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Highly Enantioselective Hydrogenation of Quinolines Using Phosphine-Free Chiral Cationic Ruthenium Catalysts: Scope, Mechanism, and Origin of Enantioselectivity

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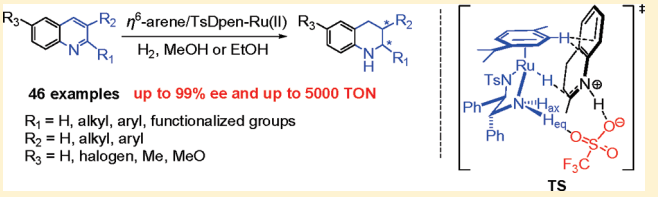
Supporting Information

ABSTRACT: Asymmetric hydrogenation of quinolines catalyzed by chiral cationic η^6-arene−*N*-tosylethylenediamine−Ru(II) complexes have been investigated. A wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, and 2-functionalized and 2,3-disubstituted quinoline derivatives, were efficiently hydrogenated to give 1,2,3,4-tetrahydroquinolines with up to >99% ee and full conversions. This catalytic protocol is applicable to the gram-scale synthesis of some biologically active tetrahydroquinolines, such as (−)-angustureine, and 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, a key intermediate for the preparation of the antibacterial agent (*S*)-flumequine. The catalytic pathway of this reaction has been investigated in detail using a combination of stoichiometric reaction, intermediate characterization, and isotope labeling patterns. The evidence obtained from these experiments revealed that quinoline is reduced via an ionic and cascade reaction pathway, including 1,4-hydride addition, isomerization, and 1,2-hydride addition, and hydrogen addition undergoes a stepwise H^+/H^- transfer process outside the coordination sphere rather than a concerted mechanism. In addition, DFT calculations indicate that 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.



INTRODUCTION

Optically active tetrahydroquinoline derivatives are an important class of building blocks for asymmetric synthesis in pharmaceutical and agrochemical industries and for the total synthesis of natural products.[1,2] For example (Figure 1), the (*S*)-enantiomer of flumequine[3] is an antibacterial agent of the quinolone family. Several tetrahydroquinoline derivatives, such as torcetrapib[2d,4] and compound **A**,[2g,5] have attracted much attention as potent inhibitors of the cholesterol ester transfer protein, a target for the treatment of low high-density lipoprotein cholesterol and atherosclerosis. The chirality of these compounds was found to play a pivotal role in their relevant bioactivities. In addition, many naturally occurring alkaloids contain the tetrahydroquinoline unit,[6] including angustureine,[6a] galipinine,[6b,c] and cuspareine.[6c] Therefore, it is highly desirable to develop efficient methods for the preparation of optically pure tetrahydroquinoline derivatives in both academia and industry.

The transition metal-catalyzed asymmetric hydrogenation of quinoline derivatives, which are easily prepared from readily available starting materials, represents one of the most atom-economic and efficient methods for the synthesis of chiral 1,2,3,4-tetrahydroquinoline derivatives.[7−12] However, most of the reported chiral Rh, Ru, and Ir complexes, which have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines,[13] failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[14] In 2003, Zhou and co-workers first reported the Ir-catalyzed highly effective asymmetric hydrogenation of 2,6-substituted quinolines with (*R*)-MeO-BIPHEP as the ligand in the presence of iodide to produce chiral tetrahydroquinolines with up to 96% ee.[8a] Following this significant lead, a variety of iridium complexes of chiral phosphorus ligands, including diphosphines, diphosphites, monodentate phosphorus ligands, and P,N-ligands, have been developed to catalyze the enantioselective hydrogenation of a wide range of 2-alkyl-substituted quinoline derivatives, and good to excellent enantioselectivities have been observed.[8−10] Recently, we have demonstrated that comparable or better results could be achieved when employing recyclable iridium complexes of

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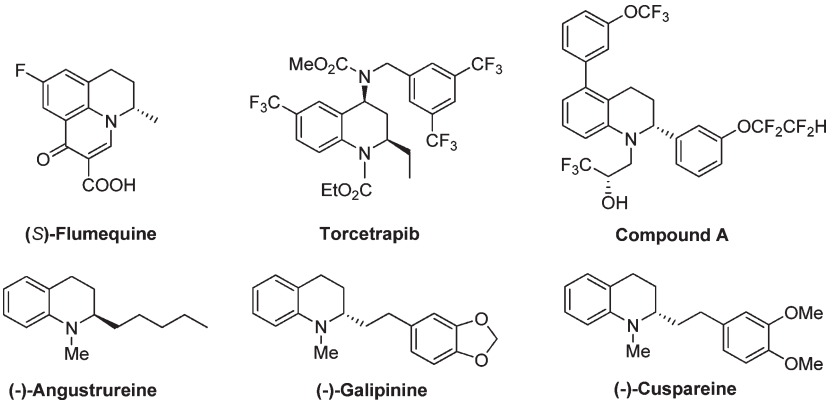
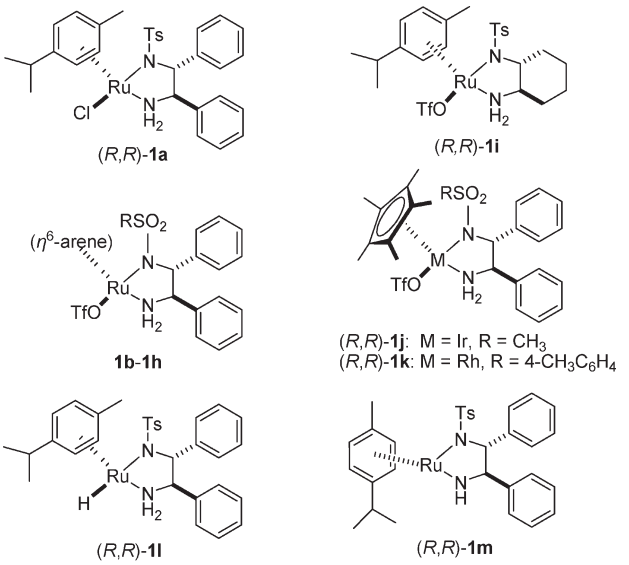


Figure 1. Selected bioactive compounds derived from chiral 1,2,3,4-tetrahydroquinoline derivatives.

P-Phos[9a] and dendrimeric BINAP[9e] in the asymmetric hydrogenation of 2,6-substituted quinolines. Despite this significant progress, the catalytic efficiency was still far from being practical, as evidenced by the fact that good results could only be obtained at a low substrate/catalyst (S/C) ratio of 100 in most cases.[8f,9d−9g] All these iridium catalysts had at least one phosphine ligand around the metal center and were often air sensitive. Furthermore, most of these catalysts were highly enantioselective only in the hydrogenation of 2-alkyl-substituted quinolines.[8e,10f] From the viewpoints of both scientific interest and practical applications, more efficient and stable catalyst systems for the asymmetric hydrogenation of quinolines are desirable.

In comparison with chiral phosphorus ligands, chiral diamine ligands are more readily available, easily tunable, and air-stable.[15] Their Ru, Rh, and Ir complexes have been extensively studied in the asymmetric transfer hydrogenation of aromatic ketones and imines,[16] although they were long neglected in the hydrogenation of unsaturated compounds.[17] Very recently, Noyori and co-workers reported that chiral η^6-arene−TsDpen−Ru(II) complex could be used for the asymmetric hydrogenation of ketones under slightly acidic conditions.[18a] Later, we found that this Ru-catalyst could catalyze the asymmetric hydrogenation of quinolines in ionic liquid or under solvent-free conditions with unprecedented reactivity and enantioselectivity.[19] Our preliminary result also suggested that the hydrogenation of quinolines occurred by an ionic catalytic pathway,[20] which was different from the mechanism of the asymmetric hydrogenation of ketones.[21] At the same time, Xiao et al. demonstrated that a cationic Cp*Rh(III)−TsDpen complex was an efficient catalyst for the asymmetric hydrogenation of cyclic imines in the presence of $AgSbF_6$.[22a] They further found that a combination of the Ir−diamine complex together with a chiral phosphate anion efficiently hydrogenate a variety of acyclic *N*-aryl imines with excellent enantioselectivities.[22b,c] Ikariya and Fan also reported that Ir- and Ru-complexes of N-sulfonylated diamine efficiently catalyzed the asymmetric hydrogenation of acyclic ketimines, respectively.[22d,e] These promising results demonstrated that Ru-, Rh-, and Ir-complexes of N-sulfonylated diamines were excellent catalysts for the asymmetric hydrogenation not only of ketones but also of quinolines and imines. Despite this significant progress, the mechanism of imine reduction with this type of catalyst remained to be elucidated,[23] in contrast to the better known asymmetric reduction of ketones.[21] To extend the scope of our practical hydrogenation of quinolines and to better understand the reaction mechanism, in this article, we report a systematic study on the asymmetric hydrogenation of a broad range of quinoline derivatives using Ru−diamine catalysts together with a detailed mechanistic study through experiments and DFT calculations. It was found that various quinoline derivatives including 2-alkyl- and 2-aryl-substituted quinolines, 2-functionalized quinolines, and 2,3-disubstituted quinolines were successfully hydrogenated with unprecedented enantioselectivities (up to >99% ee) and high turnover numbers (TON up to 5000). To the best of our knowledge, the levels of enantioselectivity and substrate generality are the highest among all known systems.[8−10] Moreover, mechanistic studies revealed that quinoline was reduced through a cascade reaction pathway, involving a 1,4-hydride addition, isomerization, and 1,2-hydride addition. The hydrogen addition underwent a stepwise H^+/H^- transfer process outside the coordination sphere, supporting an ionic rather than a concerted mechanism. This versatile catalytic protocol thus

Scheme 1



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

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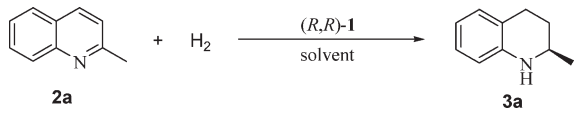
Table 1. Optimizing Conditions for Asymmetric Hydrogenation of 2-Methylquinoline[a]



entry	catalyst	solvent	temp (°C)	H_2 (atm)	time (h)	conv (%)[b]	ee (%)[c]
1	(*R*,*R*)-**1a**	MeOH	15	20	6	<5 (21)[d]	Nd (83)[d]
2	(*R*,*R*)-**1b**	MeOH	15	20	6	100	96
3	(*R*,*R*)-**1b**	EtOH	15	20	6	100	96
4	(*R*,*R*)-**1b**	*i*-PrOH	15	20	6	84	97
5	(*R*,*R*)-**1b**	THF	15	20	6	40	92
6	(*R*,*R*)-**1b**	Et_2O	15	20	6	37	93
7	(*R*,*R*)-**1b**	toluene	15	20	6	38	92
8	(*R*,*R*)-**1b**	acetone	15	20	6	78	96
9	(*R*,*R*)-**1b**	CH_2Cl_2	15	20	6	54	98
10	(*R*,*R*)-**1b**	[Bmim]PF_6	15	20	6	43	98
11	(*R*,*R*)-**1b**	H_2O	15	20	6	31	94
12	(*R*,*R*)-**1b**	MeOH	25	50	1	33	96
13	(*R*,*R*)-**1c**	MeOH	25	50	1	40	>99
14	(*R*,*R*)-**1d**	MeOH	25	50	1	23	89
15	(*R*,*R*)-**1e**	MeOH	25	50	1	74	94
16	(*R*,*R*)-**1f**	MeOH	25	50	1	17	95
17	(*R*,*R*)-**1g**	MeOH	25	50	1	19	96
18	(*R*,*R*)-**1h**	MeOH	25	50	1	22	94
19	(*R*,*R*)-**1i**	MeOH	25	50	1	15	81
20	(*R*,*R*)-**1j**	MeOH	25	50	1	48	96
21	(*R*,*R*)-**1k**	MeOH	25	50	1	27	>99
22	(*R*,*R*)-**1c**	MeOH	60	50	1	74	>99
23	(*R*,*R*)-**1c**	MeOH	25	10	2	12	>99
24[e]	(*R*,*R*)-**1c**	MeOH	25	50	14	100	99
25[f]	(*R*,*R*)-**1c**	MeOH	40	50	48	100	99

[a] Reaction conditions: 0.2 mmol of 2-methylquinoline (**2a**) in 1 mL of solvent, 1.0 mol % catalyst. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis with a chiral column. [d] Data in brackets were obtained at 60 °C. [e] 0.2 mol % (*R*,*R*)-**1c**. [f] 0.02 mol % (*R*,*R*)-**1c** and 2 mmol of **2a** in 1 mL of MeOH.

provided a facile and practical access to a variety of optically active 1,2,3,4-tetrahydroquinoline derivatives.

RESULTS AND DISCUSSION

Asymmetric Hydrogenation of Quinoline Derivatives Catalyzed by Cationic Ruthenium Catalysts. Synthesis of Ruthenium Catalysts. Since the pioneering work reported by Noyori and co-workers,[16] a number of Ru-, Rh-, and Ir-complexes of N-monosulfonylated diamines have been synthesized and proven to be powerful catalysts for asymmetric transfer hydrogenation of ketones and imines. In our study, chiral N-sulfonylated 1,2-diphenylethylenediamine (Dpen) and 1,2-cyclohexanediamine (Cydn) were chosen as the ligands. According to the well-established method and based on the modular nature of such metal complexes, 10 metal complexes bearing chloride as anions were prepared (see Supporting Information). The Cl^- anion was then replaced by TfO^- via the treatment with AgOTf, giving the corresponding cationic catalysts in quantitative yields (Scheme 1),[18a,21a] which were used directly without further purification.

Hydrogenation of 2-Alkyl-Substituted Quinolines. The hydrogenation of 2-methylquinoline (**2a**) was chosen as the standard reaction for the optimization of reaction conditions and the screening of catalysts. We first examined the catalytic activity of the RuCl complex (*R*,*R*)-**1a** at a substrate to catalyst mole ratio (*S*/*C*) of 100 in methanol under 20 atm of H_2 for 6 h. Unlike the hydrogenation of ketones reported by Noyori et al.,[18a] no conversion was observed at room temperature, and only 21% conversion with moderate enantioselectivity was obtained at elevated temperature (Table 1, entry 1). The lack of reactivity was probably caused by the strong coordination of the chloride anion to the cationic ruthenium center.[24] In sharp contrast to the Ru−Cl catalyst, the cationic Ru−OTf complex (*R*,*R*)-**1b** exhibited unprecedented reactivity and enantioselectivity in a variety of solvents including water (Table 1, entries 2−11).

As shown in Table 1, the hydrogenation proceeded smoothly in alcoholic solvent, giving 1,2,3,4-tetrahydroquinoline **3a** with excellent reactivities and enantioselectivities (entries 2−4). It was found that the reactivity and enantioselectivity were reduced when the reaction was carried out in aprotic solvents, such as THF, ether, and toluene (entries 5−7). Interestingly, high reactivity and enantioselectivity were obtained in acetone (entry 8). Despite lower reactivity, the highest enantioselectivity was achieved in both CH_2Cl_2 and [bmim]PF_6 (entries 9 and 10). It was worth noting that the reaction could be carried out in pure water with very good enantioselectivity, albeit at a low conversion (entry 11). Methanol was selected as the solvent of choice in terms of both reactivity and enantioselectivity for the screening of catalysts and reaction conditions.

Next, all catalysts described in Scheme 1 were tested and the results are listed in Table 1. Generally, the catalytic performance was significantly affected by both the substituents of the η^6-arene ligand and the *N*-sulfonate substituents (entries 12−18). Introduction of alkyl substituents into the η^6-arene of the Ru catalysts led to significant increase in both conversion and enantioselectivity (entries 12−14). The catalyst bearing hexamethylbenzene ligand (*R*,*R*)-**1c** offered >99% ee and 40% conversion after 1 h at 50 atm H_2 and room temperature (entry 13). This result suggested that the CH/π attractive interaction between the η^6-arene ligand and the aryl portion on quinoline, which was proposed as the origin of enantioselectivity in the transfer hydrogenation of aromatic ketones,[21b] might be also responsible for the excellent enantioselectivity in the asymmetric hydrogenation of 2-methylquinoline. The steric effect of *N*-sulfonate substituent was also manifested. For example, the catalyst (*R*,*R*)-**1e** having a methyl on the *N*-sulfonate group yielded product **3a** in high conversion (74%) with slightly lower ee value (94%) (entry 15). In addition, introducing electron-withdrawing *N*-sulfonate substituents into catalysts, such as (*R*,*R*)-**1g** and (*R*,*R*)-**1h**, resulted in lower conversion although the enantioselectivity remained similar (entries 17 and 18). Replacement of the diamine ligand TsDpen with TsCydn led to much lower enantioselectivity and reactivity (entry 19). Notably, the Ir- and Rh-complexes could also effectively catalyze the hydrogenation of **2a** with excellent enantioselectivity (entries 20 and 21). Thus, the Ru-complex bearing hexamethylbenzene ligand (*R*,*R*)-**1c** was chosen as the best catalyst due to its high enantioselectivity and reactivity in the reduction (entry 13).

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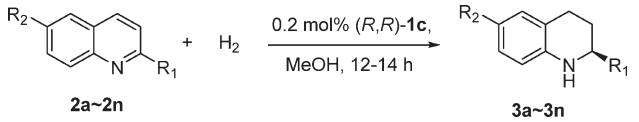
Table 2. Asymmetric Hydrogenation of 2-Alkyl-Substituted Quinoline Derivatives[a]



entry	R_2/R_1 (substrate)	conv (%)[b]	ee (%)[c]
1	H/Me (**2a**)	100 (99)	99 (*R*)
2	H/Et (**2b**)	100	>99 (*R*)
3	H/^{n}Pr (**2c**)	100	99 (*R*)
4	H/^{n}Bu (**2d**)	100	99 (*R*)
5	H/^{n}Pentyl (**2e**)	100	99 (*R*)
6	H/$(CH_3)_2CHCH_2$ (**2f**)	100	>99 (*R*)
7	H/C_8H_{17} (**2g**)	100	99 (*R*)
8	H/Bn (**2h**)	100	>99 (*S*)
9	H/ (**2i**)	100	99 (*R*)
10	H/ (**2j**)	100 (98)	99 (*R*)
11	H/ (**2k**)	100	>99 (*R*)
12	MeO/Me (**2l**)	100	>99 (*R*)
13	Me/Me (**2m**)	100	99 (*R*)
14	F/Me (**2n**)	100	98 (*R*)

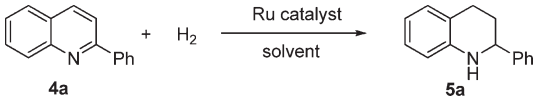
[a] Reaction conditions: 0.2 mmol of substrate in 1 mL of MeOH, 0.2 mol % (*R*,*R*)-**1c**, 50 atm H_2, 25 °C, 12−14 h. [b] Determined by ^{1}H NMR, and data in brackets are isolated yields. [c] Determined by HPLC analysis with a chiral column (see Supporting Information); absolute configuration was determined by comparison of optical rotation with literature data or by analogy (see ref 19).

In addition, increasing the reaction temperature resulted in a remarkable increase in reactivity while maintaining of the enantioselectivity (entry 22). The hydrogenation of **2a** could also be carried out at 10 atm of hydrogen, giving the same ee value but lower conversion (entry 23). The hydrogenation was completed within 14 h with a *S*/*C* of 500, yielding the product **3a** with 99% ee (entry 24). Even with 0.02 mol % (*R*,*R*)-**1c**, the reaction still proceeded smoothly and led to almost complete conversion and the same high enantioselectivity (entry 25).

Having established the optimal catalyst and reaction conditions (entry 24 in Table 1), we further explored the scope of the Ru-catalyzed asymmetric hydrogenation of 2-alkyl-substituted quinolines (Table 2). Generally, all 2-alkyl-substituted quinolines were hydrogenated with excellent reactivities and enantioselectivities (98% ∼ >99% ee). The reaction was found to be insensitive to the length of the alkyl side chain (entries 1−7) as well as the existence of phenyl groups on the side chain (entries 8−11). Substitution at the 6-position had no obvious effect on either conversion or enantioselectivity (entries 12−14). Notably, remarkable higher reactivities and comparable or better enantioselectivities for the hydrogenation of all these substrates were observed as compared with those obtained in ionic liquid.[19a]

Hydrogenation of 2-Aryl-Substituted Quinolines. Encouraged by the successful hydrogenation of 2-alkyl-substituted quinolines **2**, we then examined the hydrogenation of 2-aryl-substituted quinolines. Although chiral 2-aryl-1,2,3,4-tetrahydroquinolines are important chiral building blocks in organic synthesis and chiral drug production, for example, compound A in Figure 1, which has proven to be a potent inhibitor of the cholesterol ester transfer protein,[2g,5] the asymmetric hydrogenation of related quinoline derivatives remains undeveloped. For almost all the reported Ir/phosphine/I_2 catalytic systems, low levels of enantiomeric enrichment (<80% ee) were often observed, and only 2-phenylquinoline was examined as a unique model substrate.[25,26] Most recently, Mashima and co-workers reported a highly enantioselective hydrogenation of 2-arylquinolinium salts by using cationic dinuclear iridium halide complexes with difluorophos.[10f] Good to excellent enantioselectivities (up to 95% ee) were observed for a variety of 2-arylquinolinium salts.

Table 3. Asymmetric Hydrogenation of 2-Phenylquinoline: Condition Optimization[a]



entry	catalyst	solvent	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
1	**1c**	MeOH	25	4	78	83
2	**1b**	MeOH	25	4	72	84
3	**1d**	MeOH	25	4	68	80
4	**1e**	MeOH	25	4	67	86
5	**1f**	MeOH	25	4	13	67
6	**1h**	MeOH	25	4	63	56
7	**1i**	MeOH	25	4	67	46
8	**1e**	MeOH	0	24	64	89
9	**1e**	EtOH	0	24	99	92
10	**1e**	*i*-PrOH	0	24	84	89
11	**1e**	THF	0	24	57	73
12	**1e**	toluene	0	24	7	72
13	**1e**	CH_2Cl_2	0	24	<5	63

[a] Reaction conditions: 0.15 mmol of 2-phenylquinoline in 1 mL of solvent, 1.0 mol % catalyst, 50 atm H_2. [b] Determination by ^{1}H NMR. [c] Determined by HPLC analysis with a chiral column (see Supporting Information).

We wanted to test whether the optimal catalyst selected for the hydrogenation of 2-alkylquinoline could also work well in the hydrogenation of 2-aryl-substituted substrates. To our delight, the hydrogenation of the less basic 2-phenylquinoline proceeded smoothly in methanol by using 1 mol % of complex **1c** as the catalyst, giving the corresponding product in 78% conversion and 83% ee in 4 h (entry 1 in Table 3). Prompted by this initial result, we further screened the catalysts under the following conditions: 1.0 mol % catalyst, 50 atm H_2, MeOH, and at room temperature. As shown in Table 3, unlike in the hydrogenation of 2-alkylquinolines, less effect of the substituents of η^6-arene ligand on the enantioselectivity was observed (entries 1−3). The catalyst **1f** having a bulk *N*-sulfonate substituent showed much lower conversion and enantioselectivity (entry 5). The best enantioselectivity (86% ee) was obtained with complex (*S*,*S*)-**1e** as the catalyst (entry 4). To further improve the enantioselectivity, we then focused our attention on the effect of reaction temperature and solvent. A slightly higher ee was obtained under lower temperature (entry 8). After screening of methanol, ethanol, 2-propanol, THF, toluene, and dichloromethane as the hydrogenation solvent, the enantioselectivity was further improved to 92% in ethanol at 0 °C (entry 9). Reactions carried out in toluene and dichloromethane were almost retarded (entries 12 and 13).

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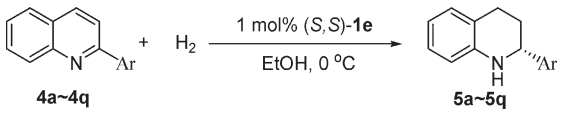
Table 4. Asymmetric Hydrogenation of 2-Aryl-Substituted Quinoline Derivatives[a]



entry	substrate (Ar)	time (h)	yield (%)[b]	ee (%)[c]
1	phenyl (**4a**)	24	94	92 (*R*)
2	2-methoxylphenyl (**4b**)	36	91	95 (*R*)
3	2-methylphenyl (**4c**)	36	95	85 (*R*)
4	2-naphthyl (**4d**)	36	95	88 (*R*)
5	2,4-dimethoxylphenyl (**4e**)	36	96	95 (*R*)
6	3-methoxylphenyl (**4f**)	24	96	89 (*R*)
7	3-hydroxyphenyl (**4g**)	36	97	90 (*R*)
8	3-chlorophenyl (**4h**)	24	95	89 (*R*)
9	3-CF_3-phenyl (**4i**)	36	91	87 (*R*)
10	4-methoxylphenyl (**4j**)	24	92	92 (*R*)
11	4-acetamidophenyl (**4k**)	24	92	91 (*R*)
12[d]	4-aminophenyl (**4l**)	48	90	97 (*R*)
13	4-bromophenyl (**4m**)	24	95	86 (*R*)
14	4-chlorophenyl (**4n**)	24	90	85 (*R*)
15	4-fluorophenyl (**4o**)	24	97	90 (*R*)
16	2-furyl (**4p**)	30	93	86 (*R*)
17	2-thiozyl (**4q**)	36	90	92 (*R*)

[a] Reaction conditions: 0.15−0.20 mmol of substrate in 2 mL of EtOH, 1.0 mol % (*S,S*)-**1e**, 50 atm H_2, 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral column (see Supporting Information); absolute configuration was determined by comparison of optical rotation with literature data or by analogues (see refs 8c and 9). [d] 5.0 mol % catalyst was used.

Under the optimal reaction conditions (entry 9 in Table 3), the hydrogenations of different 2-aryl-substituted quinolines **4a**−**q** were examined, and good to excellent enantioselectivities (85−97% ee) were obtained. It was found that both steric and electronic properties of the substituents on 2-phenyl group of the substrates have a great impact on enantioselectivity and reactivity (Table 4). Introduction of a substituent into the ortho position of the phenyl ring required longer reaction time (36 h) for achieving complete conversions (entries 2−5 vs entry 1). Conversely, most substrates having meta or para substituents on the phenyl ring gave full conversions within 24 h. The substrates bearing hydroxyl and trifluoromethyl groups at the meta position of the phenyl ring also exhibited low reactivity (entries 7 and 9). An exceptional example was the substrate **4l** having a *p*-amino group on the phenyl ring (entry 12), which needed a higher catalyst loading (5 mol %) and longer reaction time, but giving the highest enantioselectivity (97%). To the best of our knowledge, this is the highest ee value reported so far for the asymmetric hydrogenation of 2-aryl-substituted quinoline derivatives. High enantioselectivities were also observed in the hydrogenation of 2-methoxylphenylquinoline **4b** and 2,4-dimethoxylphenylquinoline **4e** (entries 2 and 5). For the former one, the enantioselectivity was remarkably higher than that obtained from Ir-difluorphos catalyst (95% ee vs 62% ee).[10f] Notably, the hydrogenation of 2-furyl-substituted and 2-thiozyl-substituted quinolines proceeded smoothly with very good enantioselectivity (entries 16 and 17).

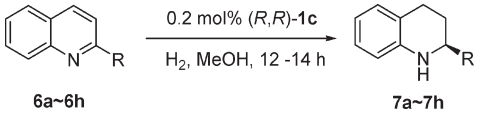
Hydrogenation of 2-Functionalized Quinolines. Chiral 2-functionalized 1,2,3,4-tetrahydroquinolines are important organic synthetic intermediates and structural units of alkaloids. Practical and efficient methods for the preparation of these compounds are still highly sought.[8e] On the basis of the excellent results obtained in the hydrogenation of 2-alkyl quinolines, we accepted the challenge of the hydrogenation of 2-functionalized quinolines by using Ru-complex (*R,R*)-**1c** as the catalyst. Under the optimized reaction conditions (entry 24 in Table 1), a variety of 2-functionalized quinoline derivatives were successfully hydrogenated to afford the corresponding tetrahydroquinoline derivatives with excellent enantioselectivities (97 to >99% ee). As shown in Table 5, the quinoline substrates bearing free hydroxyl group on the side chain could be efficiently hydrogenated in full conversion with 99% ee (entries 1−4). In the cases of 2-vinyl-substituted quinolines, hydrogenations proceeded smoothly to give the desired products with 99% ee (entries 5−7). Interestingly, the conjugated double bond (**6e**) was also hydrogenated, while the system could tolerate isolated double bonds (**6f** and **6g**). Quinolines having carboxyl acid and ester substituents (**6h** and **6i**) were inactive in this reaction (entries 8 and 9).

Hydrogenation of 2,3-Disubstituted Quinolines. Although a number of excellent examples of the asymmetric hydrogenation of quinolines have been reported, the substrate scope mainly focused on 2-substituted quinoline derivatives. Highly enantioselective hydrogenation of 2,3-disubstituted quinoline substrates remains a challenging task. To date, only one example has been reported by Zhou and co-workers.[8e] They successfully employed their Ir/diphosphines/I_2 system to the hydrogenation of a range of 2,3-disubstituted quinolines at high temperature, giving tetrahydroquinolines with up to 86% ee.

Considering that the cationic ruthenium catalysts have been successfully applied to the asymmetric hydrogenation of 2-substituted quinolines, we thus performed the hydrogenation of 2-butyl-3-pentylquinoline **8a** with 1.0 mol % (*R,R*)-**1c** in methanol under 50 atm H_2 at room temperature for 24 h. To our delight, full conversion and good enantioselectivity for the syn-product were observed (entry 1 in Table 6). After a survey of other ruthenium catalysts bearing different substituents on the sulfonyl group and the η^6-arene ligand in the hydrogenation of **8a**, catalyst (*R,R*)-**1e** was found to exhibit excellent enantioselectivity for both syn- and anti-products although the diastereoselectivity was low (entry 4 in Table 6). With the optimized catalyst in hand, different 2,3-disubstituted quinoline derivatives were investigated, and the results are listed in Table 6. Notably, all the 2,3-alkyl-disubstituted quinolines were hydrogenated smoothly to give the corresponding 1,2,3,4-tetrahydroquinolines with full conversions and 95−98% ee for syn-products, 68−86% ee for anti-products (entries 4−7). Interestingly, for the cyclic compounds **8e**−**g**, excellent diastereoselectivities (up to >95:5) were obtained, but the enantioselectivities dropped dramatically from 95% ee to 17% ee when the cycle became smaller (entries 8−10). For 2-phenyl-3-methylquinoline **8h**, low enantioselectivity but high diastereoselectivity were obtained (entry 11).

Hydrogenation of 3-Substituted, 4-Substituted, and 2,4-Disubstituted Quinolines. Encouraged by the excellent enantioselectivity and reactivity observed in the hydrogenation of 2-alkyl-substituted, 2-aryl-substituted, and 2,3-disubstituted quinolines, we attempted to employ the cationic ruthenium catalysts for the hydrogenation of other more difficult substrates, including 3-substituted and 4-substituted quinolines,

Table 5. Asymmetric Hydrogenation of 2-Functionalized Quinoline Derivatives[a]



entry	substrate (R)	product (R)	conv (%)[b]	ee (%)[c]
1	(6a)	(7a)	100 (99)	99 (*S*)
2	(6b)	(7b)	100	>99 (*S*)
3	(6c)	(7c)	100	>99 (*S*)
4[d]	(6d)	(7d)	100	99 and 99 (dr = 1:1)
5	(6e)	(7e)	100	99 (*R*)
6	(6f)	(7f)	100	99 (*S*)
7	(6g)	(7g)	100	>99 (*R*)
8	-COOH (**6h**)	-COOH (**7h**)	0	---
9	-COOMe (**6i**)	-COOMe (**7i**)	0	---

[a] Reaction conditions: 0.2 mmol of substrate in 1 mL of MeOH, 0.2 mol % (*R,R*)-**1c**, 50 atm H_2, 25 °C, 12−14 h. [b] Determined by ^{1}H NMR and data in bracket was isolated yield. [c] Determined by HPLC analysis with a chiral column; absolute configuration was determined by comparison of optical rotation with literature data or by analogue (see ref 19). [d] dr = 1:1, determined by ^{1}H NMR.

and 2,4-disubstituted quinolines. To date, successful hydrogenation of these substrates catalyzed by chiral transition-metal complexes has not been reported. As shown in Scheme 2, both 3-methylquinoline **8i** and 3-phenylquinoline **8j** were hydrogenated (under the following conditions: 1.0 mol % (*R,R*)-**1b**, 50 atm of H_2 at rt for 24 h), giving the racemic products. (This is consistent with the mechanistic interpretation described below).[27] For the 4-substituted and 2,4-disubstituted substrates **8k** and **8l**, hydrogenation could not take place.

Product Elaboration. The usefulness of the present work was exemplified in the gram-scale synthesis of a biologically active tetrahydroquinoline alkaloid, angustureine,[6a] and 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline **3n**.[3] Compound **3n** is a key intermediate for the synthesis of antibacterial agent of (*S*)-flumequine, which was obtained via resolution.[3] Asymmetric hydrogenation of the easily available quinoline derivatives **2e** and **2n** was carried out on a gram scale at a catalyst loading of 0.2 mol %, giving the tetrahydroquinolines in quantitative conversion with excellent enantioselectivity. Subsequent N-methylation of **3e** gave (−)-angustureine in high overall yields with up to 99% ee (Scheme 3).

Mechanistic Study. In our initial study with this ruthenium catalyst in ionic liquid,[19a] we proposed an ionic and cascade reaction pathway, including 1,4-hydride addition, isomerization, and 1,2-hydride addition for the reduction of quinoline. Despite such a general understanding, however, the detailed mechanism of this reaction was unclear and some key issues were still debatable. First, there was still a lack of direct experimental evidence to support the tandem C═C and C═N hydrogenation pathway. Second, hydrogenation of the cyclic imine intermediate (1,2-hydride addition to the dihydroquinoline) was the stereogenic center forming step. The origin of enantioselectivity, however, remained to be elucidated, which was also a big challenge in the asymmetric reduction of imine with such type of catalysts.[23] Here we report the results of our detailed experimental and computational mechanistic studies.

Stoichiometric Reaction. In our initial study,[19a] activation of quinoline substrate with Brønsted acid was found to be crucial for the activity and enantioselectivity in the stoichiometric reaction. Two equivalents of acid was required for achieving full conversion in the reduction of 2-methylquinoline (**2a**) with a stoichiometric amount of hydride complex (*R,R*)-**1l** in ionic liquid. In order to further investigate whether the acid was necessary for the stoichiometric hydrogenation of quinolines in protonic methanol, hydrogenation of substrates **2a** and **4a** with (*R,R*)-**1l** was carried out either in the absence or in the presence of TfOH, respectively. As shown in Table 7, similar results were observed as those in ionic liquid. The hydrogenation reaction between (*R,R*)-**1l** and **2a** or **4a** could not take place in the absence of acid, even with an excess of (*R,R*)-**1l** (10 equiv) after 15 h (entries 1 and 2). Instead, the protonated quinolines of **2a** and **4a** could react with (*R,R*)-**1l** to give the reduced product in 44% and 47%

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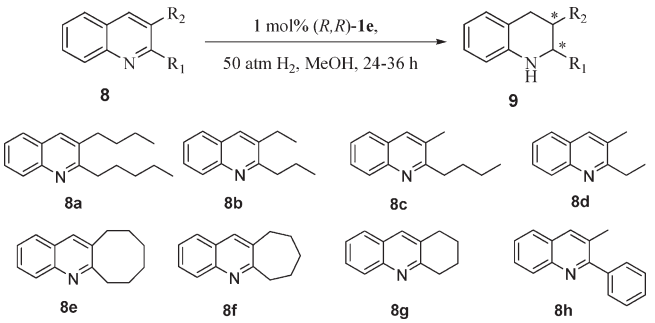
conversions with identical enantioselectivities to those of the direct hydrogenation of **2a** and **4a** (entries 3 and 4). Furthermore, when another 1 equiv of tetrahydroquinoline salt was added as the proton source, the reaction was found to proceed smoothly, affording the product with up to 96% and 89% conversions, respectively (entries 5 and 6). These results demonstrated that, unlike the hydrogenation of aromatic ketones,[21] quinoline should be activated by the Brønsted acid before hydrogenation. A similar activation effect was also demonstrated in the asymmetric hydrogenation of quinoline with the Ir/diphosphine catalyst system.[8g,10f] On the basis of these observations, we speculated that the quinoline might be reduced through a stepwise H^+/H^- transfer process outside the coordination sphere (as shown in Scheme 4), which was different from the concerted mechanism for the ketone hydrogenation.[21, 28−30]

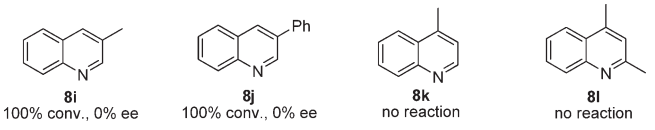
Table 6. Asymmetric Hydrogenation of 2,3-Disubstituted Quinoline Derivatives[a]



entry	substrate	catalyst	time (h)	conv (%)[b]	syn/anti[b]	ee (%)[c]
1	**8a**	(*R*,*R*)-**1c**	24	100	70/30	77 (syn), 26 (anti)
2	**8a**	(*R*,*R*)-**1b**	24	100	40/60	94 (syn), 61 (anti)
3	**8a**	(*R*,*R*)-**1d**	24	100	39/61	92 (syn), 85 (anti)
4	**8a**	(*R*,*R*)-**1e**	24	100 (95)	42/58	96 (syn), 80 (anti)
5	**8b**	(*R*,*R*)-**1e**	24	100 (94)	45/55	95 (syn), 68 (anti)
6	**8c**	(*R*,*R*)-**1e**	24	100	46/54	97 (syn), 77 (anti)
7	**8d**	(*R*,*R*)-**1e**	24	100 (96)	45/55	98 (syn), 86 (anti)
8	**8e**	(*R*,*R*)-**1e**	36	100	92/8	95 (syn)
9	**8f**	(*R*,*R*)-**1e**	36	91	90/10	79 (syn)
10	**8g**	(*R*,*R*)-**1e**	36	100	>95:5	17 (syn)
11	**8h**	(*R*,*R*)-**1e**	36	100	>95:5	21 (syn)

[a] Reaction conditions: 0.2 mmol of substrate in 1 mL of MeOH, 1.0 mol % catalyst, 50 atm H_2, 25 °C, 24−36 h. [b] Determined by ^{1}H NMR, and data in brackets are isolated yields. [c] Determined by HPLC analysis with a chiral column (see Supporting Information).

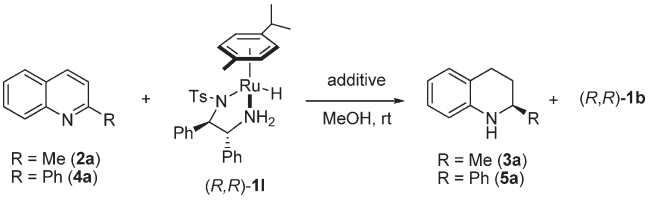
Scheme 2



Reaction Pathway of Hydrogen Transfer. In general, reduction of quinoline includes the hydrogenation sequence of C=C and C=N bonds. Theoretically, in addition to the pathway as described above (Scheme 4), another possible one is 1,2-hydride addition followed by 3,4-hydride addition (Scheme 5). To demonstrate which hydrogenation pathway is possible, the synthesis of reaction intermediates is very important and sometimes can provide direct proof to support the mechanism.

First, the intermediate (**11a**) of 1,2-hydride addition was synthesized by the reaction of quinoline with n-butyllithium.[31] The freshly resulting **11a** was immediately applied to hydrogenation with (*R*,*R*)-**1b** under 50 atm H_2. To our surprise, the intermediate **11a** could be smoothly reduced to give the product

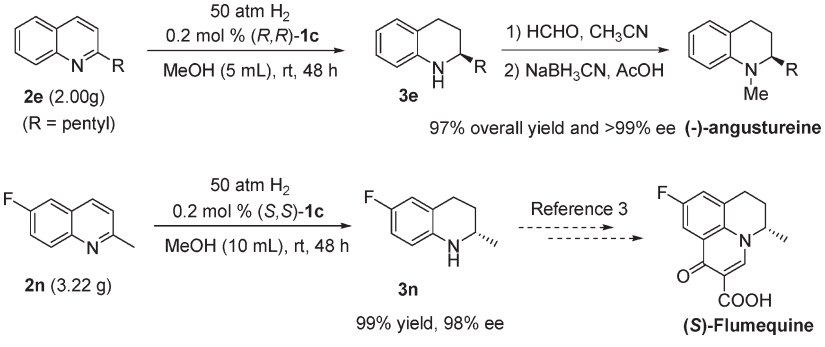
Table 7. Stoichiometric Reaction between (*R*,*R*)-1l and Quinoline 2a or 4a in MeOH[a]



entry	quinoline	additive	conv (%)[b]	ee (%)[c]
1	**2a**	none	0	–
2	**4a**	none	0	–
3	**2a**.TfOH	none	44 (48)[d]	96 (99)[d]
4	**4a**.TfOH	none	47	84
5	**2a**.TfOH	**3e**·TfOH (1 equiv)	96 (95)[d]	96 (99)[d]
6	**4a**.TfOH	**3a**·TfOH (1 equiv)	89	84

[a] Reaction conditions: 0.2 mmol of substrate and 10 equiv of (*R*,*R*)-**1l** in 1.0−2.0 mL of MeOH, rt, 15 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis with a chiral column. [d] Data in brackets were obtained in ionic liquid.[19a]

Scheme 3



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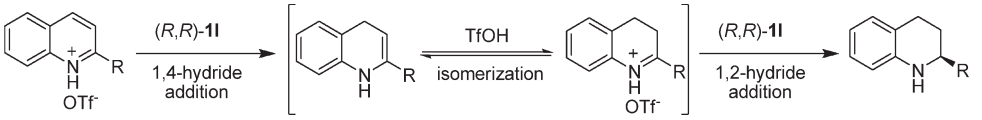
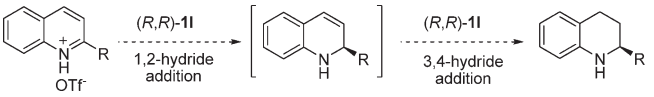
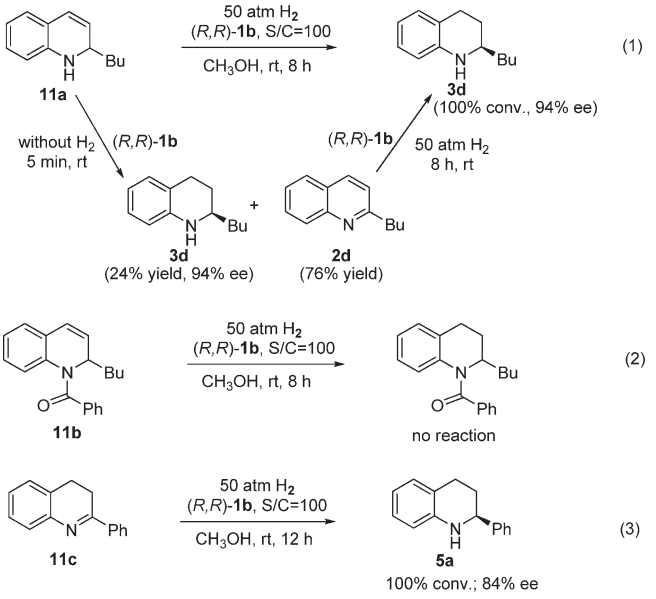
Scheme 4. Possible Hydrogenation Pathway of Quinoline Based on the Study of the Stoichiometric Reaction



Scheme 5. The Second Plausible Hydrogenation Pathway of Quinoline



Scheme 6. Hydrogenation of Intermediate with Catalyst (*R*, *R*)-1b



3d in 100% conversion with the same enantioselectivity (94% ee) as the direct hydrogenation of **2d** (Scheme 6, eq 1). After careful examination, it was found that the intermediate **11a** was rapidly dehydrogenated to form the aromatic **2d** for no more than 5 min at room temperature in the presence of the ruthenium catalyst. Interestingly, some of the reduced tetrahydroquinoline **3d** was also observed with similar enantioselectivity to that of the direct hydrogenation of **2d**, suggesting the formation of the active reducing species (*R*,*R*)-**1l** upon dehydrogenation. To overcome this problem, the stable *N*-benzoyl compound **11b** was synthesized and found to be an inactive substrate for hydrogenation under otherwise identical reaction conditions (Scheme 6, eq 2). This result indicated that the unpolarized C=C bond could not be reduced by using this ruthenium catalyst. On the other hand, according to the recently published references,[32] this kind of diamine-derived metal complex was found to be effective only for the asymmetric transfer hydrogenation of a polarized C=C bond. Therefore, on the basis of these observations, the second hydrogenation pathway might be less likely for our catalytic system.

Next, we synthesized the intermediate (**11c**) of 1,4-hydride addition in the hope of obtaining direct proof to support the first hydrogenation pathway. Considering the easy decomposition of the 2-alkyl-3,4-dihydroqinoline, we finally synthesized and fully characterized the relatively more stable intermediate 2-phenyl-3,4-dihydroqinoline (**11c**).[33] Subsequently, hydrogenation of **11c** was carried out in the presence of (*R*,*R*)-**1b** under 50 atm H_2, and the desired product **5a** was obtained in 100% conversion with 84% ee (Scheme 6, eq 3), which was the same enantioselectivity as that of the direct hydrogenation of **4a**. Although dehydrogenation of **11c** was also observed in the presence of the ruthenium catalyst (see Supporting Information), the deuterium labeling experiment (as described below) indicated that direct hydrogenation of **11c** did occur.

To further demonstrate the existence of this imine intermediate in the direct hydrogenation of **4a**, we then employed ^{1}H NMR and ESI-MS techniques for characterization of this catalytic system. ESI-MS allows the characterization of species that are actually present in the reaction solution, which has been successfully applied in the investigation of catalytic reaction mechanism.[34] In this study, the room-temperature ^{1}H NMR spectrum of the reaction mixture for hydrogenation of **4a** was taken after the reaction was carried out for 5 min. As compared with the spectra of substrate **4a** (spectrum A), product **5a** (spectrum B), and the preformed imine intermediate **11c** (spectrum C), the ^{1}H NMR spectrum of the reaction mixture (spectrum D) exhibited all the characteristic proton signals for all these compounds (Figure 2). Importantly, the well-resolved proton signal at δ 8.04−8.01 (multiplet), 7.16 (doublet), and 2.88 (singlet), which matched those of the independently synthesized intermediate imine **11c**, revealed the existence of this imine in the reaction mixture. Furthermore, the ESI-HRMS spectrum of the reaction mixture was collected in positive-ion mode and shown in Figure 3. To our pleasure, in addition to the presence of **4a**·H$^+$ (*m*/*z* 206.09609) and **5a**·H$^+$ (*m*/*z* 210.12727), the formation of the imine intermediate **11c**·H$^+$ (*m*/*z* 208.11176) was observed. To the best of our knowledge, this is the first time the imine intermediate in the hydrogenation of quinolines was unequivocally identified, offering solid support for the first pathway including 1,4-hydride addition, isomerization, and then 1,2-hydride addition processes (Scheme 4).

Deuteration Study. To further confirm that the hydrogenation occurred via the first pathway, in which the hydride was transferred to the 2- and 4-positions of quinoline, and the proton to the 1- and 3-positions of quinoline, isotope labeling experiments using deuterated gas and solvents were carried out at room temperature under the hydrogenation conditions as described above and monitored by ^{1}H NMR spectroscopy to identify the concentration of deuterium in the various positions of the hydrogenated product. First, the reaction was performed with 1.0 mol % (*R*,*R*)-**1b** under 50 atm D_2 in MeOH for 24 h. Remarkably, only the reduced product bearing 100% deuterium at both the 2- and 4-positions were observed (Scheme 7, eq 1). Instead, when hydrogenation was carried out in CD_3OD under 50 atm H_2, the deuterium atoms were found only at the 1- and

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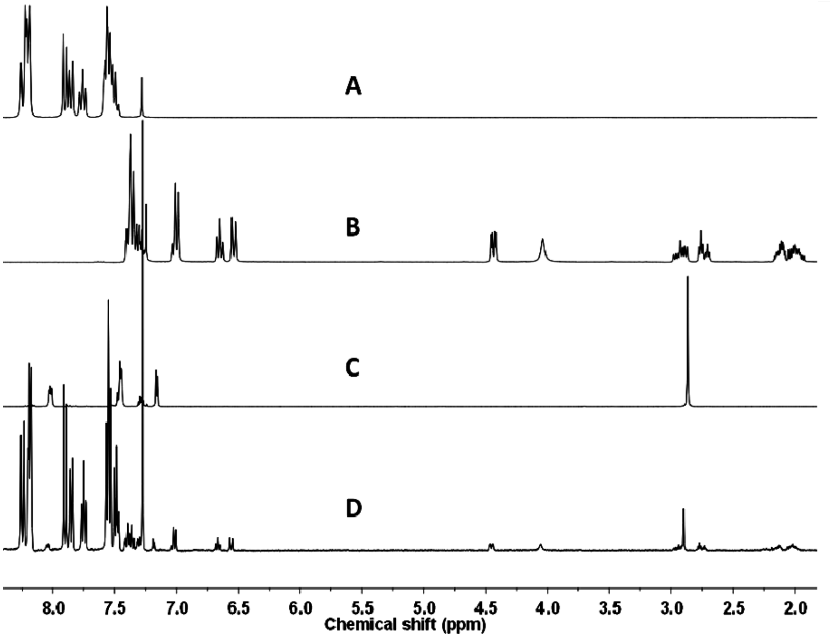

Figure 2. ^{1}H NMR (300 MHz, $CDCl_3$) spectra for characterization of the imine intermediate. (A) 2-phenylquinoline (**4a**), (B) 2-phenyl-1,2,3,4-tetrahydroquinoline (**5a**), (C) 2-phenyl-3,4-dihydroquinoline (**11c**), (D) reaction mixture for the hydrogenation of **4a** catalyzed by (*R*,*R*)-**1b** (5 min after the start of the reaction).

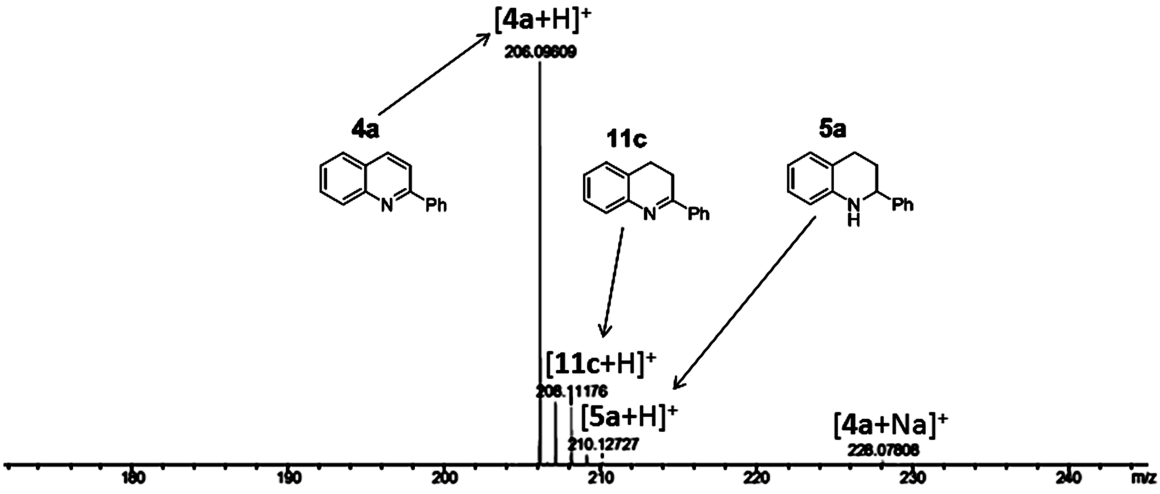

Figure 3. ESI-HRMS spectrum (positive mode) of the reaction mixture for the hydrogenation of **4a** catalyzed by (*R*,*R*)-**1b** (5 min after the start of the reaction).

3-positions of the product **3a** (Scheme 7, eq 2). Expectedly, hydrogenation proceeded smoothly with both deuterated gas and solvent, offering the reduced product with 100% deuterium incorporation at all the 1-, 2-, 3-, and 4-positions (Scheme 7, eq 3).

Considering that methanol, ethanol, 2-propanol, and other secondary alcohols were known to serve as hydrogen donors in the asymmetric transfer hydrogenation of aromatic ketones, we next conducted the hydrogenation of **2a** in $(CH_3)_2CDOH$ to test if the reaction was partly associated with transfer hydrogenation. It was found that full conversion was observed in the presence of 1.0 mol % (*R*,*R*)-**1b** under 50 atm H_2 for 24 h, giving the reduced product without any deuterium incorporation (Scheme 7, eq 4). In addition, when the 16e Ru complex (*R*,*R*)-**1m**, which was recognized as the active species in the transfer hydrogenation of aromatic ketones,[21d] was used as the catalyst for the reduction of **2a**, no reaction took place in the absence of H_2 at room temperature. Notably, even when the reaction was performed under 50 atm H_2 for 24 h, no more than 5% conversion was observed, which was in agreement with the incapability of **1m** to activate H_2.[21a] All these observations indicated that **1m** was not involved in this catalytic cycle, and the reaction was a net hydrogenation using H_2 as the hydrogen donor.

Reversibility of Hydrogenation. Although it has been demonstrated that the dehydrogenation of 1,2,3,4-tetrahydroquinoline could be carried out by using homogeneous iridium catalysts,[8e,35] this dehydrogenation reaction was not observed at the temperature utilized in this study, suggesting that 1,2-hydrogen transfer is an irreversible step (Scheme 4). As

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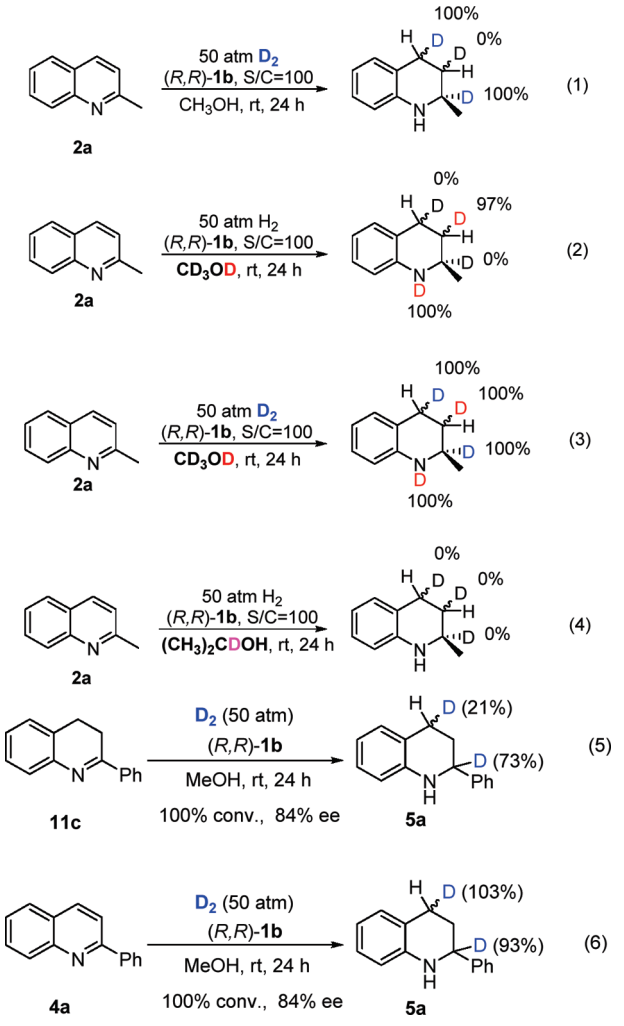
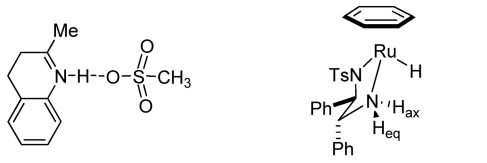
Scheme 7. Deuterium-Labeling Studies



mentioned above, we found that the complex (*R*,*R*)-**1b** could catalyze the dehydrogenation of imine **11c**, suggesting the possibility of reversible hydrogen transfer in the first step (Scheme 4). To address this issue, **11c** was first selected as the substrate and hydrogenated with 1.0 mol % (*R*,*R*)-**1b** under 50 atm D_2 in MeOH for 24 h. Notably, deuterium incorporation into both 2-position (73% of D) and 4-position (21% of D) of the reduced product was observed (Scheme 7, eq 5). This result demonstrated the formation of quinoline **4a** via dehydrogenation of **11c**, which was subsequently hydrogenated under deuterated gas with deuterium incorporation into the 4-position. The ruthenium hydride formed upon dehydrogenation was trapped by **4a** and **11c**, which was responsible for the less deuterium incorporation into the 2-position. Then, **4a** was used as the substrate for hydrogenation under identical conditions. Deuterium incorporation into 2-position (93% of D) and 4-position (103% of D) of the reduced product was observed (Scheme 7, eq 6). Unlike the hydrogenation of **2a** (Scheme 7, eq 1), the differences in deuterium incorporation into 2- and 4-positions were attributed to the reversible hydrogen transfer to **4a**, which provided ruthenium hydride and subsequently trapped by **4a**. In addition, when the reaction was performed under 1 atm D_2 for 48 h (about 50% conversion), deuterium incorporation into the 4-position of the recovered substrate **4a** was observed (For full

Scheme 8. Models for the Theoretical Study



12a dihydroquinoline/MsOH complex

13a hydride ruthenium catalyst

characterization of the deuterated **4a**, see Supporting Information). Therefore, reversible hydrogen transfer in the first step was conclusively demonstrated by deuterium scrambling into recovered quinoline **4a** at the 4-position, and 1,2,3,4-tetrahydroquinoline **5a** at the 2- and 4-positions.

DFT Study of the Mechanism and Origins of Enantioselectivity. To gain further insights into the mechanism and the origins of enantioselectivity, theoretical calculations were carried out to study the hydrogenation process of the protonated imine intermediate, which is generated by the 1,4-hydride addition and isomerization (see this also in Scheme 9 later on).[23a,36] Therefore, dihydroquinoline/MsOH (**12a**) and the hydride ruthenium catalyst (**13a**) were chosen for our computational investigation (Scheme 8). All calculations were carried out with Gaussian 03 programs.[37] Geometrical optimizations of all species were carried out by using the B3LYP functional.[38] The 6-31G (d) basis set was used for all atoms, expect for Ru, which has been described by the LANL2DZ basis set.[39] This method has been successfully applied by Noyori and co-workers to the study of mechanism of ketone reduction by the Ru catalysts.[21b,c] The reported relative free energies (ΔG) and enthalpies (ΔH) were obtained in the gas-phase calculations. Topological analysis of electron densities at bond critical points was performed with the AIM 2000 program.[40a] Unless otherwise specified, all the discussed energies in this paper are the free energies in the gas phase (ΔG).

A direct concerted double-hydrogen transfer from the catalyst (the hydrogen atoms from the Ru−H and N−H bond in **13**) could not be located, even though this mechanism has been found by Noyori in the ketone reduction by the Ru catalysts (see this in the Supporting Information, Figure S7). DFT calculations revealed that the hydrogenation of protonated imine started with the formation of a series of complexes (**14a**, **14b**, and **14c**) (Structures are shown in Figure S11 of the Supporting Information) between the protonated imine and the **Ru−H** catalyst. Among these complexes, complex **14a**, which used its sulfonate to form a hydrogen bonding network with both the $N-H_{eq}$ ($N-H_{eq}\cdots O_1$) and the proton of the protonated imine,[41] was the most stable one and was in equilibrium with complexes **14b** and **14c**, which were higher in energy than **14a** by 0.9 and 5.7 kcal/mol, respectively (see Figure S10 in the Supporting Information). In principle, all these complexes could undergo hydride transfer reactions from their Ru−H bonds to the carbon atoms of the protonated imines. However, the preferred hydride transfer could only take place from **14a** via either transition state **TS1-*re*** or **TS1-*si***, owing to the energetic reasons that hydride transfer transition states from **14b** and **14c** were higher in energy than **TS1-*re*** and **TS1-*si*** (for details of **TS2** and **TS3**, see Supporting Information).

The hydride transfer from **14a** preferred to give the *R*-configuration product (via transition state **TS1-*si***) since the transition state **TS1-*re*** leading to the *S*-configuration product

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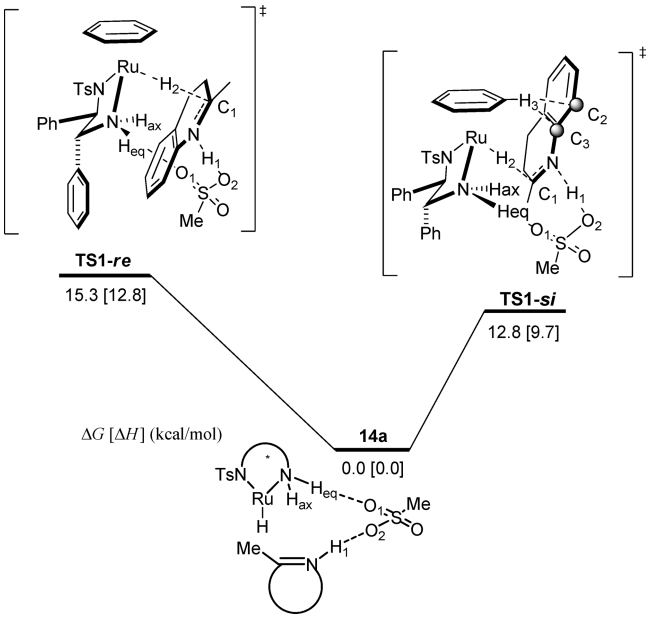

Figure 4. DFT computed energy surface of the hydrogenation of protonated imine by the ruthenium hydride catalyst. The reported energies are the calculated relative free energies (ΔG) and enthalpies (ΔH, in brackets) in the gas phase.

was higher in energy than **TS1-*si*** by 2.5 kcal/mol in the gas phase. The calculated free energy barrier for **14a** to reach **TS1-*si*** and **TS1-*re*** were 12.8 and 15.3 kcal/mol, respectively (Figure 4). This was consistent with the experimental observation, where *R*-configuration product was the dominant product. The main reason for the lower energy of **TS1-*si*** than **TS1-*re*** was the existence of a favorable CH/π attraction between the phenyl group of dihydroquinoline and the η^6-benzene in **TS1-*si***, whereas this interaction was absent in **TS1-*re***, where the phenyl ring of the protonated imine pointed in the opposite direction and there was no contact with the phenyl ring of the catalyst (see below for detailed discussion). Such CH/π attraction was realized by Noyori and co-workers in rationalizing the reduction of ketone using Ru−Ts-dpen as the catalyst and many other systems.[21b−f,42]

To better analyze the origins of enantioselectivity, we examined in detail the hydride transfer transition states from an experimentally used reaction system.[43,44] Therefore, we computed **TS4-*si*** and **TS4-*re*** for the stoichiometric reaction described in Table 7, where quinoline **2a** (protonated by TfOH) was reduced to give *R*-**3a** as the major product when the hydride catalyst (*R*,*R*)-**1l** was used. Calculations showed that **TS4-*si***, which gave the experimentally observed major *R*-product, was favored by 2.4 kcal/mol compared to **TS4-*re*** (Figure 5). Thus, these calculations gave results agreeing with the experimental observations, where the *R*-product was formed preferentially

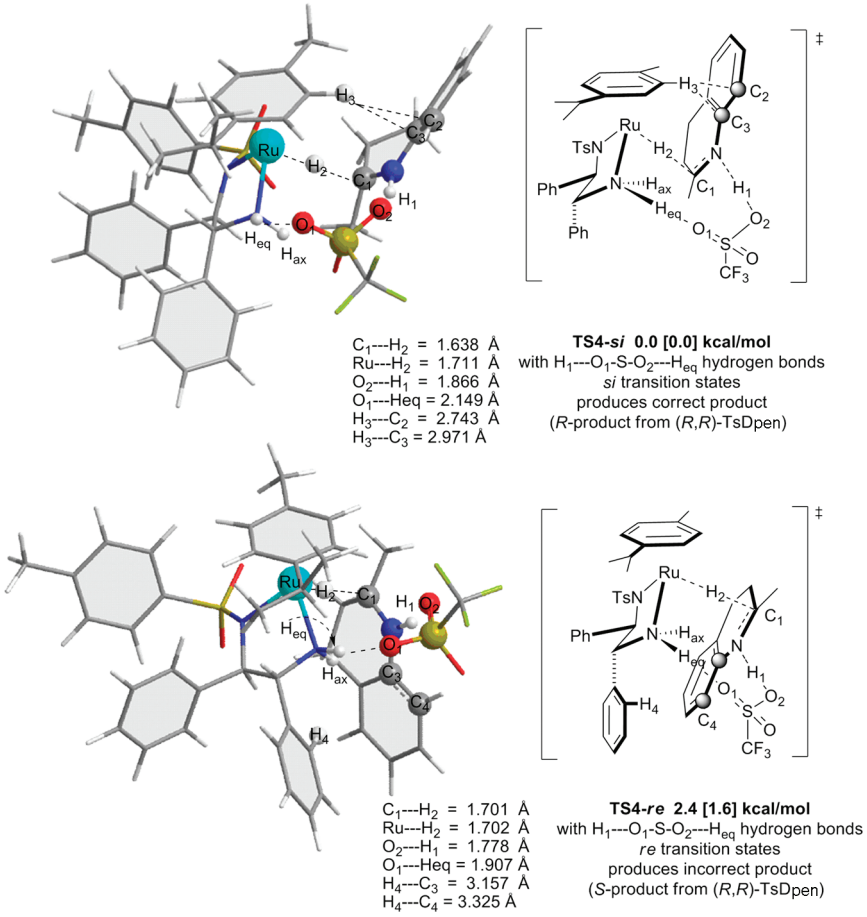

Figure 5. Calculated transition structures for the hydride transfer to imine. The calculated relative free energies ΔG and the enthalpies ΔH (in brackets) are given.

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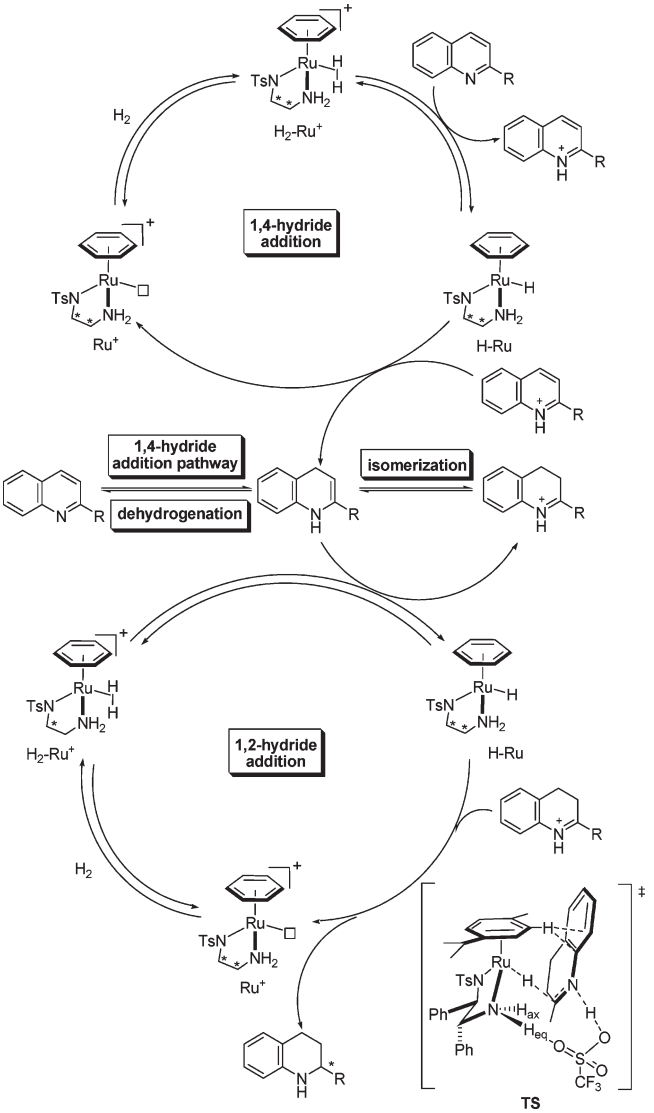
Scheme 9. Proposed Mechanism for the Asymmetric Hydrogenation of Quinoline (ethylenediamine ligands and OTf^- are omitted for clarity)



(96% in Table 8). It was found that the favored *si* addition transition state was stabilized by the CH/π attraction: in **TS4-*si***, the shortest C−H (η^6-benzene)···C(sp^2) distances are 2.743 Å ($H_3\cdots C_2$) and 2.971 Å ($H_3\cdots C_3$), close to the sum of van der Waals radii 2.9 Å for C and H. AIM analysis at the bond critical point suggested a weak interaction between H_3 and C_2, where the electron density (ρ_b) is 0.0062 au and the Laplacian values ($\Delta^2\rho_b$) is 0.01903 au, indicating that a CH/π attraction is present. The BCPs at the $O_1\cdots H_{eq}$ and $O_2\cdots H_1$ have a ρ_b of 0.0152 and 0.0320 au and a $\Delta^2\rho_b$ of 0.0508 and 0.1013 au, within the range of a classic hydrogen bond,[40b,c] suggesting that these interactions are the traditional hydrogen bonding interactions.

Proposed Catalytic Cycle. On the basis of the results obtained from the above experiments and calculations, as well as relevant study on ketone reduction by Noyori,[21b,d] we proposed a mechanism for the hydrogenation of quinoline. The cascade hydrogenation of quinoline occurs via an ionic rather than a concerted catalytic pathway, involving 1,4-hydride transfer, isomerization, and 1,2-hydride transfer. As illustrated in Scheme 9, the ionized ruthenium complex **Ru**$^+$ reversibly accommodates a dihydrogen to form dihydrogen complex **H_2-Ru**$^+$. Deprotonation of the dihydrogen ligand by quinoline generates both the active **Ru**−**H** species and the activated substrate. A subsequent 1,4-hydride transfer affords the enamine intermediate and the regenerated **Ru**$^+$. Similarly, the enamine serves as a base to deprotonate the dihydrogen ligand, resulting in the **Ru**−**H** and the iminium cation. Then 1,2-hydride transfer gives the final product, 1,2,3,4-tetrahydroquinoline, enantioselectively and regenerates **Ru**$^+$. The dihydroquinoline intermediate can be reversibly dehydrogenated by Ru-catalyst to give the quinoline, while the 1,2-hydride transfer step is irreversible under the asymmetric hydrogenation conditions. As suggested by the theoretical calculation, the activated iminium cation reacts with **Ru**−**H** via a cyclic 10-membered transition structure with the participation of TfO^- anion. Similar to the ketone reduction,[21c] the enantioselectivity originates from the CH/π attraction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of the dihydroquinoline.

■ CONCLUSION

In summary, we have demonstrated that chiral cationic η^6-arene−*N*-tosylethylenediamine−Ru(II) complexes are excellent catalysts for the asymmetric hydrogenation of quinolines. A wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, and 2-functionalized and 2,3-disubstituted quinolines, were efficiently hydrogenated under mild reaction conditions with up to >99% ee and up to 5000 TON. A 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-hydride addition, isomerization, and 1,2-hydride addition. The hydrogen 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, 1,2-hydride addition to dihydroquinoline, 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. This versatile catalytic protocol provided a facile, greener, and practical access to a variety of optically active 1,2,3,4-tetrahydroquinoline derivatives. The mechanistic results presented in this work are expected to offer new insight into the mechanism of other transition-metal-catalyzed hydrogenation of quinoline and imines.[22] Further kinetic study of this reaction and exploration of this catalytic system for the hydrogenation of other heteroaromatic compounds are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Synthetic and experimental details, the characterizations of catalysts, substrates, and products, and the analysis of enantioselectivities of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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