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Enantioselective Synthesis of Chiral Tetrahydroisoquinolines by Iridium-Catalyzed Asymmetric Hydrogenation of Enamines

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Abstract: Chiral iridium complexes based on spiro phosphoramidite ligands are demonstrated to be highly efficient catalysts for the asymmetric hydrogenation of unfunctionalized enamines with an exocyclic double bond. In combination with excess iodine or potassium iodide and under hydrogen pressure, the complex Ir/(S_a,*R*,*R*)-**3a** provides chiral *N*-alkyltetrahydroisoquinolines in high yields with up to 98% *ee*. The L/Ir ratio of 2:1 is crucial for obtaining a high reaction rate and enantioselectivity. A deuterium labeling experiment showed that an inverse isotope effect exists in this reaction. A possible catalytic cycle including an iridium(III) species bearing two monophosphoramidite ligands is also proposed.

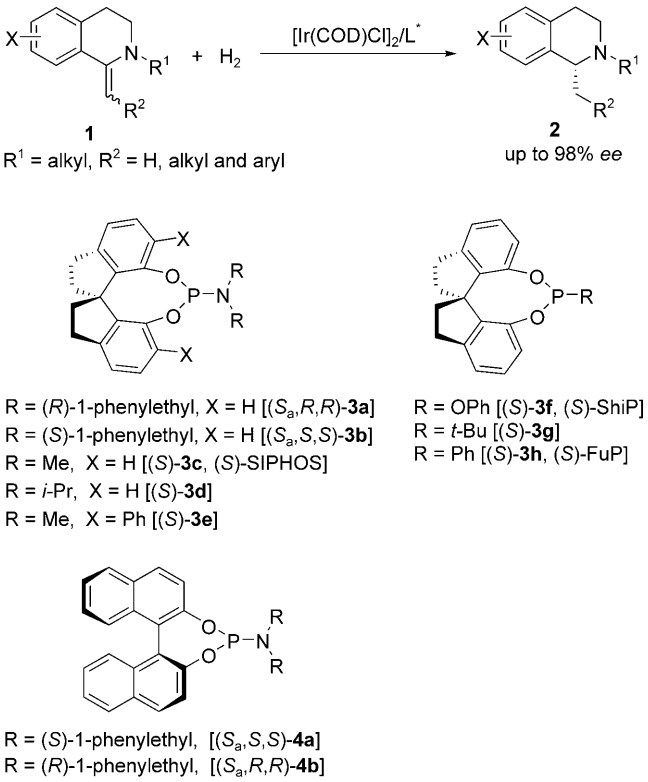
Keywords: asymmetric synthesis; enamines; hydrogenation; iridium; phosphoramidites; tetrahydroisoquinolines

Introduction

The iridium-catalyzed asymmetric hydrogenation of unsaturated compounds such as olefins, imines, and ketones is an elegant method for the preparation of chiral compounds.[1] Chiral iridium complexes bearing a chiral bidentate phosphine ligand such as BINAP,[2] Josiphos,[3] BINAPHANE,[4] MeO-BIPHEP,[5] or a phosphine-phosphoramidite ligand,[6] or a chiral P,N ligand such as PHOX[7] have been demonstrated to be very efficient catalysts for asymmetric hydrogenations. However, the monodentate phosphorus ligands, especially monophosphoramidites, which are widely used in rhodium-catalyzed asymmetric hydrogenation of functionalized olefins,[8] have been less applied in iridium-catalyzed asymmetric hydrogenations.[9] The successful examples for the iridium/monophosphoramidite-catalyzed asymmetric hydrogenations included hydrogenations of imines,[10] α- and β-dehydroamino acids derivatives,[11] substituted quinolines,[12] and enamides.[13] Recently, we reported that chiral iridium complexes of spirophosphoramidites were efficient catalysts for the asymmetric hydrogenation of cyclic enamines, providing chiral cyclic tertiary amines in high enantioselectivities.[14]

The catalytic asymmetric hydrogenation of unfunctionalized enamines is more difficult than the hydrogenation of enamides or other functionalized enamines, mainly due to the lack of an *N*-acyl group, which was demonstrated to be crucial for the enantiocontrol in the hydrogenation of functionalized enamines.[15] To date, only a few examples of the asymmetric hydrogenation of unfunctionalized enamines have been reported. The catalysts such as [(EBTHI)Ti-binaphthol],[16] Rh/diphosphinite,[17] Rh/monophosphonite,[18] and Ir/oxazoline-phosphine[19] have been successfully used in this reaction in moderate to high enantioselectivities. However, compared with the progress achieved in asymmetric hydrogenation of enamides or other functionalized enamines, the asymmetric hydrogenation of unfunctionalized enamines is still in its infancy.[20]

Tetrahydroisoquinolines, widely present in plants and several tissues in mammalian species, is a common structural motif of numerous alkaloids.[21] Asymmetric hydrogenation of *N*-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines, initiated by Achiwa in 1977,[22] has been an efficient method for the synthesis of these alkaloids.[23] However, the hydrogenation of unfunctionalized enamines for the direct synthesis of optically pure *N*-alkyltetrahydroisoquinolines, such as carnegine, armepavine, glaucine and cularine,[24] the most important members of the isoquinoline alkaloids family, has not been documented. Herein, we report the first example of the direct synthesis of chiral *N*-alkyltetrahydroisoquinolines by Ir-(S_a,*R*,*R*)-**3a** complex-



Scheme 1. Asymmetric hydrogenation of *N*-alkyl-1-alkylidene tetrahydroisoquinolines.

catalyzed asymmetric hydrogenation of *N*-alkyl-1-alkylidenetetrahydroisoquinolines **1** (Scheme 1).

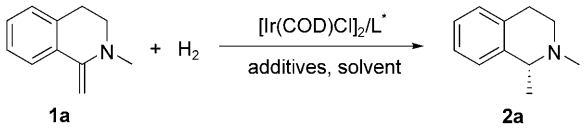
Results and Discussion

The hydrogenation of 2-methyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**1a**) was initially performed in THF under 1 atm H_2 at room temperature in the presence of 1.0 mol% iridium catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and ligand (S_a,*R*,*R*)-**3a**. The reaction was completed in 3 h and the hydrogenation product, (*R*)-1-methyl-2-methyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-**2a**], was isolated in 96% yield with 95% enantiomeric excess (*ee*) (Table 1, entry 1). Lower activity and enantioselectivity (62% *ee*, *R*) was observed using ligand (S_a,*S*,*S*)-**3b** (entry 2). These results demonstrated that (S_a,*R*,*R*)-**3a** was the ligand with matched chiralities and the configuration of product **2a** was mainly controlled by the chirality of the spiro backbone of the ligand. Screening of solvents revealed that THF was the best choice of solvent in terms of activity and enantioselectivity of reaction (entries 1, 3–7). The addition of iodine was also crucial for the reaction. Only trace amount of hydrogenation product was formed if iodine was omitted in the reactions using $[Ir(COD)Cl]_2$ or $[Ir(COD)_2]BF_4$ (entries 8 and 10). However, the $[Ir(COD)I]_2$ can catalyze the reaction without the addition of iodine, and the hydrogenation was further accelerated by adding iodine (entry 9 *vs.* 11). In addition to iodine, the iodides such as KI and Bu_4NI are also able to promote the hydrogenation. For example, the hydrogenation of **1a** was completed within 6 h in the presence of 10 mol% KI, yielding the product (*R*)-**2a** in the same *ee* value as that with added I_2 (entry 12 *vs.* 1). Ligand comparison showed that the binaphthol-based phosphoramidites (S_a,*S*,*S*)-Monophos-pe [(S_a,*S*,*S*)-**4a**] and (S_a,*R*,*R*)-Monophos-pe [(S_a,*R*,*R*)-**4b**][25] were also suitable ligands for the reaction (80% *ee* and 94% *ee*, respectively) and the configuration of product was interestingly mainly determined by the chirality of the amino moiety of the ligand Monophos-pe (entries 21 and 22). In contrast, other monodentate phosphorus ligands (entries 15–20) and bidentate phosphine ligands such as SDP, BINAP and Josiphos (data not shown) were unsuitable for this reaction, giving very low *ee* values. The activity of the catalyst Ir/(S_a,*R*,*R*)-**3a** was remarkable, leading to the hydrogenation of enamine **1a** under 1 atm H_2 at 0 °C and affording the hydrogenation product in even higher enantioselectivity (98% *ee*, entry 23).

A variety of 2-alkyl-1-alkylene-1,2,3,4-tetrahydroisoquinolines were evaluated under the optimized reaction conditions. Introducing a 7-methyl group on the phenyl ring of the substrate gave no effect on the reaction (Table 2, entry 2 *vs.* 1), but stronger electron-donating substituents such as a 6- and/or 7-methoxy on the phenyl ring of the substrate led to slightly lower enantioselectivities (entries 3–5). A small alkyl group on the nitrogen (R^1) of the enamine substrates was necessary for achieving high *ee* values of products. When the R^1 group was changed from methyl (**1a**) or ethyl (**1f**) to benzyl (**1g**) and isopropyl (**1h**), the *ee* values of product decreased dramatically from 98% *ee* to 90% *ee* and 71% *ee*, respectively (entries 7 and 8 *vs.* entries 1 and 6).

If the R^2 group on the terminal carbon of the double bond was not hydrogen, the substrates were usually prepared as a *Z*/*E* mixture. We were encouraged to find that the catalyst Ir/(S_a,*R*,*R*)-**3a** was efficient for the hydrogenations of both (*Z*)- and (*E*)-isomers. For example, when R^2 was a methyl, the enamine substrate **1i** was a mixture of *Z* and *E* isomers (3.5:1) and was hydrogenated to the amine **2i** in 95% *ee* (entry 9). A small R^2 group was important for obtaining high *ee* values of the product. When the R^2 group was ethyl (**1n**) or propyl (**1m**), the corresponding hydrogenation products were obtained in very low enantioselectivities (58% *ee* and 60% *ee*, respectively) (entries 13 and 14). The aryl-substituted enamines **1o** and **1p** (R^2 = Ph) were much less reactive and could be hydrogenated only under 50 atm of H_2 at 25 °C (entries 15 and 16). It is worth noting that the product **2e** is (*R*)-carnegine and the current hydrogenation re-

Table 1. Optimizing the reaction conditions.[a]



1a **2a**

Entry	Ligand	Solvent	Additives	Time [h]	Conversion [%][b]	*ee* [%][c]
1	(S_a,*R*,*R*)-**3a**	THF	I_2	3	100	95 (*R*)
2	(S_a,*S*,*S*)-**3b**	THF	I_2	20	100	62 (*R*)
3	(S_a,*R*,*R*)-**3a**	toluene	I_2	20	3	16 (*R*)
4	(S_a,*R*,*R*)-**3a**	Et_2O	I_2	20	14	42 (*R*)
5	(S_a,*R*,*R*)-**3a**	CH_2Cl_2	I_2	20	100	86 (*R*)
6	(S_a,*R*,*R*)-**3a**	DME	I_2	20	100	94 (*R*)
7	(S_a,*R*,*R*)-**3a**	MeOH	I_2	20	100	50 (*R*)
8	(S_a,*R*,*R*)-**3a**	THF	none	20	4	10 (*R*)
9[d]	(S_a,*R*,*R*)-**3a**	THF	none	32	93	90 (*R*)
10[e]	(S_a,*R*,*R*)-**3a**	THF	none	20	5	12 (*R*)
11[d]	(S_a,*R*,*R*)-**3a**	THF	I_2	4	100	94 (*R*)
12[f]	(S_a,*R*,*R*)-**3a**	THF	KI	6	100	95 (*R*)
13[f]	(S_a,*R*,*R*)-**3a**	THF	Bu_4NI	20	100	92 (*R*)
14	(S_a,*R*,*R*)-**3a**	THF	Et_3N	20	5	30 (*R*)
15	(*S*)-**3c**	THF	I_2	20	17	40 (*R*)
16	(*S*)-**3d**	THF	I_2	20	78	54 (*R*)
17	(*S*)-**3e**	THF	I_2	20	3	25 (*R*)
18	(*S*)-**3f**	THF	I_2	20	100	9 (*S*)
19	(*S*)-**3g**	THF	I_2	20	100	17 (*R*)
20	(*S*)-**3h**	THF	I_2	20	47	4 (*R*)
21	(S_a,*S*,*S*)-**4a**	THF	I_2	20	100	80 (*S*)
22	(S_a,*R*,*R*)-**4b**	THF	I_2	4	100	94 (*R*)
23[g]	(S_a,*R*,*R*)-**3a**	THF	I_2	6	100	98 (*R*)

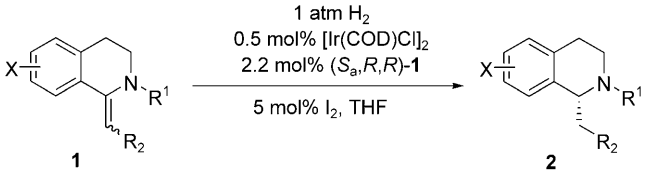
[a] *Reaction conditions:* Ir/L/add./subs. = 1:2.2:5:100, [subs.] = 0.1 M, 1 atm H_2, room temperature.
[b] Determined by GC.
[c] Determined by chiral GC (see Supporting Information).
[d] $[Ir(COD)I]_2$ as precursor.
[e] $[Ir(COD)_2]BF_4$ as precursor.
[f] 10% additives.
[g] At 0 °C.

action provides a practical and enantioselective approach to this important natural alkaloid.

In a systematic study of the influence of L/Ir ratio on the reaction, we found that the L/Ir ratio is important for obtaining high reaction rate and enantioselectivity. When the iridium catalyst was generated from one equivalent of $[Ir(COD)Cl]_2$ and two equivalents of (S_a,*R*,*R*)-**3a** (L/Ir = 1:1) (Figure 1, a), the hydrogenation of **1a** was very slow and the product **2a** was isolated in 87% *ee*. When the L/Ir ratio was increased to 2:1, the reaction became faster and the *ee* value of product **2a** was increased to 95%. Further increasing the L/Ir ratio to 3:1 resulted in a similar reaction rate and the same enantioselectivity as for the reaction with the catalyst having an L/Ir ratio of 2:1. In all these hydrogenations, the *ee* values of product **2a** were very low at the initial stage and dramatically increased after about 30 min (Figure 1, b). This result implied that an active iridium catalyst contains two (S_a,*R*,*R*)-**3a** ligands, which gave a higher reaction rate and higher enantioselectivity, was gradually formed as the reaction progressed.

To confirm that an active iridium species contains two phosphoramidite ligands, we tried to synthesize the iridium complex bearing ligand (S_a,*R*,*R*)-**3a** and monitored the reaction by ^{31}P NMR spectroscopy. Adding two equivalents of ligand to the solution of $[Ir(COD)Cl]_2$ (L/Ir = 1:1) in $CDCl_3$ led to a complete loss of the signal of the free ligand ($\delta = 135.0$ ppm) and to the appearance of a signal corresponding to bound ligand ($\delta = 97.3$ ppm) (Scheme 2), indicating the formation of the complex {Ir(COD)[(S_a,*R*,*R*)-**3a**]Cl}. This structure was confirmed by a single crystal X-ray diffraction analysis (Figure 2).[26] But when another two equivalents of ligand (S_a,*R*,*R*)-**3a** were added, no additional change was observed except for the appearance of the signal of the free ligand. After addition of five equivalents of I_2 to this solution, the signal for free ligand disappeared again within 10 min, thereby giving a new species of iridium complex with

Table 2. Asymmetric hydrogenation of enamines **1** with catalyst Ir-(S_a,*R*,*R*)-**3a**.[a] <



Entry	R^1	R^2	X	*Z*/*E*[b]	**2**	Time [h]	*ee* [%][c]
1	Me	H	H		**2a**	6	98 (*R*)
2	Me	H	7-Me		**2b**	6	98
3	Me	H	6-MeO		**2c**	6	96
4	Me	H	7-MeO		**2d**	6	94
5	Me	H	6,7-$(MeO)_2$		**2e**	6	95 (*R*)
6	Et	H	H		**2f**	6	98
7	Bn	H	H		**2g**	10	90
8	*i*-Pr	H	H		**2h**	10	71
9	Me	Me	H	3.5/1	**2i**	7	95
10	Me	Me	6-MeO	3.0/1	**2j**	7	92
11	Me	Me	7-MeO	3.2/1	**2k**	7	92
12	Et	Me	H	7.3/1	**2l**	7	96
13	Me	*n*-Pr	H	3.4/1	**2m**	10	60
14	Et	Et	H	5.7/1	**2n**	10	58
15[d]	Me	Ph	H	4.3/1	**2o**	5	74
16[d]	Et	Ph	H	5.2/1	**2p**	5	73

[a] *Reaction conditions* are the same as those in Table 1, entry 23, 100% conversion, 90–97% isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by GC or HPLC or SFC (see Supporting Information).
[d] Under 50 atm H_2 at 25 °C.

^{31}P NMR signals at δ = −42.6 and −45.5 ppm, which can catalyze the hydrogenation of **1a** (3 h, 100% conversion, 95% *ee*). However, direct addition of five equivalents of I_2 to the solution of {Ir(COD)-[(S_a,*R*,*R*)-**3a**]Cl} led to the formation of the iridium complex with signals at δ = −42.4 and −45.3 ppm, accompanied by signals for other species at δ = 71.8, 69.0, 65.4 and 62.7 ppm. The iridium species with ^{31}P NMR signals at δ = −42.6 and −45.5 ppm, which was the active catalyst in the reaction, may represent the complex {Ir[(S_a,*R*,*R*)-**3a**]$_2$$I_2$Cl}.[4a,5a]

To further demonstrate that the active catalyst had two (S_a,*R*,*R*)-**3a** ligands coordinated to the iridium ion, we examined the relationship between the optical purity of the catalyst and of the product in the reaction and observed a positive non-linear effect (Figure 3, a). The non-linear effect is believed to

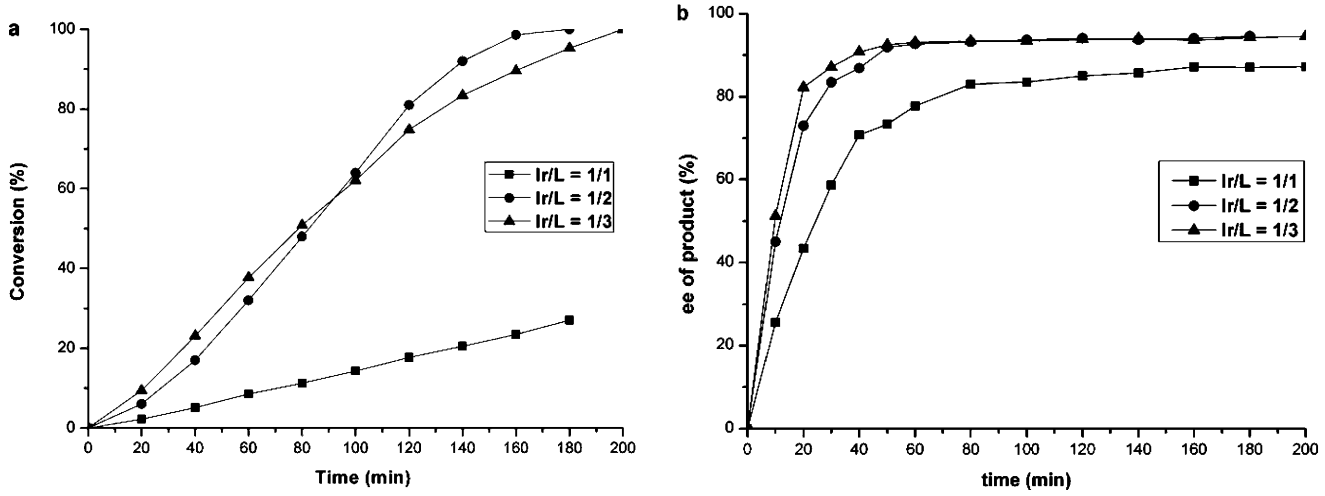
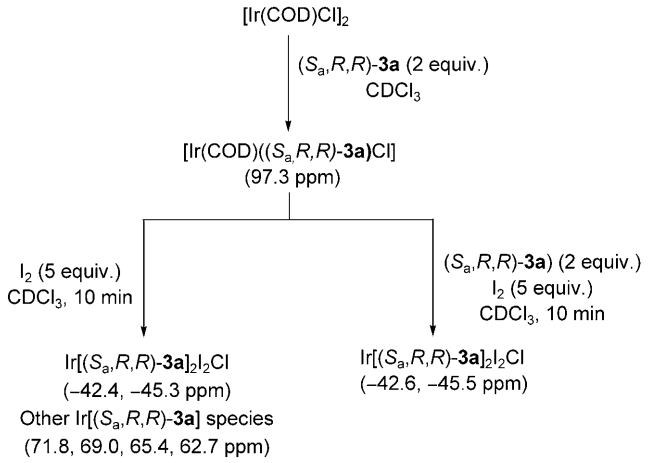


Figure 1. Plot of the effect of L/Ir ratio on the reactivity (**a**) and the *ee* value of product **2a** against time (**b**).



Scheme 2. Detection of Ir-(S_a,*R*,*R*)-**3a** species by ^{31}P NMR.

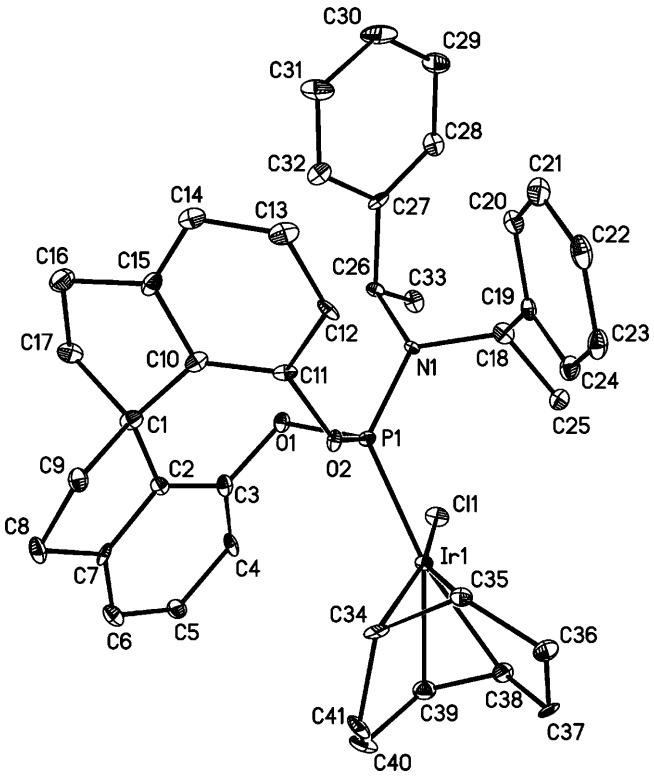


Figure 2. X-ray structure of {Ir(COD)[(S_a,*R*,*R*)-**3a**]Cl}; selected bond lengths [Å] and bond angles [°]: Ir–Cl, 2.376; Ir–P, 2.257; Cl–Ir–P, 90.51.

emerge when the catalyst contains two or more chiral ligands.[27] So, this non-linear effect provides clear proof to support the idea that the iridium complex bearing two (S_a,*R*,*R*)-**3a** ligands is the active catalytic species in the reaction.

Furthermore, a deuterium labeling experiment in the hydrogenation of **1a** was conducted under ambient D_2 pressure. The ^{1}H NMR measurement of product showed that the deuteration took place at both the α- and β-positions (Scheme 3). At the α-position, 80% deuteration was observed, while a multiple deuteration (average 82%) was exhibited at the β-position. This outcome implied that an H/D exchange took place at the β-position. The ^{13}C NMR analysis also showed six deuterated compounds in the product. But, the most surprising observation was that the hydrogenation of **1a** with D_2 was faster than that with H_2 (Figure 3, b), indicating that an inverse isotope effect existed in this reaction.[28]

Although iridium catalysts have been widely applied in the asymmetric hydrogenation of unfunctionalized olefins, the mechanism of iridium-catalyzed hydrogenation of olefins is still poorly understood.[29] To date, two types of catalytic cycles have been suggested for asymmetric hydrogenation of unfunctionalized olefins. Pflatz[30] and Chen[31] proposed an Ir(I)-Ir(III) catalytic cycle, whereas Brandt[32] and Burgess and Hall[33] proposed an Ir(III)-Ir(V) catalytic cycle. In the iridium-catalyzed asymmetric hydrogenations of imines and quinolines, in which the addition of iodine or iodide species was found to be important for obtaining high activity and enantioselectivity, Osborn,[34] Zhang[4a] and Zhou[5a] suggested a catalytic cycle involving an Ir(III)-monohydride intermediate.

Since the additive KI gave a result identical to that obtained by the addition of iodine and because of the obvious inverse isotope effect in current reaction, we proposed an Ir(I)-Ir(III) catalytic cycle involving an Ir-dihydride species for the hydrogenation of unfunctionalized enamines (Scheme 4). With the help of excess I_2 or KI, the Ir(I)-complex **B** (or its dimer **C**) with two phosphoramidite ligands was generated. Oxidative addition of H_2 to Ir(I)-complex **B** yielded the Ir(III)-dihydride intermediate **D**. An enamine was then coordinated to the metal of **D** in a η^2 fashion to form complex **E**. Subsequently, a hydride was transferred from the metal to the unsaturated carbon adjacent to the nitrogen atom, forming an alkyl hydride complex **F**. Finally, the reductive elimination of alkyl hydride of complex **F** gave the product **2a** and regenerated the Ir(I)-complex **B**.

The oxidative addition of H_2 to Ir(I)-complex **B** is generally recognized as the rate-determining step in the hydrogenation of olefins[35] and the inverse isotope effect has also been reported in this step in several examples.[36] Furthermore, the reductive elimination step was likely associated with the C–H/C–D bond-making/bond-breaking *via* a C–H···Ir intermediate **G**,[37] explaining the formation of multiple-deuterated products.

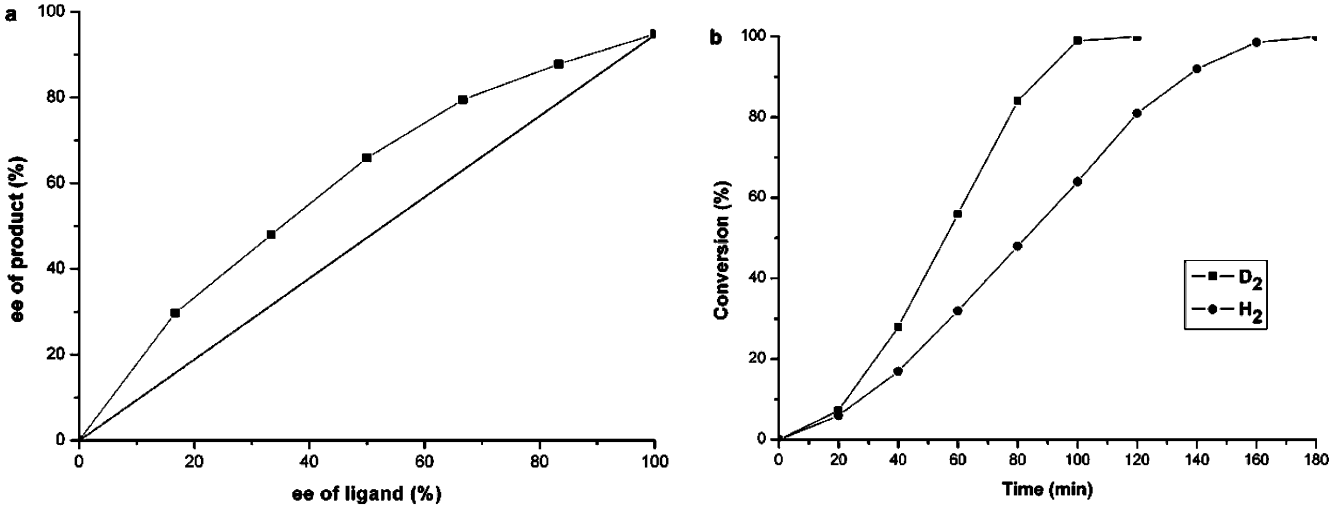
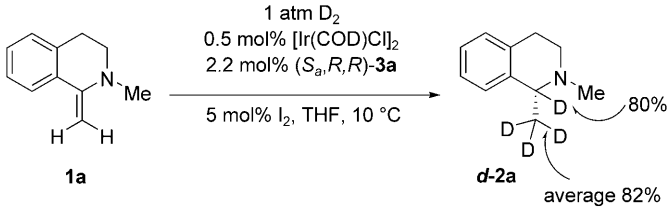


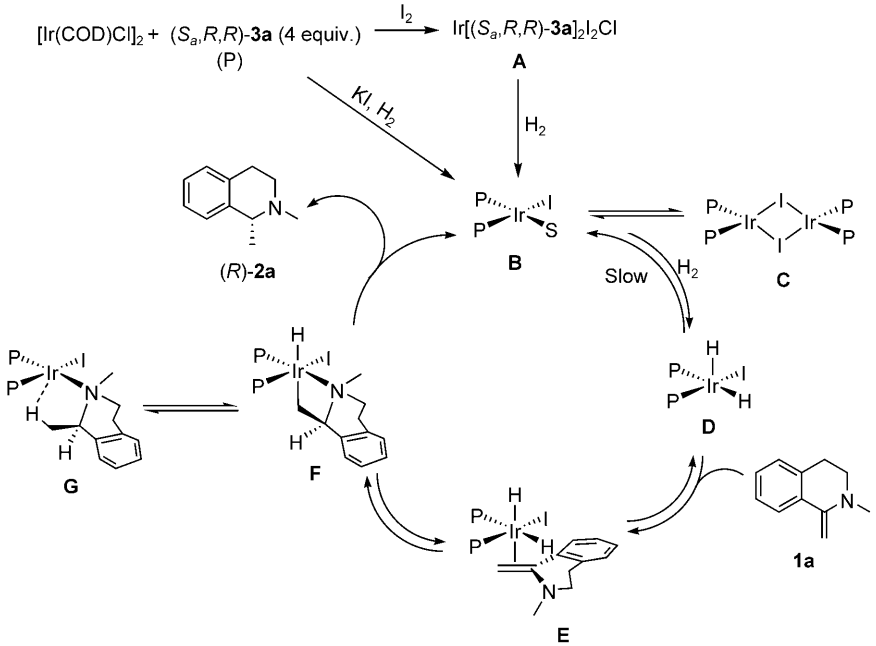
Figure 3. Non-linear effect (**a**) and the conversion of **1a** with H_2 or D_2 against time in hydrogenation (**b**).



Scheme 3. Hydrogenation of **1a** with D_2.

Conclusions

In conclusion, we have disclosed a highly efficient enantioselective hydrogenation of unfunctionalized enamines with an exocyclic double bond, which provided the corresponding chiral *N*-alkyltetrahydroisoquinolines in high yields with up to 98% *ee*. A possible catalytic cycle including an Ir(III) species bearing two monophosphoramidite ligands was also proposed.



Scheme 4. Proposed catalytic cycle for the Ir/(S_a,*R*,*R*)-**3a**-catalyzed asymmetric hydrogenation of enamines **1**.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of Enamines

To a dry Schlenk tube equipped with a stirring bar was added $[Ir(COD)Cl]_2$ (1.7 mg, 2.5 μmol), (S_a,*R*,*R*)-**3a** (5.6 mg, 11 μmol) and anhydrous THF (5.0 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, and iodine (6.4 mg, 25 μmol) and enamines 1 (0.5 mmol) were added. The nitrogen atmosphere in the tube was replaced by hydrogen three times and the reaction solution was stirred at 0 °C under 1.0 atm H_2 for 6–10 h (the conversion was determined by TLC or GC analysis). After removed the solvent under vacuum the residue was purified by flash chromatography on a silica gel column with petroleum ether/ethyl acetate. The enantiomeric excess of the product was determined by GC, or HPLC, or SFC analysis with chiral column (see Supporting Information).

Acknowledgements

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