenced by the counteranion of catalyst. High conversion and enantioselectivity could be obtained in [BMIM]PF_6 when all manipulations were conducted in air (Table 4). The same reactivity and enantioselectivity were retained even after the exposure of catalyst to air for 30 days. In contrast, significant decreases in conversion and enantioselectivity were observed in MeOH and CH_2Cl_2.

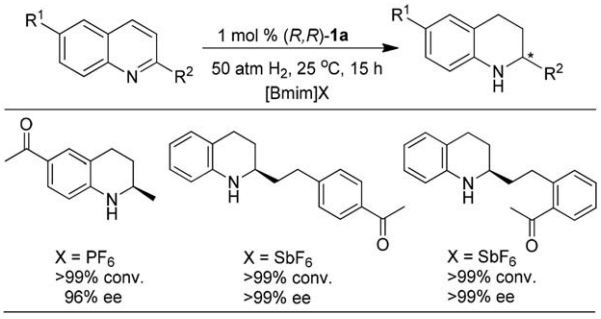
More importantly, the hydrogenation of quinoline derivatives bearing a carbonyl group was selective for the C=N (quinoline) over the C=O (ketone) double bonds (Scheme 16) in ionic liquids, while such a unique chemoselectivity was not observed in methanol. By selecting catalysts of different absolute configurations and reaction sequences, all four stereoisomers of the hydrogenated products were acquired in full conversions with excellent enantioselectivities and diastereoselectivities (Scheme 17).

Table 4. Asymmetric hydrogenation of 2-methylquinoline: catalyst stability.



entry	solvent	conv. (%)	ee (%)
1	[Bmim]PF_6	98	98 (99)
2	MeOH	6	85 (94)
3	CH_2Cl_2	16	92 (97)
4[a]	[Bmim]PF_6	>99	99 (99)

[a]The catalyst in [Bmim]PF_6 was stored in air for a month before use. Data in parentheses were obtained in degassed solvents.

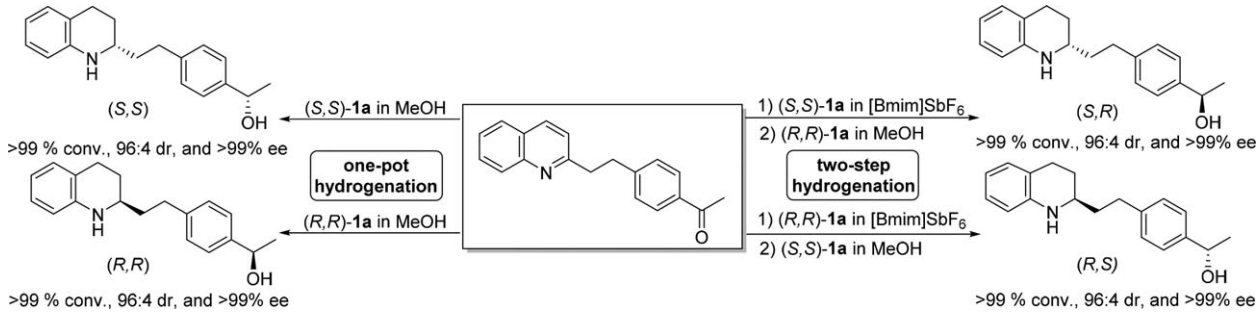


Scheme 16. Asymmetric hydrogenation of quinoline derivatives bearing a C=O functional group in ionic liquids.

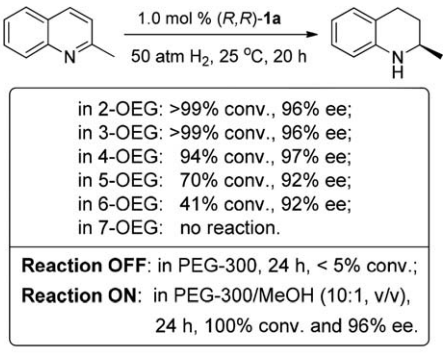
After the completion of hydrogenation, the reduced products were separated by *n*-hexane extraction, and the Ru-catalyst was remained in the ionic liquid phase. By directly adding another batch of substrate, the next cycle of hydrogenation was conducted under the identical reaction conditions. The ruthenium catalyst **1a** could be reused at least 6 times without obvious loss of reactivity and enantioselectivity. Meanwhile, another silica gel supported ionic liquid-phase catalytic system was also applied to the asymmetric hydrogenation of 2-methylquinoline in *n*-hexane. The heterogenized catalyst could be easily separated *via* filtration, and the catalyst reuse was also achieved.

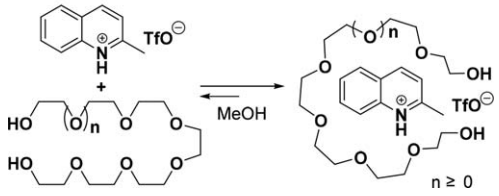
4.3. Asymmetric Hydrogenation in PEGs and OEGs

As a new type of alternative solvents, liquid poly(ethylene glycol)s (PEGs) are cheap, non-volatile, non-halogenated, and have low toxicity and high chemical stability.[37] More importantly, PEGs have been considered as host solvents for their ability in association with cations. Very recently, we examined the asymmetric hydrogenation of 2-methylquinoline by using chiral cationic Ru-diamine catalysts in PEGs.[38] Surprisingly, no conversion was observed. To seek the reason for this



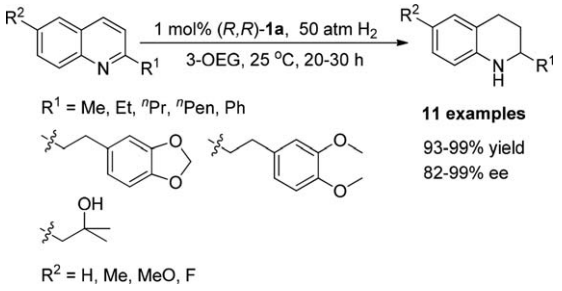
Scheme 17. Synthesis of all four stereoisomers based on the unique chemoselectivity in ionic liquids.





Scheme 18. Asymmetric hydrogenation in PEGs/OEGs and equition of host-guest assembly between long chain PEG/OEG and quinolinium salt.

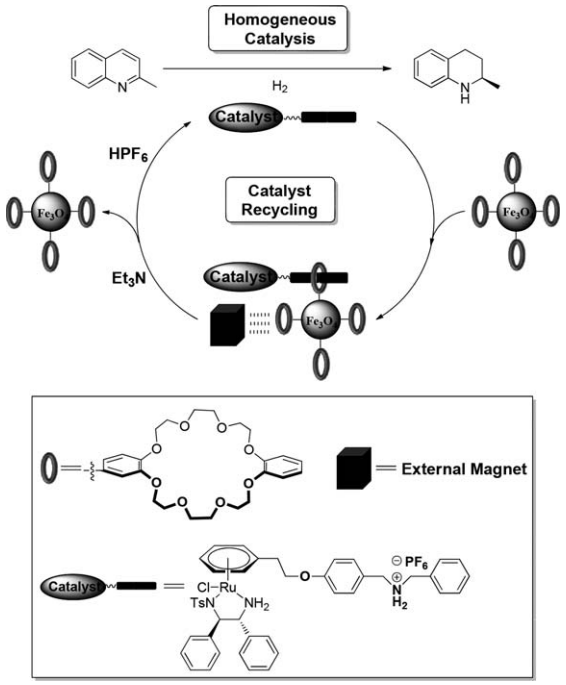
reaction shut-off, oligo(ethylene glycol)s (OEGs) in different lengths were synthesized and tested. It was found that the reactivity and selectivity were influenced by the length of OEG used. Upon the length increasing, gradual decrease of reactivity and enantioselectivity occurred. When the OEG length reached 7 ethylene glycol units, the hydrogenation was stopped, just as those in PEGs. Further investigations *via* ESI-HRMS and designed control experiments indicated that a supramolecular host-guest assembly between long chain OEG/PEG and quinolinium salt was formed, in which quinoline substrate is inert to hydrogenation for the encapsulation. The hydrogenation in PEG-300 could be turned on by adding a little amount of methanol (Scheme 18). Afterwards, the asymmetric hydrogenation of a range of 2-substituted quinolines was successfully achieved in 3-OEG (Scheme 19), and the catalyst recycling and reuse were realized by using both 3-OEG monophasic and 3-OEG/*n*-hexane biphasic catalytic systems.



Scheme 19. Asymmetric hydrogenation of quinolines in an oligo(ethylene glycol).

4.4. Catalyst Recycling Protocol *via* Magnetic Nanoparticles

Recently, magnetic nanoparticles (MNPs) have emerged as a robust, readily available, high-surface-area heterogeneous support in catalytic transformations.[39] Unlike most of the reported magnetically recoverable nanocatalysts, in which the catalytically active center is connected *via* a covalent bonding, we developed a non-covalent catalyst anchoring strategy for asymmetric hydrogenation of quinolines. By using a dialkylammonium salt tagged chiral Ru/TsDPEN catalyst, a novel catalyst separation and recycling protocol combining magnetic nanoparticles and host-guest assembly was developed (Scheme 20).[40] Hydrogenation of 2-methylquinoline proceeded smoothly under homogeneous conditions in dichloromethane. Upon the completion of the reaction, dibenzo[24]crown-8-modified Fe_3O_4 nanoparticles were added to facilitate the simple catalyst separation *via* a magnet-assisted decantation, on basis of the formation of a pseudorotaxane complex. The obtained MNP-supported catalyst was then disassembled to regenerate the homogeneous catalyst. Thus, five consecutive catalytic runs were performed, and almost the same enantioselectivity was obtained. This controlled reversibly anchoring strategy for catalyst recycling could realize monophasic catalysis and biphasic separation, which combines the advantages of both homogeneous and heterogeneous catalysis.



Scheme 20. Illustration of homogeneous catalysis and catalyst recycling by combining MNPs and host-guest assembly.

5. Summary and Outlook

In summary, chiral cationic ruthenium(II) or iridium(III)/η-arene-*N*-monosulfonylated diamine complexes have been demonstrated to be highly effective and selective catalysts for the asymmetric hydrogenation of quinolines and their analogues. On the basis of screening a large variety of transition metal complexes, a wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, 2-functionalized, and 2,3-disubstituted quinolines were efficiently hydrogenated under mild reaction conditions with up to >99% ee and up to 5000 TON. Remarkable enhancement in reactivity was observed in the solvent-free hydrogenation. Meanwhile, chemoselective hydrogenation of specific substrates, 2-(aroylmethyl)quinolines, bearing a C=O functional group, were also achieved by using different reduction strategies. This catalytic system was also applied for the asymmetric hydrogenation of more challenging substrates, alkyl- and aryl-substituted 1,5- and 1,8-naphthyridine derivatives, providing 1,2,3,4-tetrahydronaphthyridines with good to excellent enantioselectivities. A systematically mechanistic study by combining stoichiometric reaction, intermediate characterization, and isotope labeling patterns revealed that quinoline was reduced *via* an ionic and cascade reaction pathway, including 1,4-dihydrogen addition, tautomerization, and 1,2-dihydrogen addition. The dihydrogen addition underwent a stepwise H^+/H^- transfer process outside the coordination sphere rather than a concerted mechanism. Further theoretical calculations on the transition states of the stereogenic step suggested that the enantioselectivity originated from the CH/π attraction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of dihydroquinoline *via* a 10-membered ring transition state with the participation of TfO^- anion. In addition, the Ru-catalyzed asymmetric hydrogenation of quinolines could be carried out in undegassed water, neat [BMIM]PF_6, or short chain OEGs. The Ru-catalyst could be easily recycled by using RTILs and OEGs as solvents, as well as *via* magnetic nanoparticles. Interestingly, the hydrogenation of quinoline derivatives bearing a carbonyl group in [BMIM]PF_6 was selective for the C=N (quinoline) over the C=O (ketone) double bonds. Thus, this versatile catalytic protocol provides a facile, green, and practical access to a variety of optically active 1,2,3,4-tetrahydroquinoline derivatives, which are key building blocks for the synthesis of some important natural alkaloids and pharmaceuticals.

However, there are still limitations of this phosphorus-free catalytic system in the asymmetric hydrogenation of quinoline derivatives. For examples, the hydrogenation of 4-substituted quinolines and the stereoselective control for the hydrogenation of 3-substituted quinolines are still challenging in this research area. And there are tons of functionalized quinoline derivatives awaiting to be reduced efficiently and selectively to afford a much more broad range of 1,2,3,4-tetrahydroquinoline derivatives, which are important for drug discovery and fine chemical industry. In addition, the counteranion was proposed to participate in the catalytic cycle, and its role in the stereoselective control is also waiting for further study.[41] Despite of these limitations in the asymmetric hydrogenation of quinolines, we believe that this catalytic protocol will have potential applications in the asymmetric hydrogenation of other more challenging *N*-containing heteroaromatic compounds.[42]

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