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Highly Enantioselective Iridium-Catalyzed Hydrogenation of 2-Benzylquinolines and 2-Functionalized and 2,3-Disubstituted Quinolines

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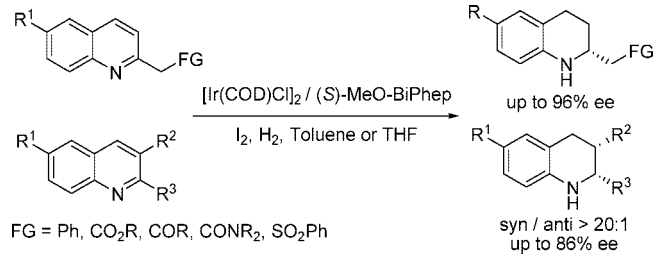

The enantioselective hydrogenation of 2-benzylquinolines and 2-functionalized and 2,3-disubstituted quinolines was developed by using the $[Ir(COD)Cl]_2$/bisphosphine/I_2 system with up to 96% ee. Moreover, mechanistic studies revealed the hydrogenation mechanism of quinoline involves a 1,4-hydride addition, isomerization, and 1,2-hydride addition, and the catalytic active species may be a Ir(III) complex with chloride and iodide.

Introduction

Asymmetric hydrogenation of aromatic and heteroaromatic compounds is a very useful reaction as it provides a convenient access to numerous saturated or partially saturated chiral cyclic compounds, whose synthesis by direct cyclization is often difficult.[1] In the past decades, some successful examples for the hydrogenation of heteroaromatic compounds were achieved. Quinoxaline,[2] pyridine,[3] indole,[4] pyrrole,[5] and furan[6] have been hydrogenated with over 90% ee. Very recently, we developed Ir-catalyzed asymmetric hydrogenation of quinoline derivatives using $[Ir(COD)Cl]_2$/MeO-BiPhep/I_2 as catalyst with high enantioselectivity,[7] and this methodology has been successfully applied to the synthesis of some tetrahydroquinoline alkaloids.[8]

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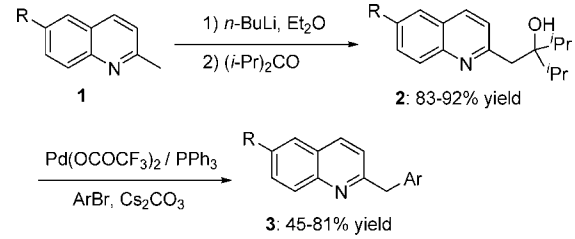
After we reported our initial work on iridium-catalyzed asymmetric hydrogenation of quinolines, several other groups communicated their results in this area.[9−15] Fan, Xu, and Chan reported an air-stable catalyst system Ir/P-Phos/I_2 for the asymmetric hydrogenation of quinoline derivatives with 92% ee.[9a] Similar results were subsequently described by their group with chiral ligands based on H_8-BINAPO and 1,1′-spirobiindane backbone.[9] Reetz found that chiral BINOL-derived diphosphonites further linked to an achiral diphenyl ether unit were also effective for the asymmetric hydrogenation of quinolines.[10] In 2006, Chan showed the usefulness of PQ-Phos as a chiral ligand in this hydrogenation reaction.[11] Fan and co-workers developed enantioselective hydrogenation of quinolines by Ir(BINAP)-cored dendrimers with dramatic enhancement of catalytic activity, and the TON was up to 43 000.[12a] Later, the same group reported ruthenium- and iridium-catalyzed asymmetric hydrogenation of quinolines with up to 99% ee.[12b,c] Rueping developed BINOL-derived chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation of 2-substituted and 3-substituted quinolines with up to 99% ee and 86% ee, respectively.[13] Du explored double axially chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation of 2-substituted and 2,3-disubstituted quinolines using Hantzsch esters as the hydrogen source.[14] Despite all the aforementioned excellent examples, the substrate scope mainly focused on 2-alkyl, 2-aryl-substituted, and 3-substituted quinoline derivatives. Highly enantioselective hydrogenation of other quinoline substrates elaborately remains a challenging task, particularly with 2-benzylquinolines and 2-functionalized and 2,3-disubstituted quinolines, since the hydrogenation products are important organic synthetic intermediates and structural units of alkaloids and biologically active compounds. In this article, we present highly enantioselective Ir-catalyzed asymmetric hydrogenation of 2-benzylquinolines and 2-functionalized and 2,3-disubstituted quinolines with up to 96% ee. Moreover, mechanistic studies revealed the hydrogenation mechanism of quinolines involves a 1,4-hydride addition, isomerization, and 1,2-hydride addition, and the catalytic active species may be an Ir(III) complex with chloride and iodide.

SCHEME 1. The Synthesis of 2-Benzylquinolines



Results and Discussion

Asymmetric hydrogenation of 2-benzylquinolines is the most convenient route to 2-benzyltetrahydroquinolin derivatives, but no effective synthetic method of 2-benzylquinolines is provided. In 2007, Oshima and co-workers reported a potent method for the synthesis of 2-benzylpyridine derivatives from 2-(2-pyridyl)ethanol derivatives and aryl halides by Pd-catalyzed chelation-assisted cleavage of unstrained Csp^3-Csp^3 bonds.[16] To our delight, 2-benzylquinolines could also be conveniently prepared according to the above procedure. Treatment of aryl halides in the presence of cesium carbonate and a palladium catalyst in refluxing xylene or toluene provided 2-benzylquinolines with moderate to good yields (Scheme 1).

The hydrogenation of these 2-benzyl-substituted quinolines was studied after their synthesis. In our initial study, 2-benzylquinoline was chosen as the model substrate for reaction optimization. On the basis of our previous results,[7] we first examined the effect of solvents on the reactivity and enantioselectivity using $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep/I_2 as the catalyst. As shown in Table 1, the reaction was strongly solvent-dependent. Low reactivity and moderate enantioselectivity were obtained in CH_2Cl_2. Excellent reactivity and the highest enantioselectivity were obtained in toluene (Table 1, entry 4). Subsequently, some commercially available chiral bidentate phosphine ligands were also tested (Table 1, entries 4−8), and (*S*)-MeO-BiPhep gave the best results with 94% ee (Table 1, entry 4). It should be noted that the hydrogenation could not take place in the absence of iodine.

Having established the optimal conditions, we explored the scope of the Ir-catalyzed asymmetric hydrogenation of 2-benzyl-substituted quinolines, and the results were summarized in Table 2. The reactions were carried out in toluene at room temperature under 700 psi of hydrogen. In general, all the quinolines were hydrogenated completely to give the corresponding 1,2,3,4-tetrahydroquinolines. Excellent enantioselectivities and high yields were obtained regardless of the electronic properties and steric hindrance of substituent groups (Table 2, entries 1−9). 2-Benzyl-6-fluoroquinoline (**3g**) gave the highest enantioselec-

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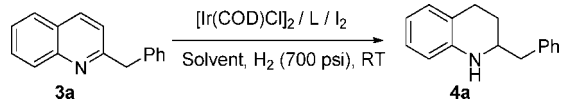
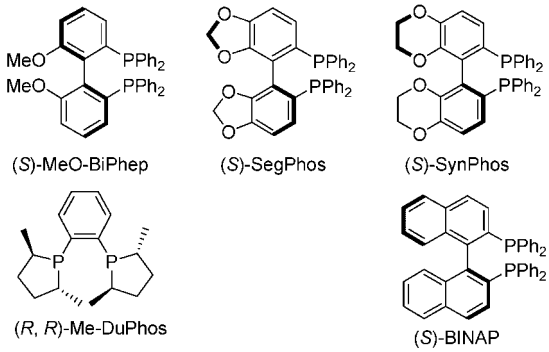
TABLE 1. Ir-Catalyzed Asymmetric Hydrogenation of 2-Benzylquinoline[a]

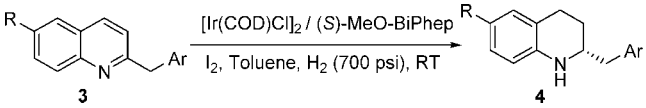


Entry	Ligand	Solvent	Yield (%)[b]	Ee (%)[c]
1	(*S*)-MeO-BiPhep	CH_2Cl_2	53[d]	80
2	(*S*)-MeO-BiPhep	THF	91	83
3	(*S*)-MeO-BiPhep	Benzene	96	93
4	(*S*)-MeO-BiPhep	Toluene	95	94
5	(*S*)-SegPhos	Toluene	96	93
6	(*S*)-SynPhos	Toluene	93	91
7	(*R,R*)-Me-DuPhos	Toluene	29[d]	3
8	(*S*)-BINAP	Toluene	89	72



[a] Conditions: 0.25 mmol of quinoline, $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol%), 3 mL of solvent. [b] Based on **3a**. [c] Determined by HPLC. [d] Determined by ^1H NMR analysis.

TABLE 2. Ir-Catalyzed Asymmetric Hydrogenation of 2-Benzylquinolines[a]



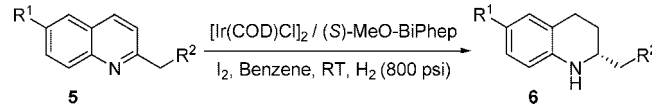
entry	R/Ar	yield (%)[b]	ee (%)[c]	config [d]
1	H/C_6H_5	95 (**4a**)	94	(*R*)
2	H/2-MeC_6H_4	88 (**4b**)	95	(*R*)
3	H/1-$C_{10}H_7$	93 (**4c**)	95	(*R*)
4	H/2-$CF_3C_6H_4$	92 (**4d**)	88	(*R*)
5	H/4-$CF_3C_6H_4$	89 (**4e**)	93	(*R*)
6	H/4-FC_6H_4	93 (**4f**)	94	(*R*)
7	F/C_6H_5	97 (**4g**)	96	(*R*)
8	Me/C_6H_5	93 (**4h**)	95	(*R*)
9	H/3,4-$(MeO)_2C_6H_3$	93 (**4i**)	94	(*R*)

[a] Conditions: 0.25 mmol of quinoline, $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol%), 3 mL of toluene. [b] Based on **3**. [c] Determined by HPLC. [d] Determined by comparison of rotation sign with the literature data or by analogue.

tivity with 96% ee (Table 2, entry 7). A slightly lower enantioselectivity (88% ee) was obtained when the aryl substituent was 2-trifluoromethylphenyl (Table 2, entry 4).

Asymmetric Hydrogenation of 2-Functionalized Quinolines. Next, we challenged the hydrogenation of 2-functionalized quinolines, which were prepared from their corresponding 2-methylquinolines according to the known procedures (see the Supporting Information). Under the optimized reaction conditions—$Ir(COD)Cl]_2$/(*S*)-MeO-Biphep/I_2, benzene as solvent, 800 psi of H_2—a variety of 2-functionalized quinoline derivatives could be successfully hydrogenated to afford their corresponding derivatives (**6**). As illustrated in Table 3, full conversions were achieved with all the functionalized quinolines. For the quinoline substrates bearing alkyl ketones, the ee values were slightly affected by the electronic properties and steric hindrance of substituents, such as methyl ketone and propyl ketone, 90% ee and 84% ee were obtained, respectively (Table 3, entries 2 and 3). With arylketone-substituted quinolines, the ee values of all the products were excellent regardless of the electronic properties and steric hindrance (Table 3, entries 1, 4−10, and 12−14). In the case of 2-vinyl-substituted quinoline, both the double bond and the pyridine ring of quinoline can be hydrogenated with 95% ee (Table 3, entry 15). Interestingly, the system could tolerate the esters, amide, and benzenesulfonyl groups and all these substrates were transformed to the corresponding tetrahydroquinoline derivatives with 80−92% ee values (Table 3, entries 16−19). It is noted that substrates with hydroxyl by TBS protected could also be hydrogenated smoothly with high enantioselectivities (Table 3, entries 20−21), which could be converted to the key intermediate of the alkaloid of gephyrotoxin conveniently by two steps with high yields (Scheme 2).[17]

TABLE 3. Ir-Catalyzed Hydrogenation of 2-Functionalized Quinolines[a]



entry	R^1/R^2	yield[b]	ee[c] (config)[d]
1	H/COPh	91 (**6a**)	96 (*R*)
2	H/COMe	93 (**6b**)	90 (*R*)
3	H/CO(*n*-Pr)	91 (**6c**)	84 (*R*)
4	H/CO(*p*-MeOPh)	84 (**6d**)	83 (*R*)
5	H/CO(*o*-MeOPh)	78 (**6e**)	95 (*R*)
6	H/CO(*p*-MePh)	89 (**6f**)	95 (*R*)
7	H/CO(*o*-MePh)	97 (**6g**)	96 (*R*)
8	H/CO(*p*-^{i}PrPh)	97 (**6h**)	95 (*R*)
9	H/CO(*p*-CF_3Ph)	90 (**6i**)	95 (*R*)
10	H/CO(1-naphthyl)	89 (**6j**)	95 (*R*)
11	H/CO$(CH_2)_2$Ph	90 (**6k**)	87 (*R*)
12	Me/COPh	82 (**6l**)	94 (*R*)
13	F/COPh	92 (**6m**)	96 (*R*)
14	H/CO(3,4-$(MeO)_2$Ph)	95 (**6n**)	94 (*R*)
15	H/*p*-MeOPhCH=CH [e]	80 (**6o**)	95 (*S*)
16	H/COOMe	88 (**6p**)	82 (*R*)
17	H/COOEt	93 (**6q**)	92 (*R*)
18	H/$CONEt_2$	98 (**6r**)	80 (*R*)
19	H/SO_2Ph	97 (**6s**)	90 (*R*)
20	H/$(CH_2)_3$OTBS	90 (**6t**)	94 (*S*)
21	H/$(CH_2)_4$OTBS	65 (**6u**)	89 (*S*)

[a] Conditions: 0.25 mmol of quinoline, $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol%), 3 mL of benzene. [b] Based on **5**. [c] Determined by HPLC. [d] Determined by comparison of rotation sign with the literature data or by analogue. [e] The double bond was also hydrogenated.

Mechanism Study. The Function of Iodine. In the past decades, the additives have been elegantly used by chemists in asymmetric catalysis. The addition of suitable achiral additives, which could support the chiral catalyst system and enhance the yield, especially, in some cases also enhance the enantioselectivity efficiently and the success of this strategy can be

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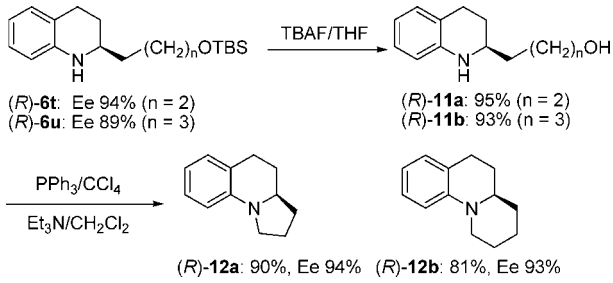
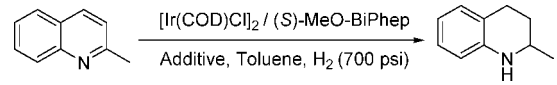
SCHEME 2. The Synthesis of the Key Intermediate of Gephyrotoxin

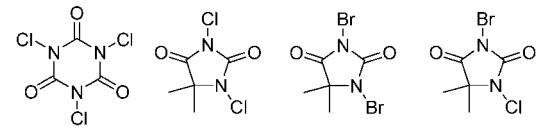


recognized by a comparison of the results obtained with and without the additives.[18] Recently, molecular iodine and iodides were also found to be effective additives in asymmetric hydrogenation.[19] In 1990, an interesting additive effect was observed by the Osborn group, when investigating the iridium-catalyzed asymmetric hydrogenation of imines using KI as additive.[19a] Later, Togni also showed the usefulness of this strategy to asymmetric hydrogenation of MEA-imine in the Syngenta Metolachlor process using iodine as additive.[19b] Xumu Zhang and co-workers reported the iridium-catalyzed asymmetric hydrogenation of arylimines also using I_2 as an additive.[19d] They suggested that the active catalyst was the Ir(III) hydrido chloro iodo species generated by oxidative addition of I_2 to the Ir(I) precursor in the presence of hydrogen with hydrogen iodide elimination, but no strong evidence was provided. This strategy was also applied to the Ir-catalyzed enantioselective reductive amination of aryl ketones by the same group.[19e] Bolm studied the iridium-catalyzed asymmetric hydrogenation of imines in the presence of iodine.[19f] Charette and Legault developed an efficient iodine-activated hydrogenation of *N*-iminopyridinium ylides.[3b] Zhou's group introduced rhodium-catalyzed asymmetric hydrogenation of enamines using monodente spiro phosphonite ligands in the presence of iodine.[19g] Zhang and co-workers explored ruthenium-catalyzed asymmetric hydrogenation of sulfonyl ketones with excellent reactivity and enantioselectivity also in the presence of iodine, and mechanism study revealed that in situ generated anhydrous hydrogen iodide might be the operating additive.[19h] Dorta, Togni, and co-workers explored the mechanism of Ir-catalyzed asymmetric hydrogenation of MEA-imine in the Syngenta Metolachlor process in the presence of iodine, and successfully isolated the adduct of iridium with iodine and catalyst-substrate adduct;[19i] the adduct of iridium complex with iodine, which was formed by oxidative addition of iodine, was structurally characterized by single-crystal X-ray diffraction as iodo-bridged dinuclear species and tested as a single catalyst precursor for the asymmetric hydrogenation. Their mechanism study indicated that both chloride and iodide are crucial for the activity and enantioselectivity.

TABLE 4. Effect of Additives on Activity and Enantioselectivity



Entry [a]	Additive	Yield (%) [b]	Ee (%) [c]
1	TCIA	>95	89
2	NBS [d]	95	91
3	NIS [d]	95	92
4	IBr	>95	93
5	ICl	>95	93
6	DCDMH	>95	91
7	DBDMH	95	92
8	BCDMH	>95	92
9	KI	15	2
10	n-Bu_4NBH_4	<5	-
11	None	<5	-
12	MeI	40	71
13	I_2	>95	94



[a] Conditions: 1 mmol of quinoline, $[Ir(COD)Cl]_2$ (0.5 mol %), ligand (1.1 mol %), additive (10 mol%), 3 mL of toluene. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC. [d] NBS: *N*-bromosuccinimide. NIS: *N*-iodosuccininide.

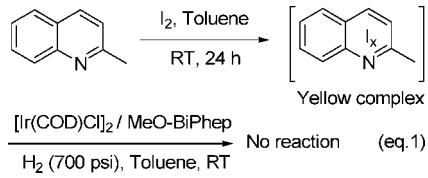
Recently, we developed Ir-catalyzed asymmetric hydrogenation of quinolines with excellent enantioselectivities using I_2 as an additive.[7] The hydrogenation reaction cannot take place in the absence of iodine. In our initial studies, besides iodine, we also tested the impact of other additives such as NBS, TCIA, IBr, n-Bu_4NBH_4, MeI, etc. Full conversion and good enantioselectivities were obtained with TCIA, IBr, ICl, BCDMH, and DCDMH as the additives (Table 4). Almost full conversion and good enantioselectivities were obtained with NBS, NIS, and DBDMH. Interestingly, MeI could also give 40% of conversion with moderate enantioselectivity (Table 4, entry 12). The best result was obtained by using iodine as the additive.

In the above results, it appeared that the additive was necessary for the asymmetric hydrogenation of quinolines. Two kinds of functions of iodine were suggested: one is the substrate activation by formation of a complex of iodine and quinoline—the iridium catalyst can hydrogenate the complex of iodine and quinoline; the other is catalyst activation—a new and highly active catalyst is formed by the oxidative addition. To differentiate the two activation strategies, 2-methylquinoline was allowed to react with iodine in toluene for 24 h according to the known literature.[20] A yellow complex was obtained and subjected to asymmetric hydrogenation with use of $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep as catalyst in the absence of iodine; surpris-

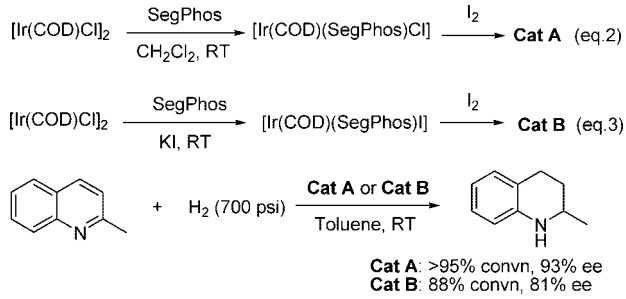
(18) (a) Cornils, B.; Hermann, W. A., Eds. In *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, Germany, 1996; Vol. 2, pp 74 and−351. For reviews see: (b) Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577. (c) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059–1070. (d) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47. (e) Maitlis, P. M.; Haynes, A.; James, B. R.; Catellani, M.; Chiusoli, G. P. *Dalton Trans.* **2004**, 3409–3419. (f) Wang, C.-Y.; Xi, Z.-F *Chem. Soc. Rev.* **2007**, *36*, 1395–1406. See also: (g) Jiang, Q.-Z.; Jiang, Y.-T.; Xiao, D.-M.; Cao, P.; Zhang, X.-M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100–1103. (h) Buriak, J. M.; Klein, J. C.; Herrington, D. G.; Osborn, J. A. *Chem. Eur. J.* **2000**, *6*, 139–150.

(19) (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401. (b) Togni, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1475–1477. (c) Spindler, F.; Blaser, H.-U. *Enantiomer* **1999**, *4*, 557–568. (d) Xiao, D.-M.; Zhang, X.-M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425–3428. (e) Chi, Y.-X.; Zhou, Y.-G.; Zhang, X.-M. *J. Org. Chem.* **2003**, *68*, 4120–4122. (f) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564–7567. (g) Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774–11775. (h) Wan, X.-B.; Meng, Q.-H.; Zhang, H.-W.; Sun, Y.-H.; Fan, W.-Z.; Zhang, Z.-G. *Org. Lett.* **2007**, *9*, 5613–5616. (i) Dorta, R.; Broggini, D.; Stoop, R.; Ruegger, H.; Spindler, F.; Togni, A. *Chem. Eur. J.* **2004**, *10*, 267–278.

ingly, no product was detected (eq 1), which suggested that the substrate activation may not be possible.



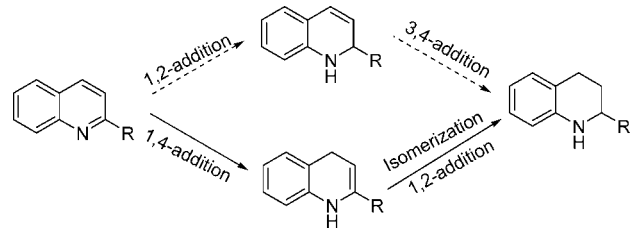
Next, the function of catalyst activation was investigated: iodine was added to a mixture of the complex $[Ir(COD)Cl]_2$/(*S*)-SegPhos, which was obtained in CH_2Cl_2 by stirring for 30 min at room temperature, and then stirred for 12 h. After the solvent was removed under reduced pressure, a brown solid **Cat A** was afforded (eq 2). However, **Cat A** was a very complex mixture according to the ^{31}P NMR spectrum due to the coexistence of chloride and iodide. It is very exciting that the desired product with 93% ee was achieved for the hydrogenation of 2-methylquinoline by using the brown solid **Cat A** as a catalyst. To obtain relatively pure catalyst, chloride should be exchanged for iodide. So, the complex $[Ir(COD)Cl]_2$/(*S*)-SegPhos was treated with 1 equiv of KI in acetone to afford [Ir(COD)(SegPhos)I], then the complex was treated with an equimolar amount of iodine in toluene and a new species **Cat B** was formed according to Dorta's method (eq 3).[19i] Surprisingly, this dinuclear Ir precatalyst **Cat B** gave 88% conversion and 81% enantioselectivity, which is lower than **Cat A** in reactivity and enantioselectivity. It is shown that chloride and iodide are crucial for the reactivity and enantioselectivity. The above experimental results and the work of Osborn and Dorta reveal that the iodine activates the catalyst in the hydrogenation of quinolines.



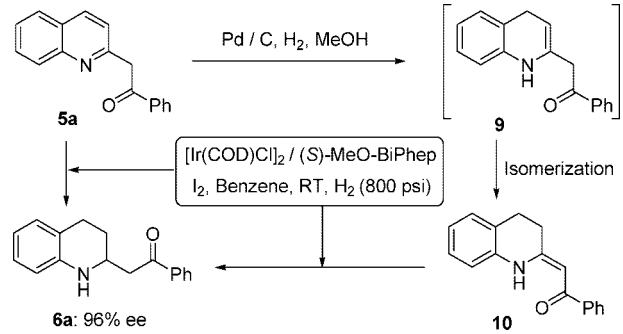
The Hydrogenation Process Study. By analysis of the iridium-catalyzed hydrogenation sequence of C═C and C═N bonds of quinolines, we envisioned that there might be two possible pathways for the hydrogenation of quinoline derivatives (Scheme 3). The first pathway is 1,2-hydride addition, then 3,4-hydride addition; the second one is 1,4-hydride addition, isomerization, and then 1,2-hydride addition.

To demonstrate which pathway is possible, the synthesis of reaction intermediate is very important and sometimes could provide direct proof to support the mechanism. The intermediate of 1,2-hydride addition can be synthesized conveniently by the reaction of quinoline with methyl lithium. However, the intermediate is easy to dehydrogenate to form the aromatic 2-methylquinoline at room temperature by using $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep/I_2 as catalyst in the absence of hydrogen in 5 min (eq 4). Unfortunately, this experiment could not solve the above problem. Next, we sought the synthesis of the intermediate of 1,4-hydride addition.

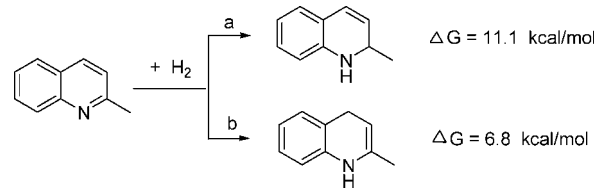
SCHEME 3. The Possible Hydrogenation Pathway of Quinolines

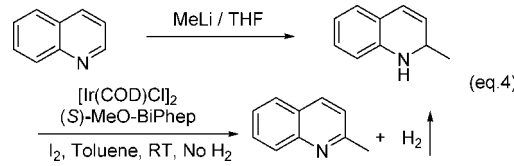


SCHEME 4. The Synthesis and Hydrogenation of Intermediate Enamine 10



SCHEME 5. Computed Thermodynamic Values for Hydride Addition of 2-Methylquinoline



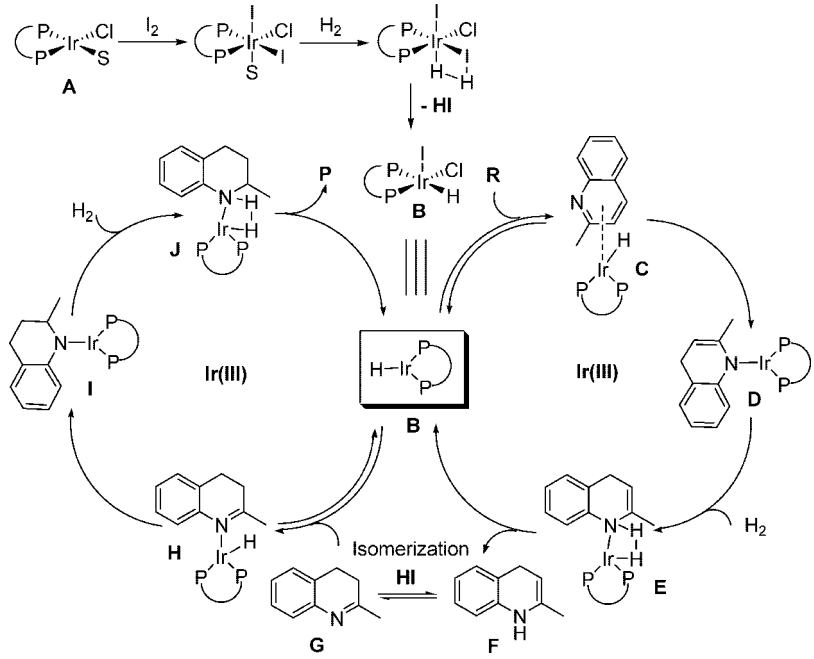


The intermediates of 1,4-hydride addition are somewhat not stable at room temperature,[21] and difficult to separate. To obtain the stable intermediate of this reaction, compound **5a** bearing a functional group was chosen as the starting material (Scheme 4). To our pleasure, when **5a** was treated by using Pd/C with hydrogen in MeOH, the steady intermediate **10** was achieved after isomerization from the intermediate **9**. Subsequently, the hydrogenation of enamine **10** was carried out, and the desired product was obtained with 96% ee, which was the same enantioselectivity as direct hydrogenation of compound **5a**. We can also detect the existence of intermediate **10** in the direct hydrogenation of compound **5a** with a low pressure of hydrogen and in a shorter reaction time. The above experiments demon-

(20) (a) Boraei, A. A.-A. A.; Alla, E. M. A.; Mahmoud, M. R. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 603–606. (b) Reid, C.; Mulliken, R. S. *J. Am. Chem. Soc.* **1954**, *76*, 3869–3874. (c) Krishna, V. G.; Bhowmik, B. B. *J. Am. Chem. Soc.* **1968**, *90*, 1700–1705.

(21) (a) Coates, R. M.; Johnson, E. F. *J. Am. Chem. Soc.* **1971**, *93*, 4016–4027. (b) Bubting, J. W.; Meathrel, W. G. *Tetrahedron Lett.* **1971**, *12*, 133–136. (c) Birch, J.; Lehman, P. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2754–2759.

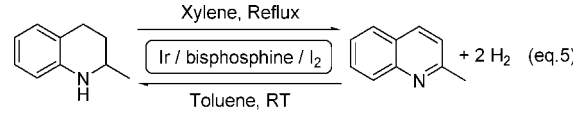
SCHEME 6. The Proposed Possible Mechanism for Ir-Catalyzed Asymmetric Hydrogenation of Quinolines



strated the second pathway might be possible and reasonable. To further understand hydrogenation sequence of C═C and C═N bonds of quinolines, a computational study was performed to rationalize the experimental observations. 2-Methylquinoline was selected as the model substrate and the reaction sequence was examined. Thermodynamic values for hydride addition to 2-methylquinoline were calculated at the DFT/B3LYP level by using the 6-311++G(d,p) basis set. As shown in Scheme 5, the computational result suggested that the first step, 1,4-hydride addition, was more favorable than 1,2-hydride addition.[22a] Therefore, the computational result offered another proof to support the above experimental phenomena.

By analysis of the above hydrogenation phenomena of quinolines and the suggestions of the groups Zhang[19d] and Rueping,[13c] we envisioned that the catalytic process with I_2 as an additive might be a cascade reaction involving a 1,4-hydride addition, isomerization, and 1,2-hydride addition (Scheme 6). We proposed that the oxidative addition of I_2 to Ir(I) to generate the Ir(III) species is also possible in iridium-catalyzed asymmetric hydrogenation of quinolines in the presence of iodine, and the active catalytic species might be the Ir(III) hydrido chloro iodo complex. Therefore, a plausible mechanism was proposed as follows: The oxidative addition of I_2 to the Ir(I) species precursor **A** generates the Ir(III) species, and subsequent heterolytic cleavage of H_2 can occur to form the Ir(III)-H species **B** with hydrogen iodide elimination. The quinoline substrate could coordinate with Ir(III) species **B** (the I and Cl were omitted for clearness), and then 1,4-hydride transfer affords the intermediate **D**. Subsequently the heterolytic cleavage of H_2 with the intermediate **D** gives an enamine **F** and regenerates the Ir(III)-H species **B**. The enamine **F** isomerizes to yield imine **G**, which might be catalyzed by the generated HI acting as a strong Brønsted acid, which was also explained by Rueping.[13c] Imine intermediate **G** could coordinate with Ir(III)-H species **B** to form the intermediate **H**, followed by insertion and σ-bond metathesis to release the product 1,2,3,4-tetrahydroquinolines **P** to complete the catalytic cycle.

Interestingly, the hydrogenation catalyst $[Ir(COD)Cl]_2$/bisphosphine/I_2 was found to also catalyze the dehydrogenation aromatization of 1,2,3,4-tetrahydroquinolines, and hydrogen gas was released. The dehydrogenation reaction was carried out in xylene at reflux temperature for 48 h and the desired product was obtained with 92% yield (eq 5), which provides a potential catalytic system for reversible hydrogenation and dehydrogenation reactions of nitrogen heterocycles[22] toward recyclable hydrogen storage.[23]



Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines. Considering that iridium has been successfully applied to asymmetric hydrogenation of 2-substituted quinolines. Then we examined the $[Ir(COD)Cl]_2$/MeO-BiPhep/toluene/I_2 system for the hydrogenation of 2,3-dimethylquinoline. Unfortunately, it was found that almost racemic product was obtained when the reaction was carried out in toluene at room temperature under 700 psi of hydrogen for 12 h.

On the basis of the above mechanism and observations, we thought that the hydrogenation mechanism of 2,3-disubstituted quinolines was somewhat different from that of 2-substituted quinolines (Scheme 7). For the hydrogenation of 2-substituted quinoline, the hydrogenation of the C═N bond is the enantioselectivity-controlled step (Scheme 6, **H** to **I**), while the enantioselectivity-controlled step of 2,3-disubstituted quinolines is the isomerization of enamine to imine and the hydrogenation of the C═N bond, which is in fact a dynamic kinetic resolution process. To obtain high enantioselectivity, it should meet the

(22) For some examples for dehydrogenation of nitrogen heterocycles, see: (a) Moores, A.; Poyatos, M.; Luo, Y.; Crabtree, R. H. *New J. Chem.* **2006**, *30*, 1675–1678. (b) Pez, G. P.; Scott, A. R.; Cooper, A. C.; Cheng, H. EP Pat. Appl. 2004, 1475349. (c) Schwarz, D. E.; Cameron, T. M.; Hay, P. J.; Scott, B. L.; Tumas, W.; Thorn, D. L. *Chem. Commun.* **2005**, 5919–5921. (d) Cui, Y.; Kwok, S.; Bucholtz, A.; Davis, B.; Whitney, R. A.; Jessop, P. G. *New J. Chem.* **2008**, *32*, 1027–1037. (e) Clot, E.; Eisenstein, O.; Crabtree, R. H. *Chem. Commun.* **2007**, 2231–2233.

(23) For a review, see: van den Berg, A. W. C.; Areán, C. O. *Chem. Commun.* **2008**, 668–681, and references cited therein.

SCHEME 7. The Possible Mechanism of Ir-Catalyzed Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines

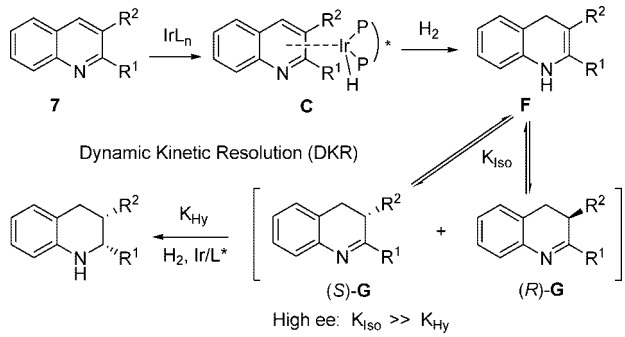
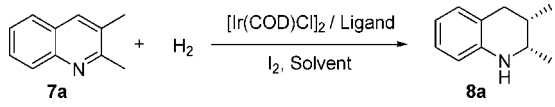


TABLE 5. Ir-Catalyzed Asymmetric Hydrogenation of 2,3-Dimethylquinoline[a]



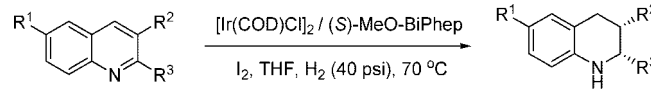
entry	ligand	solvent	*T* (°C)	*P* (psi)	yield (%)[b]	syn/anti[c]	ee of syn[c]
1	(*S*)-MeO-BiPhep	THF	25	700	93	20:1	5
2	(*S*)-MeO-BiPhep	THF	25	200	83	20:1	21
3	(*S*)-MeO-BiPhep	THF	25	80	88[d]	20:1	41
4	(*S*)-MeO-BiPhep	THF	60	80	85	20:1	66
5	(*S*)-MeO-BiPhep	THF	60	40	88[d]	20:1	72
6	(*S*)-MeO-BiPhep	THF	70	40	95	20:1	73
7	(*S*)-MeO-BiPhep	toluene	70	40	57[d]	20:1	55
8	(*S*)-MeO-BiPhep	dioxane	70	40	85	4:1	50
9	(*S*)-MeO-BiPhep	EtOAc	70	40	93	20:1	67
10	(*S*)-MeO-BiPhep	TBME	70	40	8[d]	10:1	40
11	(*S*)-SegPhos	THF	70	40	95	20:1	72
12	(*S*)-SynPhos	THF	70	40	93	20:1	70
13	(*R,R*)-Me-DuPhos	THF	70	40	27[d]	5:1	1
14	(*S*)-BINAP	THF	70	40	95	20:1	60

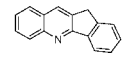
[a] Conditions: 0.25 mmol of quinoline, $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol %), 3 mL of solvent, 12−16 h, [b] Based on **7a**. [c] Determined by HPLC. [d] The convn was determined by ^1H NMR analysis.

requirement that $K_{iso} \gg K_{hy}$. A high temperature could accelerate the rate of isomerization (K_{iso}) of (*S*)-**G** and (*R*)-**G**, and a low pressure of hydrogen gas can decrease the rate of hydrogenation (K_{hy}). Therefore, the asymmetric hydrogenation reactions should be performed in high reaction temperature and low hydrogen pressure.

Next, the effect of pressure and temperature on reactivity and enatioselectivity was studied. When hydrogen gas pressure decreases from 700 to 200 psi, a higher enantioselectivity was obtained (Table 5, 21% vs. 5% ee). When the reaction was performed under 80 psi of hydrogen 41% ee and 88% conversion were obtained. The reaction temperature has a significant effect on the enantioselectivity: 66% ee with full conversion was obtained when the reaction temperature was increased from 25 to 60 °C. The best combination of reaction temperature and pressure of hydrogenation was 70 °C and 40 psi of hydrogen pressure (Table 5, entry 6). Then, the solvent effect was studied again; the reaction proceeded well in THF, dioxane, and ethyl acetate, and low activity was observed in toluene and TBME. The highest enatioselectivity was obtained in THF. Subsequently, some commercially available chiral bisphosphine ligands were tested for the asymmetric hydrogenation of 2,3-dimethylquinoline, and (*S*)-MeO-BiPhep gave the best result

TABLE 6. Iridium-Catalyzed Asymmetric Hydrogenation of 2,3-Disubstituted Quinolines[a]



Entry	$R^1/R^2/R^3$	Yield (%)[b]	Syn/anti[c]	Ee (%)[c]
1	H/Me/Me	92 (**8a**)	> 20:1	73
2	H/Me/Et	93 (**8b**)	> 20:1	85
3	H/Me/*i*-Pr	94 (**8c**)	> 20:1	86
4	H/Me/*n*-Bu	94 (**8d**)	> 20:1	83
5	H/Me/*n*-Pentyl	91 (**8e**)	> 20:1	83
6	H/Me/3-Butenyl	90 (**8d**)[d]	> 20:1	83
7	H/Me/Phenethyl	97 (**8g**)	> 20:1	80
8	H/Me/Benzyl	98 (**8h**)	> 20:1	81
9	Me/Me/Et	91 (**8i**)	> 20:1	84
10	F/Me/Et	89 (**8j**)	> 20:1	83
11	MeO/Me/Et	76 (**8k**)	> 20:1	85
12	H/$(CH_2)_4$	96 (**8l**)	> 20:1	39
13	H/Me/Ph	90 (**8m**)	> 20:1	38
14		93 (**8n**)	> 20:1	86

[a] Conditions: 0.25 mmol of quinoline, $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol%), 3 mL of toluene. [b] Based on **7**. [c] Determined by HPLC. [d] The product was **8d**.

(73% ee). Therefore, the optimized reaction condition is the following: $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep/I_2/THF/70 °C/H_2 (40 psi).

Under the optimized condition, a variety of 2,3-disubstituted quinoline derivatives were investigated. To our pleasure, 2-ethyl-3-methylquinoline was hydrogenated with a higher ee (85% ee) than 2,3-dimethylquinoline (Table 6, entry 2), which was probably attributable to the steric effect. Several 2,3-alkyl-disubstituted quinolines were hydrogenated smoothly to give the corresponding 1,2,3,4-tetrahydroquinolines with full conversions and in 73−86% ee (Table 6, entries 1−11). The C═C double bond in the side chain of substrate **7f** (Table 6, entry 6) could be hydrogenated under the standard conditions. For 2,3,6-trisubstituted quinolines, the reactions proceeded well, and excellent reactivities with good enantioselectivities were obtained (Table 6, entries 9−11). Interestingly, for the cyclic compounds ***8l*** and **8n**, excellent reactivities and diastereoselectivities (up to >20:1, major in the cis isomer) were obtained (Table 6, entries 12 and 14), which was complementary for the trans configuration reported by Du using chiral phosphoric acid as catalyst.[14] For 2-phenyl-substituted quinoline compound **8m**, only moderate 38% ee was obtained, and the reason for this is not clear. It is noteworthy that the successful hydrogenation of 2,3-disubstituted quinolines provides new evidence for the hydrogenation mechanism proposed by us.

Conclusions

In summary, we developed a highly enantioselective hydrogenation of 2-benzylquinolines and 2-functionalized and 2,3-disubstituted quinolines with the $[Ir(COD)Cl]_2$/bisphosphine/I_2

system under mild reaction conditions, and up to 96% ee value was obtained, which provides an efficient and convenient route to synthesize tetrahydroquinolines and their derivatives. Moreover, mechanistic studies revealed the hydrogenation of quinolines involves a 1,4-hydride addition, isomerization, and 1,2-hydride addition. The function of iodine is to activate the Ir(I) to form highly active Ir(III) species. Further investigation on the range of substrates and other heteroaromatic systems is in progress.

Experimental Section

Typical Procedure for Hydrogenation of 2-Benzylquinoline 3a. A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-MeO-BiPhep (3.2 mg, 0.0055 mmol) in toluene (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate **3a** (55 mg, 0.25 mmol) together with 2 mL of toluene were added and the solution was stirred for another 10 min. The hydrogenation was performed at room temperature under H_2 (700 psi) for 12−16 h. After the hydrogen was carefully released, the reaction mixture was purified with a silica gel column eluted with ethyl acetate/petroleum to give pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OD-H, OJ-H, AS-H, and AD-H).

(*R*)-2-Benzyl-1,2,3,4-tetrahydroquinoline (4a): colorless oil, 95% yield, 94% ee, $[\alpha]^{RT}_D$ −104.5 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (m, 1H), 1.99−2.03 (m, 1H), 2.67−2.87 (m, 4H), 3.49−3.51 (m, 1H), 3.73 (br, 1H), 6.37 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 6.95 (m, 2H), 7.22−7.31 (m, 3H), 7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 28.4, 43.2, 52.8, 114.4, 117.4, 121.5, 126.7, 126.9, 128.8, 129.5, 138.7, 144.5; HPLC (OJ-H; elute: hexanes/*i*-PrOH = 95/5; detector: 254 nm; flow rate: 0.8 mL/min), (*S*) t_1 = 15.9 min, (*R*) t_2 = 17.6 min.

Typical Procedure for Hydrogenation of 2-Functionalized Quinoline 5a. A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-MeO-BiPhep (3.2 mg, 0.0055 mmol) in benzene (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate **5a** (62 mg, 0.25 mmol) together with 2 mL of benzene were added and the solution was stirred for another 10 min. The hydrogenation was performed at room temperature under H_2 (800 psi) for 12−16 h. After the hydrogen was carefully released, the reaction mixture was purified with a silica gel column eluted with ethyl acetate/petroleum to give pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OD-H, OJ-H, AS-H, and AD-H).

(*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-phenylethanone (6a): pale yellow oil, 91% yield, 96% ee, $[\alpha]^{25}_D$ −96.6 (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.80−1.84 (m, 1H), 2.00−2.05 (m, 1H), 2.74−2.80 (m, 1H), 2.85−2.89 (m, 1H), 3.16−3.18 (m, 2H), 3.92−3.96 (m, 1H), 4.58 (br, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 6.96 (t, J = 7.1 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.58 (t, J = 7.0 Hz, 1H), 7.96 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 28.4, 45.2, 47.4, 114.9, 117.5, 121.1, 127.1, 128.2, 128.9, 129.4, 133.6, 137.0, 144.5, 199.7; HRMS calcd for $C_{17}H_{17}NONa$ $[M + Na]^+$ 274.1208, found 274.1204; HPLC (OD-H column; hexanes/*i*-PrOH = 80/20; flow rate = 0.8 mL/min) t_1= 8.5 min, t_2 = 10.2 min.

Typical Procedure for Hydrogenation of 2,3-Disubstituted Quinoline 7a. A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-MeO-BiPhep (3.2 mg, 0.0055 mmol) in THF (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate **7a** (39 mg, 0.25 mmol) together with 2 mL THF were added and the solution was stirred for another 10 min. The hydrogenation was performed at 70 °C under H_2 (40 psi) for 12−16 h. After the hydrogen was carefully released, the reaction mixture was purified by a silica gel column eluted with ethyl acetate/petroleum to give pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OD-H, OJ-H, AS-H, and AD-H).

***cis*-2,3-Dimethyl-1,2,3,4-tetrahydroquinoline (8a):** colorless oil, 92% yield, 73% ee, $[\alpha]^{RT}_D$ −19.25 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 7.2 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 2.00−2.05 (m, 1H), 2.49 (dd, J = 16.0, 6.0 Hz, 1H), 2.90 (dd, J = 16.4, 5.2 Hz, 1H), 3.42−3.47 (m, 1H), 3.66 (br, 1H), 6.46 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 18.3, 30.7, 34.0, 50.1, 114.0, 117.1, 120.2, 126.8, 130.0, 144.1; HPLC (OJ-H; elute: hexanes/*i*-PrOH = 95/5; detector: 254 nm; flow rate: 0.8 mL/min), minor isomer t_1 = 12.7 min, major isomer t_2 = 16.6 min.

Typical Procedure for Hydrogenation of Exocyclic Enamines 10. A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-MeO-BiPhep (3.2 mg, 0.0055 mmol) in benzene (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate **10** (62 mg, 0.25 mmol) together with 2 mL of benzene were added and the solution was stirred for another 10 min. The hydrogenation was performed at room temperature under H_2 (800 psi) for 12−16 h. After the hydrogen was carefully released, the reaction mixture was purified by a silica gel column eluted with ethyl acetate/petroleum to give pure product **6a**. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OJ-H).

Typical Procedure for Dehydrogenation of 2-Methyl-1,2,3,4-tetrahydroquinoline. A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-SynPhos (3.6 mg, 0.0055 mmol) in xylene (1 mL) was stirred at room temperature for 10 min in a Schlenk tube, then I_2 (6.4 mg, 0.025 mmol) was added and the solution was stirred for another 10 min, then 2-methyl-1,2,3,4-tetrahydroquinoline (0.074, 0.50 mmol) together with 2 mL of xylene were added. The resulting mixture was allowed to stir at reflux temperature for 48 h. The reaction mixture was purified by a silica gel column eluted with ethyl acetate/petroleum to give pure product 2-methylquinoline (**1a**): colorless oil, 92% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3H), 7.27 (m, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.67 (dt, J = 8.2, 1.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 122.1, 125.8, 126.6, 127.6, 128.8, 129.6, 136.3, 148.1, 159.1.

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Supporting Information Available: Experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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