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Research Article

Enantiodivergent Synthesis of Chiral Tetrahydroquinoline Derivatives via Ir-Catalyzed Asymmetric Hydrogenation: Solvent-Dependent Enantioselective Control and Mechanistic Investigations

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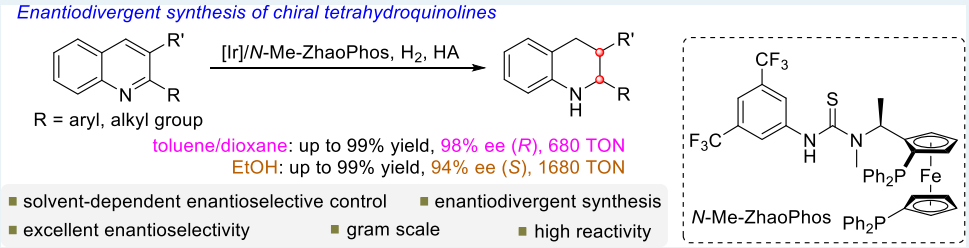

ABSTRACT: Ir-catalyzed asymmetric hydrogenation of quinolines was developed, and both enantiomers of chiral tetrahydroquinoline derivatives could be easily obtained, respectively, in high yields with good enantioselectivities through the adjustment of reaction solvents (toluene/dioxane: up to 99% yield, 98% ee (*R*), TON = 680; EtOH: up to 99% yield, 94% ee (*S*), TON = 1680). It provided an efficient and simple synthetic strategy for the enantiodivergent synthesis of chiral tetrahydroquinolines, and gram-scale asymmetric hydrogenation proceeded well with low-catalyst loading in these two reaction systems. A series of deuterium-labeling experiments, control experiments, and ^{1}H NMR and electrospray ionization-mass spectrometry experiments have been conducted, and a reasonable and possible reaction process was revealed on the basis of these useful observations.

KEYWORDS: *enantiodivergent synthesis, asymmetric catalysis, chiral tetrahydroquinolines, hydrogenation, enantioselectivity*

INTRODUCTION

Asymmetric catalytic synthesis has been regarded as an efficient and powerful method to access chiral molecules, which is mainly based on the employment of chiral transition-metal catalysis and organocatalysis.[1] The synthesis of both enantiomers of a target chiral molecule is usually in demand for the preparation of chiral enantiomeric catalysts.[2] However, a great many chiral catalysts are only available in a single configuration. To overcome this problem and realize enantiodivergent synthesis, a remarkable protocol is that adjusting other reaction parameters while using the same catalyst, which can be easily implemented by altering the metal precursor, introducing an additive, or modifying the reaction conditions. Among these accessible alternatives, the reaction solvent as an ideal condition parameter can be easily modified to realize enantiodivergent synthesis. There are rare examples of achieving dual well-controlled enantioselectivity by changing the solvents.[3]

Enantioenriched 1,2,3,4-tetrahydroquinoline derivatives are versatile chiral heterocycles, which not only worked as favorable synthetic intermediates but also are represented as privileged heterocyclic subunits in various natural products, pharmaceuticals, and biologically active compounds (Figure 1).[4] As a consequence, their great importance stimulated considerable research interest for the development of efficient synthetic protocols. After immense effort has been devoted, some catalytic synthetic methods have been well established, such as enantioselective α-N-arylation of tetrahydroquinolines,[5] asymmetric Friedländer condensation/transfer hydrogenation,[6a] asymmetric cascade addition/cycloisomerization/transfer hydrogenation,[6b] intramolecular hydroamination/asymmetric transfer hydrogenation,[7] and direct asymmetric hydrogenation of prochiral quinolines[8] (Scheme 1). Among these available enantioselective approaches, the direct asymmetric reduction of prochiral quinolines is a powerful and convenient synthetic methodology to prepare chiral tetrahydroquinolines through transition-metal catalysis and organocatalysis.[9−11] However, most of these transition-metal catalysts failed to deliver satisfactory enantioselectivities in the asymmetric hydrogenation of aryl-substituted quinolines,[11] which were mainly due to their high aromatic stability, coordinating ability, and intrinsic low reactivity. Therefore,

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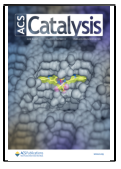


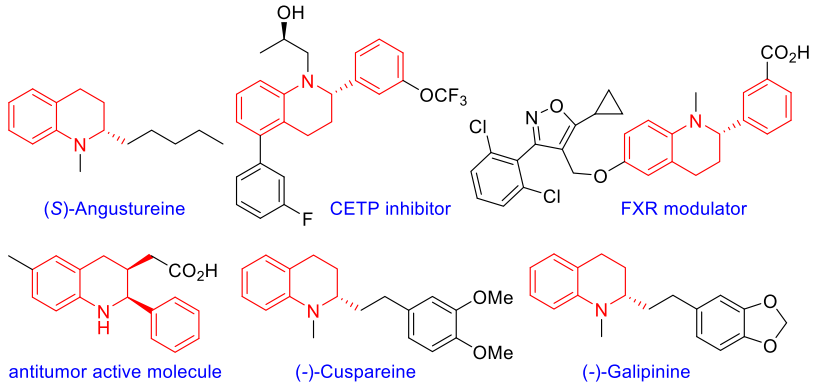
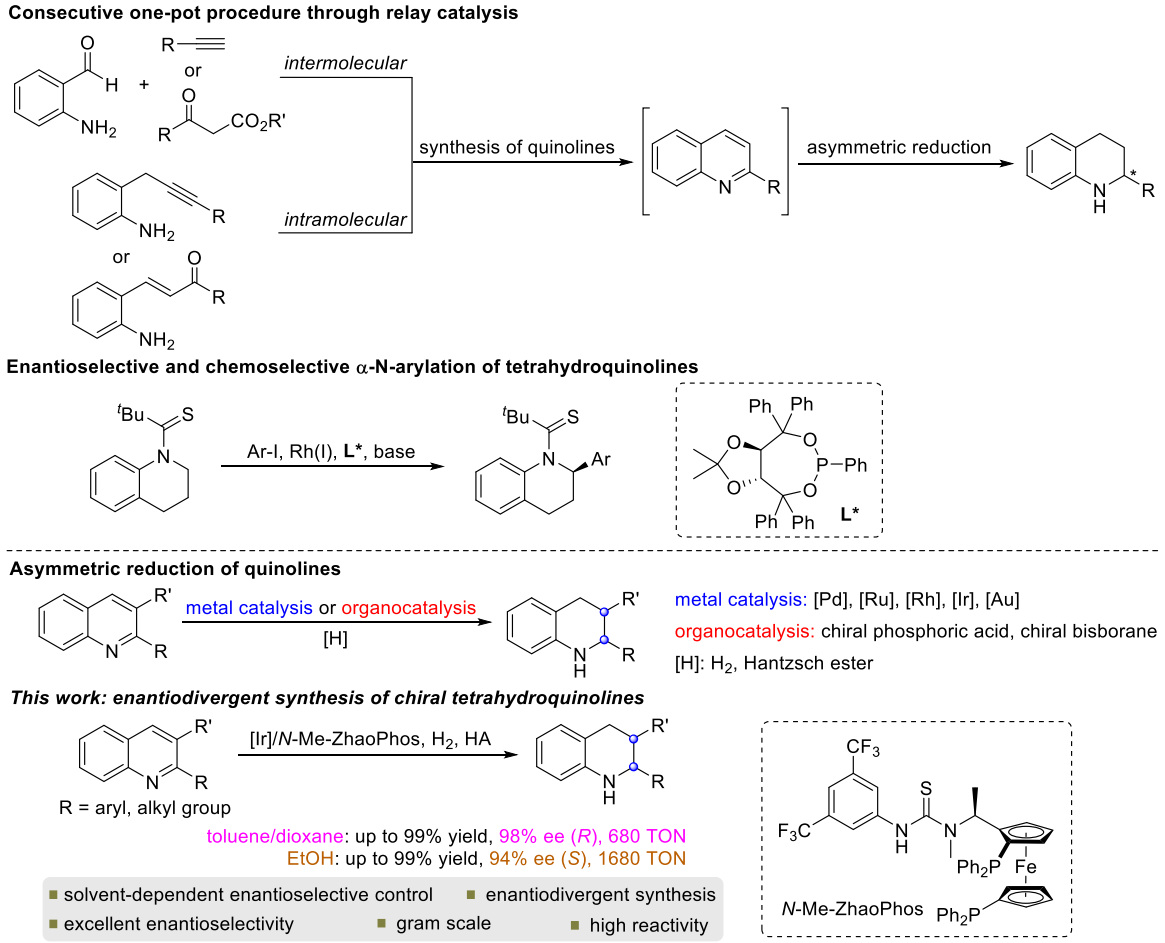


Figure 1. Examples of bioactive compounds featuring chiral tetrahydroquinoline motifs.

Scheme 1. Synthetic Strategy for Chiral 1,2,3,4-Tetrahydroquinoline Derivatives



there is a great demand to develop efficient transition-metal catalytic systems to realize the challenging hydrogenation of aryl-substituted quinolines. Moreover, until now, there is no example involving the enantiodivergent synthesis of chiral tetrahydroquinolines through the same transition-metal complex catalysis. Considering the great importance of noncovalent interactions[12] and the continuous research on the chiral bifunctional ferrocene-based bisphosphine−thiourea system,[9r,13] we envision that the noncovalent anion-binding interaction between the chiral bisphosphine-thiourea ligand and the aryl-substituted quinoline substrates could be achieved by the introduction of Brønsted acid, which can activate the quinoline ring, resulting in the great improvement of reactivity and stereoselectivity control. Considering the solvent effect on the noncovalent secondary interaction, we believe that the solvent alternation could provide the possibility to realize enantiodivergent synthesis, especially the variation from an aprotic solvent to a protic solvent. Herein, we successfully developed highly efficient Ir/N−Me-ZhaoPhos-catalyzed asymmetric hydrogenation of challenging aryl-substituted quinolines, and both enantiomers of chiral tetrahydroquinolines could be obtained through the reaction solvent adjustment in good yields with excellent enantioselectivities (Scheme 1).

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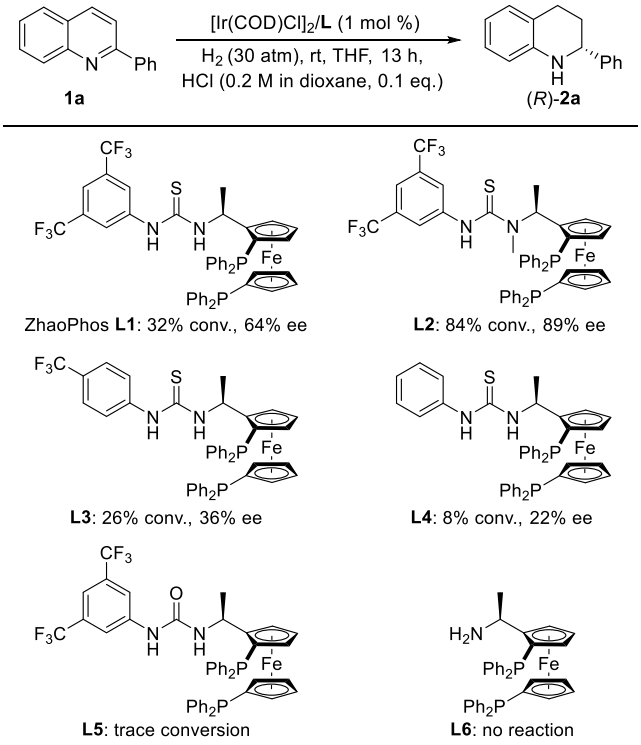
RESULTS AND DISCUSSION

Optimization of Reaction Conditions. Initially, the readily available 2-phenylquinoline **1a** was selected as the model substrate for the Ir-catalyzed asymmetric hydrogenation of 2-aryl quinolines with 0.1 equiv HCl (0.2 M in dioxane) as the additive in THF at room temperature to identify the optimal reaction conditions. As listed in Table 1, a series of our

Table 1. Screening Ligands for Ir-Catalyzed Asymmetric Hydrogenation of 2-Phenylquinoline (1a)[a]

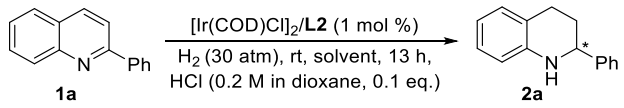


[a]Reaction conditions: 0.1 mmol substrate **1a**, 1.0 mol % [Ir(COD)-Cl]$_2$/ligand, H_2 (30 atm), 1.0 mL THF, room temperature, 13 h, and HCl (0.2 M in dioxane, 0.1 equiv). Conversion was determined by ^{1}H NMR analysis. The ee value was determined by chiral HPLC analysis using a chiral stationary phase.

chiral bisphosphine-(thio)urea ligands were employed in this Ir-catalyzed asymmetric hydrogenation. The common privileged ligand ZhaoPhos **L1** indeed promoted this transformation with moderate enantioselectivity, *albeit* in poor conversion (32% conversion, 64% ee). Encouraged by these promising results, other related bisphosphine-(thio)urea ligands were further evaluated. The N-methylated ZhaoPhos **L2** bearing one hydrogen-bonding donor provided good conversion and enantioselectivity (84% conversion, 89% ee), which could be conducive to the precise activation of the substrates. Ligand **L3** containing one trifluoromethyl group and ligand **L4** without a trifluoromethyl group on the phenyl ring failed to give satisfactory results, and poor conversions and enantioselectivities were obtained (8−26% conversions; 22−36% ee). Ligand **L5** containing a urea unit was also investigated, and trace conversion was observed. In addition, ligand **L6** without a thiourea motif did not promote this hydrogenation.

In an attempt to further improve the reactivity and enantioselectivity, a variety of solvents were then screened with the preferred ligand N-methylated ZhaoPhos **L2**. Reaction solvents always have a great influence on the reactivity and stereoselectivity in asymmetric catalytic synthesis. We found that the configuration of the hydrogenation product was indeed strikingly dependent on the solvents. Hydrogenation product (*S*)-**2a** could be obtained in strong polar solvents, such as alcoholic solvents, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) (Table 2, entries 1−8). Among these solvents, alcoholic

Table 2. Screening Solvents for Ir-Catalyzed Asymmetric Hydrogenation of 2-Phenylquinoline (1a)[a]



entry	solvent	conv. (%)[b]	ee (%)[c]
1	MeOH	>99	87 (*S*)
2	EtOH	>99	89 (*S*)
3	^{i}PrOH	>99	83 (*S*)
4	CF_3CH_2OH	90	80 (*S*)
5	$(CF_3)_2CHOH$	10	65 (*S*)
6	CH_3CN	16	10 (*S*)
7	DMF	20	70 (*S*)
8	DMSO	6	82 (*S*)
9	CH_2Cl_2	47	82 (*R*)
10	$ClCH_2CH_2Cl$	64	77 (*R*)
11	toluene	52	93 (*R*)
12	dioxane	>99	91 (*R*)
13	THF	>99	84 (*R*)
14	ethyl acetate	>99	86 (*R*)

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 30 atm H_2 pressure for 13 h, 0.1 mmol **1a**, 0.1 equiv HCl (0.2 M in dioxane), and 1.0 mL solvent. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC analysis.

solvents provided better results, especially MeOH, EtOH, ^{i}PrOH, and trifluoroethanol, which afforded high conversions and good to excellent enantioselectivities (90−>99% conversions and 80−89% ee). As expected, the hydrogenation product with reversed enantioselectivity can be achieved when this reaction was performed in weak polar solvents, and most of them provided good to excellent enantioselective control (Table 2, entries 9−14). Although moderate conversion was obtained in toluene, 93% ee can be achieved (52% conversion, Table 2, entry 11). In addition, full conversion and 91% ee were achieved in dioxane (Table 2, entry 12). The reaction solvent may affect the anion-binding interaction between the substrate and the ligand. These reaction results indicated that this appealing asymmetric methodology afforded an efficient method for the enantiodivergent synthesis just through the change of reaction solvents.

Encouraged by the results presented above, our attention then turned toward improving the enantioselectivity of this Ir-catalyzed asymmetric hydrogenation in EtOH, toluene, and dioxane to access both enantiomers, respectively. The additive Brønsted acid may affect the formation of anion-binding activation among the substrate, Brønsted acid, and ligand, which should have a great impact on the reaction results. As shown in Table 3, a variety of Brønsted acids with different strengths were sequentially investigated. As to the access of (*S*)-hydrogenation product **2a**, TfOH, HCl, TFA, and AcOH

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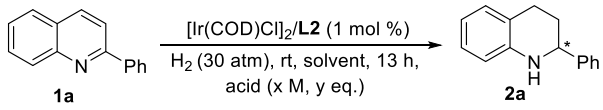
Table 3. Screening Brønsted Acids for Ir-Catalyzed Asymmetric Hydrogenation of 2-Phenylquinoline (1a)[a]



entry	solvent	acid	pK_a[b]	x M	y equiv	conv. (%)[c]	ee (%)[d]
1	EtOH	TfOH	−14	0.2	0.1	96	89 (*S*)
2	EtOH	HCl	−8	0.2	0.1	>99	89 (*S*)
3	EtOH	CF_3CO_2H	−0.25	0.2	0.1	>99	89 (*S*)
4	EtOH	CH_3CO_2H	4.76	0.2	0.1	97	90 (*S*)
5	EtOH	CH_3CO_2H	4.76	4.0	0.2	>99	90 (*S*)
6	dioxane	TfOH	−14	0.2	0.1	>99	23 (*R*)
7	dioxane	HCl	−8	0.2	0.1	>99	91 (*R*)
8	dioxane	CF_3CO_2H	−0.25	0.2	0.1	>99	62 (*R*)
9	dioxane	CH_3CO_2H	4.76	0.2	0.1	Trace	NA
10	toluene	TfOH	−14	0.2	0.1	72	71 (*R*)
11	toluene	HCl	−8	0.2	0.1	43	93 (*R*)
12	toluene	CF_3CO_2H	−0.25	0.2	0.1	51	65 (*R*)
13	toluene	CH_3CO_2H	4.76	0.2	0.1	trace	NA
14	toluene	HCl	−8	0.2	0.2	59	93 (*R*)
15	toluene/dioxane = 9:1	HCl	−8	0.2	0.2	81	90 (*R*)
16	toluene/dioxane = 8:2	HCl	−8	0.2	0.2	>99	92 (*R*)
17	toluene/dioxane = 7:3	HCl	−8	0.2	0.2	>99	89 (*R*)

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 30 atm H_2 pressure for 13 h, 0.1 mmol **1a**, 0.1 equiv HCl (0.2 M in dioxane), and 1.0 mL solvent; the configuration of product **2a** was determined by comparing the optical data with those reported in the literature.[9d,10a,b,14] [b]From Evans' pK_a table. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis.

were applied to this hydrogenation in EtOH, and the reactivities and enantioselectivities almost remained at the same level with 96−99% conversions and 89−90% ee (Table 3, entries 1−4). When the AcOH concentration and amount were increased, full conversion was observed (Table 3, entry 5). Meanwhile, these four acids were also investigated in toluene and dioxane, individually. They exhibited similar performances, and HCl provided the best enantioselectivities with (*R*)-**2a** (Table 3, entries 7 and 11). In addition, there is trace conversion in the presence of a weak acid, AcOH (Table 3, entries 9, 13). Better conversion can be obtained when more HCl was added to the reaction system (59% conversion, 93% ee, Table 3, entry 11 *vs* entry 14). In order to achieve both full conversion and high enantioselectivity, mixed preferential solvents of toluene and dioxane were investigated (Table 3, entries 15−17). A mixture solvent of toluene/dioxane (v/v = 8:2) proved to be the best choice as a reaction solvent (>99% conversion, 92% ee, Table 3, entry 16).

Substrate Scope Study. With the two optimized reaction conditions in hand, we explored the substrate scope and generality of the Ir/*N*−Me-Zhaophos-catalyzed asymmetric hydrogenation in EtOH and in the mixed solvents of toluene and dioxane, respectively, to access both enantiomers. This asymmetric catalytic methodology provided an efficient way to realize the synthesis of both enantiomers of chiral 1,2,3,4-tetrahydroquinolines, promoted by the same catalyst in different solvents. These reaction results are summarized in Scheme 2. A series of 2-aryl-substituted quinolines could be hydrogenated smoothly to give the desired products in high yields, along with good to excellent enantioselectivities (toluene and dioxane solvent system: 86−98% yields, 81−98% ee; EtOH solvent system: 94−99% yields, 80−94% ee). For most 2-aryl-substituted quinoline substrates, the introduction of substituents with different electronic properties and positions on the phenyl ring had little effect on the reactivity and ee value, which are compatible in these two reaction systems. Interestingly, 2-(*o*-tolyl)quinoline **1b** gave the product **2b** in full conversion, 96% yield and 98% ee in the toluene and dioxane mixed solvent, while only 80% ee was achieved in the EtOH system. The 2-naphthyl-substituted substrate **1o** also worked well in both reaction solvent systems with 92% ee and 90% ee, respectively. The challenging heteroaromatic substrate 2-(thiophen-3-yl)quinoline **1p** also displayed high reactivities and good enantioselectivities. The alkyl substrate 2-methylquinoline **1q** was hydrogenated smoothly, resulting in moderate enantioselectivity in the toluene and dioxane mixed solvent (77% ee), unfortunately, with poor enantioselectivity in EtOH (23% ee). Moreover, we further inspected the effect of different substituted groups on the benzene ring; substituted 2-phenylquinolines (**1r**−**1u**) were employed in this asymmetric hydrogenation. They are generally suitable reaction partners in both systems, affording the corresponding enantiomeric hydrogenation products in high yields and good to excellent enantioselectivities (toluene and dioxane solvent system: 91−98% yield, 81−94% ee; EtOH solvent system: 92−97% yield, 91−93% ee). It is slightly strange that the substrate 2-(3,4-dimethoxyphenyl)-6-fluoro-quinoline **1v** nearly could not undergo this transformation in the toluene and dioxane mixed solvent, while it was hydrogenated well in EtOH to access product **2v** with full conversion, 98% yield and 94% ee. In addition, several functionalized 2-substituted quinoline substrates, such as ethyl quinoline-2-carboxylate (**1w**), 2-(phenylethynyl)quinoline (**1x**), and (*E*)-2-styrylquinoline (**1y**), were also investigated in this hydrogenation under optimized reaction conditions. It is noteworthy that ethyl quinoline-2-carboxylate (**1w**) was hydrogenated well in these two reaction systems, affording the corresponding hydrogenation product (**2w**) with the same configuration in full conversion, high yields, and moderate enantioselectivities (95% yield and 65% ee in the toluene and dioxane mixed solvent and

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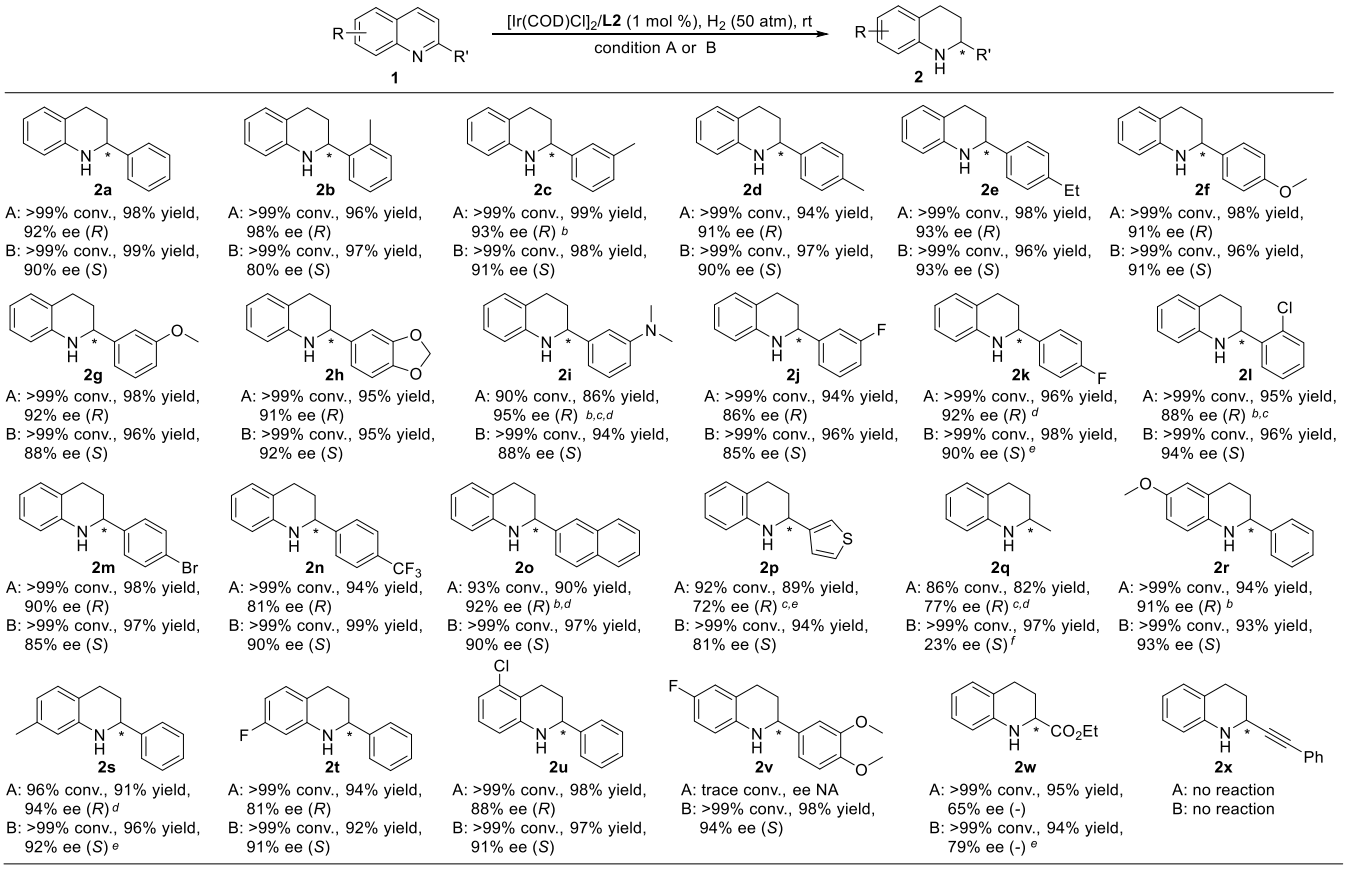
Scheme 2. Substrate Scope Study for Ir-Catalyzed Asymmetric Hydrogenation of 2-Substituted Quinolines[a]

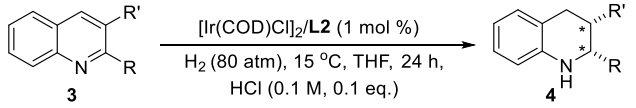


[a]Condition A: 0.1 mmol substrate **1**, 1.0 mol % $[Ir(COD)Cl]_2$/**L2**, H_2 (50 atm), 1.0 mL toluene/dioxane = 8/2, room temperature, 24 h, HCl (0.2 M in dioxane, 0.2 equiv); condition B: 0.1 mmol substrate **1**, 1.0 mol % $[Ir(COD)Cl]_2$/**L2**, H_2 (50 atm), 1.0 mL EtOH, room temperature, 12 h, HOAc (4 M in EtOH, 0.2 equiv). Conversion was determined by ^{1}H NMR analysis. Yield was isolated yield. Ee was determined by chiral HPLC analysis. (b) 0.1 equiv HCl. (c) Dioxane instead of toluene/dioxane = 8:2. (d) 48 h. (e) 24 h. (f) ^{i}PrOH instead of EtOH.

94% yield and 79% ee in EtOH). It is possible that the ester group in ethyl quinoline-2-carboxylate as the hydrogen-bonding acceptor group may interrupt the interaction between the quinoline ring and the ligand. Unfortunately, 2-(phenylethynyl)quinoline (**1x**) did not work, and no reaction was observed. The alkenyl group of (*E*)-2-styrylquinoline (**1y**) may be partly reduced, which led to mess reaction systems.

Promoted by the success in Ir-catalyzed enantioselective hydrogenation of a variety of 2-substituted quinolines, we then focused on the further exploration of the substrate scope with more challenging 2,3-disubstituted quinolines (see the optimized reaction conditions in Supporting Information). As shown in Table 4, a range of different 2,3-disubstituted quinolines were subjected to enantioselective hydrogenation in our catalytic system, which led to the desired products chiral *cis*-1,2,3,4-tetrahydroquinolines with full conversions, 95−98% yields, >25:1 dr, and 89−92% ee. We found that the 3-methyl (**3a**), ethyl (**3b**), or *n*-propyl (**3c**) 2-phenyl-substituted quinoline substrates were well tolerated and proceeded efficiently to obtain desired products (**4a**−**4c**) with high yields and excellent stereoselectivities (95−98% yields, >25:1 dr, and 92% ee, Table 4, entries 1−3). Moreover, we also examined the substituent on the phenyl ring (**3d**), which had a little influence on the control of the enantioselectivities, and 97% yield, >25:1 dr, and 89% ee were obtained (Table 4, entry 4).

Table 4. Substrate Scope Study for Ir-Catalyzed Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines[a]



entry	R	R′	4	yield (%)[b]	cis/trans (%)[c]	ee (%)[d]
1	Ph	Me	**4a**	98	>25:1	92
2	Ph	Et	**4b**	97	>25:1	92
3	Ph	^{n}Pr	**4c**	95	>25:1	92
4	4-Me-Ph	Me	**4d**	97	>25:1	89

[a]Reaction conditions: 0.1 mmol substrate **3**, 1.0 mol % $[Ir(COD)Cl]_2$/**L2**, H_2 (80 atm), 1.0 mL THF, 15 °C, HCl (0.1 M in dioxane, 0.1 equiv), and 24 h. [b]Yield is isolated yield. [c]The conversion and *cis*/*trans* value were determined by ^{1}H NMR analysis. [d]Ee value was determined by HPLC analysis using a chiral stationary phase.

Mechanism Investigation. As mentioned above, the cis-hydrogenation products were obtained with 2,3-disubstituted quinolines as the substrates. According to the high cis-selectivity of hydrogenation products, we speculated that the substrate 2,3-disubstituted quinolines may undergo 1,4-hydride addition to give an enamine intermediate **int-I**. It should be easily isomerized to form a chiral imine intermediate **int-II**/**II′** similar to the process of dynamic kinetic resolution in a chiral environment, which was then hydrogenated to generate cis-

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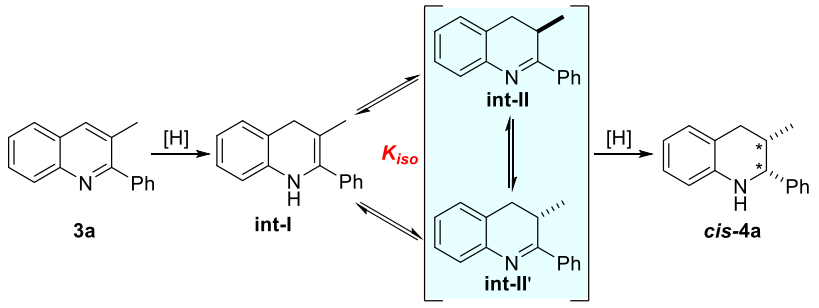
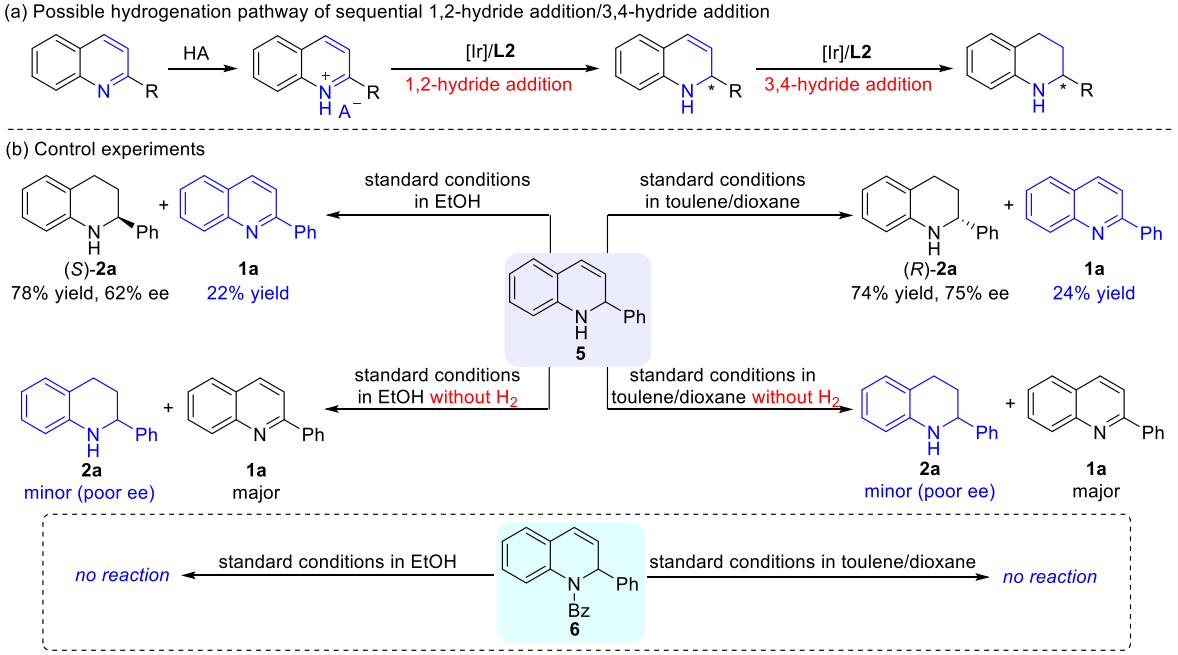
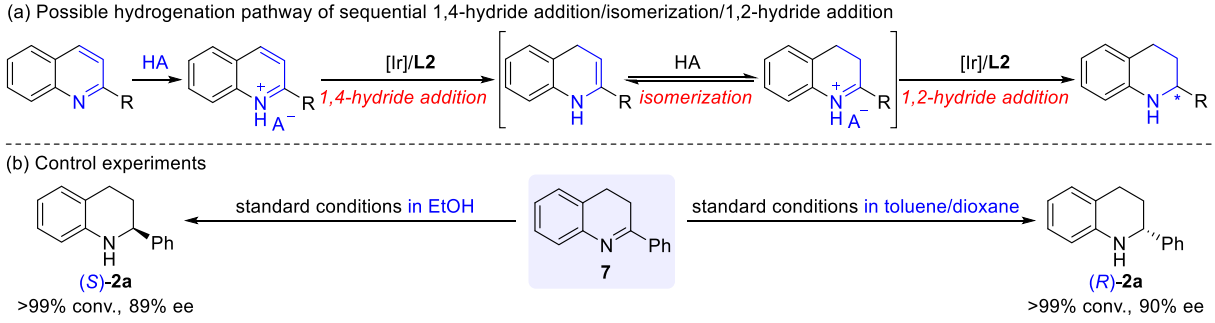
Scheme 3. Possible Hydrogenation Process of 2,3-Disubstituted Quinolines



Scheme 4. Possible Reaction Pathway of Sequential 1,2-Hydride Addition/3,4-Hydride Addition and Control Experiments



Scheme 5. Possible Reaction Pathway of Sequential 1,4-Hydride Addition/Isomerization/1,2-Hydride Addition and Control Experiments



products (Scheme 3). Meanwhile, it also has the possibility that the intermediate **int-I** could be hydrogenated directly to give the cis-products.

The reduction of quinoline has always been involved in the sequential hydrogenation sequence of C=C and C=N bonds. As shown in Scheme 4a, one possible pathway is 1,2-hydride addition followed by 3,4-hydride addition. In order to verify this pathway, we synthesized the 1,2-hydride addition intermediate 1,2-dihydroquinoline **5**, and it was applied to these two catalytic systems, which provided both 2-phenylquinoline **1a** and the hydrogenation product tetrahydroquinoline **2a** with moderate enantioselectivity. In addition, we found that compound 1,2-dihydroquinoline **5** seemed to go through a similar disproportionation process without H_2, resulting in the formation of aromatic quinoline **1a** and tetrahydroquinoline **2a**. To avoid this transformation, the *N*-benzoyl compound **6** was prepared and then was employed in this reduction. It was found as an inactive substrate under the same reaction conditions, and the C=C bond could not be reduced by using this iridium catalyst. According to these results, this hydrogenation pathway possessed much less possibility for our catalytic system.

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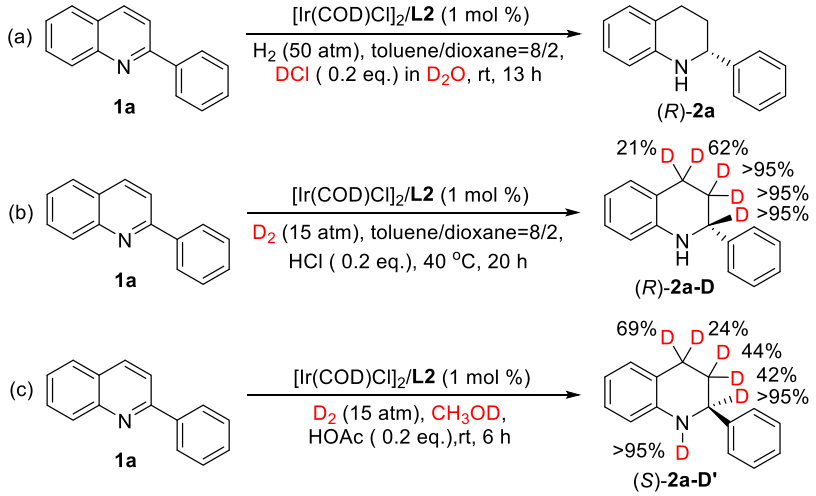
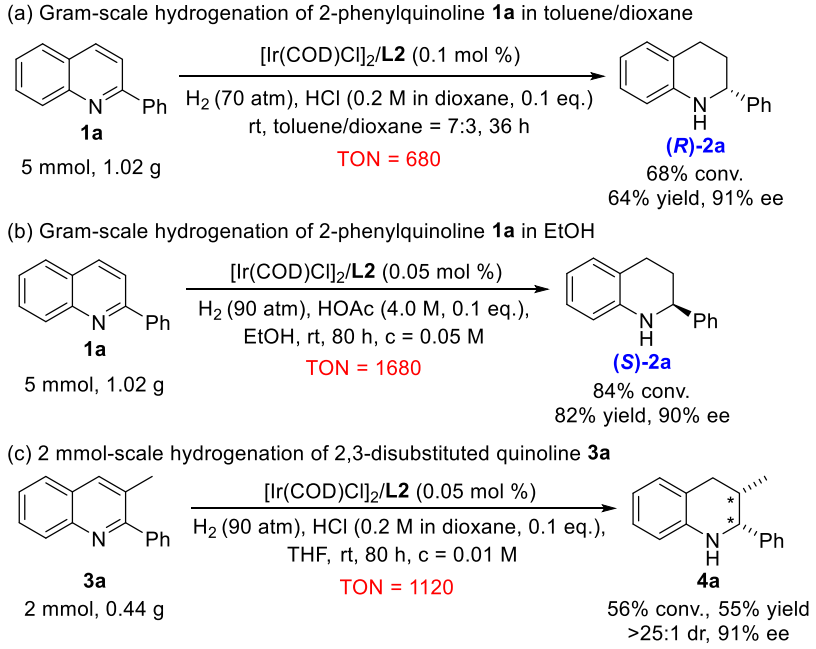
Scheme 6. Deuterium-Labeling Experiments



Scheme 7. Gram-Scale Ir-Catalyzed Asymmetric Hydrogenation of Quinolines



In addition, this hydrogenation may follow another pathway with sequential 1,4-hydride addition to generate enamine first, and then isomerized to an imine intermediate, which went through a 1,2-hydride addition (Scheme 5). We prepared the intermediate 3,4-dihydroquinoline **7**, which was hydrogenated well in the two solvent system to access both enantiomers of the desired product **2a**. Nearly same enantioselectivities and reactivities were obtained with the above model quinoline substrate **1a**. All these observations indicated that compound **7** may be involved in this catalytic cycle, and this hydrogenation pathway may be preferred through the sequential 1,4-hydride addition/isomerization/1,2-hydride addition.

To further verify the existence of imine intermediate **7** in the hydrogenation process, ^{1}H NMR spectroscopy and electrospray ionization-mass spectrometry (ESI-MS) were combined to characterize it. ^{1}H NMR spectra of hydrogenation product **2a**, imine intermediate **7**, and the reaction mixture of two systems are successively listed as A−D (see Supporting Information). As expected, the proton signals of the imine intermediate and the hydrogenation product were found in spectra C and D, which demonstrated their existence in these reaction systems. Moreover, the reaction mixture in toluene and dioxane was further investigated by ESI-MS in the positive-ion mode, and the signal peaks of substrate **1a**·H$^+$ (m/z 206.0964), imine intermediate **7**·H$^+$ (m/z 208.1099), and hydrogenation product **2a**·H$^+$ (m/z 210.1276) were observed. These wonderful observations are in accordance with the process of 1,4-hydride addition/isomerization/1,2-hydride addition demonstrated in Scheme 5.

A series of isotope-labeling experiments were conducted to further confirm the above possible hydrogenation pathway (Scheme 6). The Ir-catalyzed asymmetric hydrogenation of quinoline was first performed under 50 atm H_2 in toluene/dioxane in the presence of DCl/D_2O solution, and the hydrogenation product almost without deuterium atoms was obtained (Scheme 6a). In addition, the hydrogenation reaction was repeated under 15 atm D_2 in these two reaction systems, respectively. We found that the desired products were

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ACS Catal. 2021, 11, 7281−7291

deuterium-incorporated at 2-, 3-, and 4-positions (Scheme 6b,c). In the toluene/dioxane system, hydrogenation product (*R*)-**2a-D** with >95% deuterium incorporation at 2- and 3-positions and part-deuterium incorporation at the 4-position was obtained; meanwhile, the hydrogenation product (*S*)-**2a-D′** with >95% deuterium incorporation at 1- and 2-positions and part-deuterium incorporation at 3- and 4-positions was obtained in CH_3OD, which demonstrated that they may go through different reaction transition states.

Synthetic Utility. In order to demonstrate the scalability and utility of the present methodology, the gram-scale synthesis of (*R*) or (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline **2a** was efficiently realized in the presence of low-catalyst loading with good reactivity and excellent enantioselectivity (Scheme 7a,b, toluene and dioxane: 68% conversion, 64% yield, 91% ee, TON = 680; EtOH: 84% conversion, 82% yield, 90% ee, TON = 1680). Meanwhile, 2 mmol-scale reduction of 2,3-disubstituted quinoline 3-methyl-2-phenylquinoline **3a** was also achieved in moderate conversion with excellent diastereoselectivity and enantioselectivity (56% conversion, 55% yield, 91% ee, TON = 1120, Scheme 7c).

CONCLUSIONS

In summary, a solvent-controlled highly enantioselective Ir-catalyzed asymmetric hydrogenation of quinolines was developed. The enantiodivergent synthesis of chiral tetrahydroquinolines could be more facilely realized by adjustment of the solvents (toluene/dioxane: up to 99% yield, 98% ee (*R*), TON = 680; EtOH: up to 99% yield, 94% ee (*S*), TON = 1680). This study would provide an efficient method for the preparation of compounds of biological interest such as chiral tetrahydroquinolines. Gram-scale asymmetric hydrogenation easily proceeded in the presence of low-catalyst loading. According to the results of deuterium-labeling experiments, control experiments, ^{1}H NMR, and ESI-MS experiments, a reasonable and possible reaction pathway was provided for illustration. The reaction results presented here clearly indicate that the solvent is a very important parameter in asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01353.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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