DOI: 10.1002/adsc.200900870

Highly Enantioselective Hydrogenation of Quinoline and Pyridine Derivatives with Iridium-(P-Phos) Catalyst

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Received: December 17, 2009; Published online: April 7, 2010; Accepted: March 16, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900870.

Abstract: The use of a chiral iridium catalyst generated *in situ* from the (cyclooctadiene)iridium chloride dimer, $[Ir(COD)Cl]_2$, the P-Phos ligand [4,4′-bis(diphenylphosphino)-2,2′,6,6′-tetramethoxy-3,3′-bipyridine] and iodine (I_2) for the asymmetric hydrogenation of 2,6-substituted quinolines and trisubstituted pyridines [2-substituted 7,8-dihydroquinolin-5(6*H*)-one derivatives] is reported. The catalyst worked efficiently to hydrogenate a series of quinoline derivatives to provide chiral 1,2,3,4-tetrahydroquinolines in high yields and up to 96% *ee*. The hydrogenation was carried out at high S/C (substrate to catalyst) ratios of 2000–50000, reaching up to 4000 h^{-1} TOF (turnover frequency) and up to 43000 TON (turnover number). The catalytic activity is found to be additive-controlled. At low catalyst loadings, decreasing the amount of additive I_2 was necessary to maintain the good conversion. The same catalyst system could also enantioselectively hydrogenate trisubstituted pyridines, affording the chiral hexahydroquinolinone derivatives in nearly quantitative yields and up to 99% *ee*. Interestingly, increasing the amount of I_2 favored high reactivity and enantioselectivity in this case. The high efficacy and enantioselectivity enable the present catalyst system of high practical potential.

Keywords: asymmetric hydrogenation; iridium catalysis; P-Phos; pyridines; quinolines

Introduction

Optically active tetrahydroquinolines and decahydroquinolines are important structural units in a number of natural and synthetic products with a wide variety of biological activities.[1] Therefore, it is not surprising that the development of efficient methods to prepare these enantiomerically enriched heterocycles has been an appealing goal in both academia and industry for many years.[1a,b]

Asymmetric homogeneous hydrogenation of heteroaromatic compounds to chiral heterocycles using inexpensive molecular hydrogen and a small amount of chiral transition metal catalyst is perhaps the most straightforward, efficient and atom-economic method, and has been widely employed in the reduction of a series of heteroaryl compounds.[2–11] Zhou and coworkers first reported the Ir-catalyzed asymmetric hydrogenation of 2,6-substituted quinolines with (*R*)-MeO-BIPHEP [6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl] as the ligand to produce chiral tetrahydroquinolines with up to 96% *ee*.[8a,b,e] Later the same group found that iridium catalyst generated from $[Ir(COD)Cl]_2$ (COD = 1,5-cyclooctadiene) and chiral ferrocenyloxazoline P,N ligand or poly(ethylene glycol)-supported ligand was capable of effectively catalyzing the asymmetric hydrogenation of quinolines.[8c,d] Following this significant lead, a number of catalyst systems have been developed to asymmetrically hydrogenate the same class of substrates, and good to excellent enantioselectivities have been observed.[9] We have recently demonstrated that compa-

rable or better results could be achieved when employing P-Phos [4,4′-bis(diphenylphosphino)-2,2′,6,6′-tetramethoxy-3,3′-bipyridine],[10a,f] PQ-Phos {(6,8-dimethyl-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine-1,13-diyl)bis(diphenylphosphine)},[10c] dendrimer-supported BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl][10e] or chiral diphosphinite[10b,d] as the ligand in Ir-catalyzed hydrogenation of 2,6-substituted quinolines. We also described the excellent performance of phosphine-free ruthenium[11a,c] and iridium[11b] complexes to enantioselectively hydrogenate quinoline derivatives. Despite this significant progress, the catalyst efficiency is still far from being practical, as evidenced by the fact that good results could only be obtained at a lower S/C (substrate to catalyst) ratio of 100 in most cases.[8–11] From the viewpoints of both scientific interest and practical applications, it is highly desirable to develop more efficient catalyst systems for the enantioselective hydrogenation of quinolines.

In contrast to the hydrogenation of quinolines, rather few examples of transition metal-catalyzed asymmetric hydrogenation of substituted pyridines have been reported to date, and most of them focused on the reduction of mono- or disubstituted pyridines.[4] In 2007, Rueping et al. found that BINOL (1,1′-binaphthyl-2,2′-diol)-derived chiral phosphoric acids could efficiently catalyze the asymmetric transfer hydrogenation of trisubstituted pyridines by using Hantzsch dihydropyridine as hydrogen source.[12] Enantioenriched hexahydroquinolinones (up to 92% *ee*) were obtained, which could be easily transformed into chiral decahydroquinolines. Shortly after, Zhou and co-workers successfully accomplished Ir-catalyzed asymmetric hydrogenation of this class of challenging substrates, affording the chiral hexahydroquinolinone products with good to excellent enantioselectivities (84–97% *ee*).[4f] However, this catalytic system suffered from low reactivity (S/C ratio of 50). Therefore, it is still a big challenge to realize the highly efficient hydrogenation of pyridine derivatives.

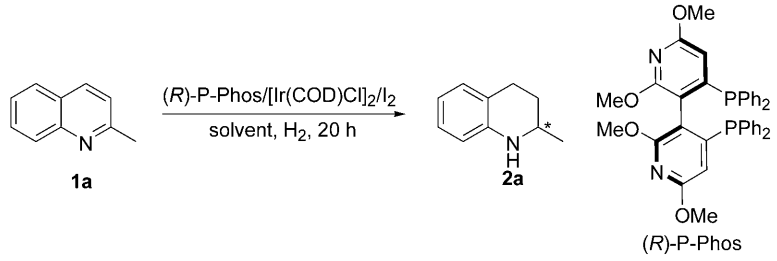
We have recently demonstrated the effectiveness of chiral dipyridylphosphane ligands such as P-Phos in many catalytic asymmetric hydrogenation reactions.[13] Among them, it is notable that the ruthenium complexes, $[Ru(C_6H_6)(P\text{-}Phos)Cl_2]$ and $[RuCl_2(P\text{-}Phos)(DPEN)]$ (DPEN = 1,2-diphenylethane-1,2-diamine) display good air-stability even in solution, which is attributed to the dipyridyl structure of the ligand.[14] Inspired by these exciting findings, we extended the application of this ligand in the asymmetric hydrogenation of heteroaryl compounds. Indeed, in our preliminary communication we found that the Ir-(P-Phos) catalyst was air-stable and recyclable for the asymmetric hydrogenation of quinolines, providing the products in high yields and excellent enantioselectivities.[10a] However, a low S/C ratio of 100 was necessary for good performance of the catalyst. Herein we report a more extensive study into the Ir-catalyzed enantioselective hydrogenation of quinolines with the P-Phos ligand, and the reaction could be carried out at high S/C ratios (up to 50000) with high TON (turnover number) values (up to 43000) and excellent *ee* values (up to 96%) under inert conditions. Interestingly, this catalyst system was also successfully applied to the asymmetric hydrogenation of pyridine derivatives, 2-substituted 7,8-dihydroquinolin-5(6*H*)-ones, furnishing excellent yields and enantioselectivities (up to 99% *ee*).

Results and Discussion

With P-Phos as the ligand and 2-methylquinoline (**1a**) as the model substrate, a systematic study was performed to establish the optimum hydrogenation conditions for the asymmetric hydrogenation of quinolines. Initial hydrogenation experiments were conducted at 700 psi hydrogen pressure and room temperature, employing 1 mol% catalyst generated *in situ* from (*R*)-P-Phos, $[Ir(COD)Cl]_2$ and I_2. Since the obtained iridium catalyst was air-stable,[10a] the manipulations prior to the charging of hydrogen were conducted in air and solvents were used without pre-degassing and drying. A series of organic solvents was firstly screened. It was clear that the choice of solvent was critical in achieving good catalytic activity and enantioselectivity, and the most active and enantioselective catalyst was observed in THF (tetrahydrofuran) (Table 1, entries 1–8). In contrast, with all the other solvents tested, a lower conversion and/or enantioselectivity were obtained. With THF as the solvent, lowering the reaction temperature only slightly improved the enantioselectivity (Table 1, entry 9). A higher reaction temperature led to a decrease of both conversion and enantioselectivity (Table 1, entry 10). The hydrogen pressure did not have much effect on enantioselectivity (Table 1, entry 11), but a lower pressure decreased the conversion (entry 12). Further experimental studies demonstrated that changing the catalyst precursor to a cationic $[Ir(COD)]BF_4$ or $[Ir(COD)]PF_6$ resulted in the deterioration of both reactivity and enantioselectivity with the inversion of the product configuration from *R* to *S* (Table 1, entries 13 and 14). In sharp contrast to Ir-(P-Phos), catalyst Ir-(MeO-BIPHEP) gave the product with only 21% conversion and 28% enantioselectivity under otherwise identical conditions (entry 15). This could be conceivably due to the high air-sensitivity of the Ir-(MeO-BIPHEP) catalyst.

Considering the remarkable impact of the additive on catalytic activity and enantioselectivity in the asymmetric hydrogenation of heteroaryl compounds,[2] we then examined the additive effect. It was notable

Table 1. Asymmetric hydrogenation of **1a** catalyzed by Ir-(P-Phos).[a]



Entry	Solvent	H_2 [psi]	Temperature [°C]	Conversion [%][b]	*ee* [%][b,c]
1	toluene	700	25	84	84 (*R*)
2	benzene	700	25	55	91 (*R*)
3	CH_2Cl_2	700	25	47	88 (*R*)
4[d]	DCE	700	25	76	89 (*R*)
5	THF	700	25	>99	91 (*R*)
6	MeOH	700	25	33	48 (*R*)
7	EtOH	700	25	83	18 (*R*)
8	*i*-PrOH	700	25	60	84 (*R*)
9	THF	700	0	92	92 (*R*)
10	THF	700	55	85	38 (*R*)
11	THF	1500	25	>99	91 (*R*)
12	THF	100	25	90	91 (*R*)
13[e]	THF	700	25	37	47 (*S*)
14[f]	THF	700	25	83	14 (*S*)
15[g]	THF	700	25	28	21 (*R*)

[a] *Reaction conditions:* 1 mmol **1a**, $[Ir(COD)Cl]_2$ (0.5 mol%), (*R*)-P-Phos (1.1 mol%), I_2 (10 mol%), 2 mL undegassed solvent, 20 h.
[b] The conversions were determined by ^1H NMR and the enantioselectivities were determined by HPLC analysis with OJ-H column.
[c] The absolute configurations were determined by comparison with the literature data.
[d] DCE: 1,2-dichloroethane.
[e] $[Ir(COD)]BF_4$ was used.
[f] $[Ir(COD)]PF_6$ was used.
[g] (*R*)-MeO-BIPHEP was used.

that in the absence of any additive, only 15% conversion and 58% enantioselectivity were observed (Table 2, entry 1). However, replacing I_2 with other additives, such as KI, NaI, BiI_3, LiCl, or $(n\text{-Bu})_4NI$, only led to a slow reaction and decreased enantioselectivity (Table 2, entries 3–7). Obviously the use of I_2 as the additive was the best choice.

The good performance of Ir-(P-Phos) prompted us to further enhance the catalytic efficiency. When the S/C ratio was increased to 1000, it was observed that the conversion dropped to 86% in 20 h although with unchanged enantioselectivity of 91% (Table 3, entry 1). Further increasing the S/C ratio to 5000 led to a much lower conversion (16%) and still high *ee* (91%) (Table 3, entry 2). We envisioned that the experimental procedures in air and the use of undegassed and undried solvent resulted in the presence of oxygen in the reaction system, which would cause the partial deactivation and/or decomposition of the catalyst in the hydrogenation process, thereby deteriorating the catalyst activity. This deactivation and/or decomposition did not obviously affect the reaction in the case of high catalyst loading, but remarkably re-

Table 2. Effect of additive on catalytic asymmetric hydrogenation of **1a**.[a]

Entry	Additive	Conversion [%][b]	*ee* [%][c]
1	none	15	58
2	I_2	>99	91
3	KI	78	89
4	NaI	2	8
5	BiI_3	90	88
6	LiCl	20	60
7	$(n\text{-Bu})_4NI$	67	67

[a] *Reaction conditions:* 1 mmol **1a**, $[Ir(COD)Cl]_2$ (0.5 mol%), (*R*)-P-Phos (1.1 mol%), additive (10 mol%), 2 mL undegassed THF, room temperature, experimental procedures in air, 20 h.
[b] The conversions were determined by ^1H NMR.
[c] The enantioselectivities were determined by HPLC analysis with an OJ-H column.

Table 3. Effect of S/C ratio on catalytic asymmetric hydrogenation of **1a**.[a]

Entry	S/C	I_2 [mol%]	Time [h]	Conversion [%][b]	*ee* [%][c]
1	1000	10	20	86	91 (*R*)
2	5000	10	20	16	91 (*R*)
3[d]	5000	10	20	86	91 (*R*)
4[d]	5000	5	20	>99	91 (*R*)
5[d,e]	5000	5	20	63	84 (*R*)
6[d]	10000	2.5	20	>99	91 (*R*)
7[d]	10000	2.5	1	40	91 (*R*)
8[d,e]	10000	2.5	20	61	80 (*R*)
9[d,f]	10000	2.5	20	78	89 (*R*)
10[d,g]	10000	2.5	20	60	90 (*R*)
11[d]	20000	2.5	20	>99	90 (*R*)
12[d,h]	50000	1.25	40	86	90 (*R*)

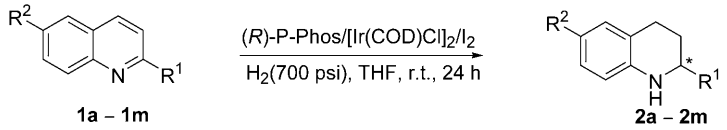
[a] *Reaction conditions:* 2 mmol **1a**, 700 psi H_2, I_2, 2 mL undegassed THF, room temperature, experimental procedures in air, 20 h.
[b] The conversions were determined by ^1H NMR.
[c] The enantioselectivities were determined by HPLC analysis with OJ-H column.
[d] Degassed THF was used with the experimental procedures under N_2 in a glove box.
[e] (*R*)-MeO-BIPHEP was used.
[f] (*R*)-Synphos was used.
[g] (*R*)-Spiropo was used.
[h] 12 mmol substrate in 12 mL degassed THF.

duced the catalytic activity at a high S/C ratio. In this context, the use of dried and degassed solvent in the absence of air might enhance the catalytic efficiency. As expected, under oxygen-free conditions the reaction proceeded smoothly in dried THF at an S/C ratio of 5000 to afford 86% conversion and unchanged enantioselectivity (Table 3, entry 3). Surprisingly, when we decreased the amount of I_2 from 10 mol% to 5 mol%, the reaction went to completion in 20 h without compromising the enantioselectivity (Table 3, entry 4). It was obvious that the amount of I_2 had a critical effect on the hydrogenation, and decreasing the amount of I_2 facilitated the reaction at a high S/C ratio. Similar observations were made in the Ir-catalyzed asymmetric hydrogenation of quinolines with dendrimer-supported BINAP ligand.[10e] As a result, a small amount of 2.5 mol% I_2 was well suited to give full conversion and high enantioselectivity at a high S/C ratio of 10000 (Table 3, entry 6). Notably a high TOF (turnover frequency) of 4000 h^{-1} was observed, and to the best of our knowledge, this was the highest TOF obtained so far for the asymmetric hydrogenation of quinolines (Table 3, entry 7). Further study indicated that the catalyst maintained its activity and enantioselectivity well even at a high S/C ratio of 20000 (Table 3, entry 11). When the S/C ratio was increased to 50000, the catalytic system still gave 86% conversion with retained enantioselectivity in the presence of 1.25 mol% I_2, providing a high TON value of 43000 (Table 3, entry 12). For comparison, the performance of Ir-(MeO-BIPHEP), Ir-Synphos [Synphos = 6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin] and Ir-Spiropo {Spiropo = 7,7′-bis(diphenylphosphinooxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]} catalyst systems was examined, and lower conversions and/or enantioselectivities were observed under otherwise identical conditions (Table 3, entry 4 *vs.* entry 5; entries 8–10 *vs.* entry 6).

A series of 2-substituted and 2, 6-disubstituted quinoline derivatives was then subjected to hydrogenation at a high S/C ratio, and the results are listed in Table 4. The results demonstrated that 2-alkyl-substituted quinoline derivatives could undergo smooth hydrogenation at a high S/C ratio of 10000, giving high isolated yields and good enantioselectivities (Table 4, entries 1–6). The reaction was relatively insensitive to the length of the side chain of 2-alkylated quinolines. Replacing the alkyl group at the 2-position with phenyl group still gave excellent catalytic activity but lower enantioselectivity (Table 4, entry 7). The introduction of either an electron-withdrawing or an electron-donating group on the 6-position had no significant effect on enantioselectivity, but the presence of an electron-donating group reduced the catalytic activity (Table 4, entries 8–10). It was observed that a low S/C ratio of 2000 was necessary for the hydrogenation of electron-donating group-containing substrates **1i** and **1j** to high conversion; while the hydrogenation of electron-withdrawing group-containing substrate **1h** could proceed smoothly at a high S/C ratio of 10000. The presence of a hydroxy group at the side chain enabled the hydrogenation to provide up to 96% *ee* (Table 4, entries 11–13), albeit at a low S/C ratio of 2000. It is noted that the asymmetric hydrogenation of 3-methylquinoline proceeded smoothly at an S/C ratio of 10000 with a full conversion in 24 h, but only the racemic product was obtained.

With 7,8-dihydro-2-methylquinolin-5(6*H*)-one (**1n**) as a model substrate, we next evaluated the performance of the Ir-(P-Phos) catalyst system in the asymmetric hydrogenation of trisubstituted pyridines under oxygen-free conditions. Considering the importance of the solvent effect, a series of organic solvents was tested with the catalyst generated *in situ* from (*S*)-P-Phos and $[Ir(COD)Cl]_2$ and I_2. As can be seen in Table 5, the hydrogenation was sensitive to the choice of reaction medium, and the best enantioselectivity of 89% was obtained in dichloromethane albeit at a lower conversion (Table 5, entry 1). In contrast, other aprotic solvents such as toluene, benzene, PEGDME (polyethylene glycol dimethyl ether, MW ~ 500), DCE (1,2-dichloroethane) and THF gave either lower conversions and/or lower enantioselectivities (Table 5, entries 2–6). Complete conversion was ob-

Table 4. Asymmetric hydrogenation of 2,6-substituted quinoline derivatives catalyzed by Ir-(P-Phos).[a]

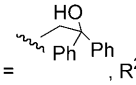


1a – 1m **2a – 2m**

1a: R^1 = methyl, R^2 = H; **1b**: R^1 = ethyl, R^2 = H; **1c**: R^1 = propyl, R^2 = H;
1d: R^1 = butyl, R^2 = H; **1e**: R^1 = pentyl, R^2 = H; **1f**: R^1 = phenylethyl, R^2 = H;
1g: R^1 = phenyl, R^2 = H; **1h**: R^1 = methyl, R^2 = F;
1i: R^1 = methyl, R^2 = methyl; **1j**: R^1 = methyl, R^2 = methoxy;

1k: R^1 = 

, R^2 = H; **1l**: R^1 = 

, R^2 = H; **1m**: R^1 = 

, R^2 = H.

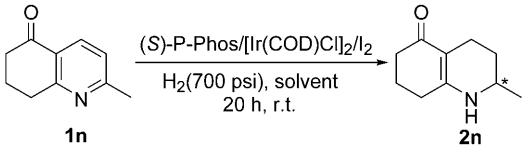
Entry	Substrate	S/C	Yield [%][b]	*ee* [%][c,d]
1	**1a**	10000	99 (**2a**)	91 (*R*)
2	**1b**	10000	98 (**2b**)	92 (*R*)
3	**1c**	10000	98 (**2c**)	91 (*R*)
4	**1d**	10000	99 (**2d**)	90 (*R*)
5	**1e**	10000	99 (**2e**)	92 (*R*)
6	**1f**	10000	99 (**2f**)	90 (*R*)
7	**1g**	10000	98 (**2g**)	60 (*S*)
8	**1h**	10000	99 (**2h**)	88 (*R*)
9	**1i**	2000	99 (**2i**)	88 (*R*)
10	**1j**	2000	89 (**2j**)	90 (*R*)
11	**1k**	2000	98 (**2k**)	92 (*S*)
12	**1l**	2000	97 (**2l**)	96 (*S*)
13	**1m**	2000	97 (**2m**)	87 (*S*)

[a] *Reaction conditions:* 0.3 mmol substrate, I_2 (2.5 mol% for **1a**–**1h**; 5 mol% for **1i**–**1m**), 0.6 mL degassed THF, room temperature, 24 h.
[b] Isolated yield.
[c] The enantioselectivities were determined by HPLC analysis with OJ-H (**2a**–**2e, 2g, 2i**–**2j**), OD-H (**2h**, **2k** and **2m**), AS-H (**2f**) and OJ (**2l**) columns.
[d] The absolute configurations were determined by comparison with the literature data.

served in methanol, but a lower *ee* of 66% was obtained (Table 5, entry 7). With dichloromethane as the reaction medium, we then turned our attention to the additive effect. The observation of the critical effect of I_2 in the asymmetric hydrogenation of quinolines prompted us to investigate whether the catalytic performance could be improved by varying the amount of I_2 (Table 5, entries 8–11). In the absence of any additive, no reaction was observed. Increasing the amount of I_2 to 10 mol% led to 87% conversion and 91% enantioselectivity. Adding 20 mol% I_2 gave a complete conversion and a better *ee* of 95%. When more I_2 was added to the reaction mixture, full conversion and slightly lower enantioselectivity were obtained (Table 5, entry 11). Lowering the reaction temperature to 0 °C had no obvious effect on either reactivity or enantioselectivity, but higher reaction temperature reduced the enantioselectivity (Table 5, entries 12 and 13). Decreasing the hydrogen pressure resulted in unchanged reactivity but lower enantioselectivity (Table 5, entry 14). To test the effect of air on the reaction, the operation prior to the charging of hydrogen was carried out in air and the solvent was used without drying and degassing. Disappointingly, only 87% conversion and 88% enantioselectivity were observed (Table 5, entry 15). Next the catalytic performance of Ir-(P-Phos) at different S/C ratios was investigated. It was found that increasing the S/C ratio from 200 to 1000 had no significant effect on the reactivity, but the enantioselectivities decreased gradually (95% *vs.* 88%) (Table 5, entries 16–18). Switching the ligand to MeO-BIPHEP, Synphos or Spiropo at an S/C ratio of 100 resulted in a similar conversion, but the enantioselectivity was reduced (Table 5, entries 19–21).

Based on the optimal conditions, the asymmetric hydrogenation of a series of trisubstituted pyridine derivatives was conducted, and the results are listed in Table 6. Generally, nearly quantitative yields were obtained for all the substrates along with high enantioselectivities. Excellent *ee* values were obtained in the hydrogenation of 2-alkyl-substituted substrates, and the length of the alkyl group affected the enantioselectivity slightly (Table 6, entries 1–7). For example,

Table 5. Asymmetric hydrogenation of **1n** catalyzed by Ir-(P-Phos).[a]

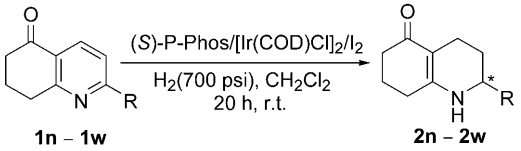


Entry	Solvent	I_2 [%]	Temperature [°C]	Conversion [%][b]	*ee* [%][b,c]
1	CH_2Cl_2	2	25	41	89 (*S*)
2	benzene	2	25	43	74 (*S*)
3	toluene	2	25	29	71 (*S*)
4	DCE	2	25	42	85 (*S*)
5	THF	2	25	79	59 (*S*)
6	PEGDME	2	25	45	52 (*S*)
7	MeOH	2	25	>99	66 (*S*)
8	CH_2Cl_2	0	25	<1	Nd
9	CH_2Cl_2	10	25	87	91 (*S*)
10	CH_2Cl_2	20	25	>99	95 (*S*)
11	CH_2Cl_2	25	25	>99	94 (*S*)
12	CH_2Cl_2	20	0	>99	94 (*S*)
13	CH_2Cl_2	20	40	>99	90 (*S*)
14[d]	CH_2Cl_2	20	25	>99	91 (*S*)
15[e]	CH_2Cl_2	20	25	87	88 (*S*)
16[f]	CH_2Cl_2	20	25	>99	91 (*S*)
17[g]	CH_2Cl_2	20	25	>99	89 (*S*)
18[h]	CH_2Cl_2	20	25	95	88 (*S*)
19[i]	CH_2Cl_2	20	25	>99	89 (*R*)
20[j]	CH_2Cl_2	20	25	>99	88 (*R*)
21[k]	CH_2Cl_2	20	25	>99	89 (*R*)

[a] *Reaction conditions:* 0.15 mmol **1n**, $[Ir(COD)Cl]_2$ (0.5 mol%), (*S*)-P-Phos (1.1 mol%), I_2, 0.7 mL degassed solvent, room temperature, 20 h.
[b] The conversions were determined by ^1H NMR and the enantioselectivities were determined by HPLC analysis with OD-H column.
[c] The absolute configurations were determined by comparison with the literature data.
[d] With 100 psi H_2.
[e] The catalyst was prepared in undegassed CH_2Cl_2 without use of glove box.
[f] S/C = 200.
[g] S/C = 500.
[h] S/C = 1000.
[i] (*R*)-MeO-BIPHEP was used.
[j] (*R*)-Synphos was used.
[k] (*R*)-Spiropo was used.

substrate **1t** underwent exceedingly efficient hydrogenation to give 98% yield and 99% enantioselectivity (Table 6, entry 7). It was notable that asymmetric hydrogenation of pyridine **1n** led to 98% yield and 95% *ee* (Table 6, entry 1). When Ir-(MeO-BIPHEP) was used for this reaction, the yield and enantioselectivity were reported to be 80% and 86%, respectively.[4f] Replacing the alkyl group at 2-position with the phenyl group eroded the enantioselectivity (Table 6, entry 8), but the 2-benzyl- and 2-phenethyl-substituted 7,8-dihydroquinolin-5(6*H*)-ones underwent smooth hydrogenation to afford 92% and 96% *ee*, respectively (Table 6, entries 9 and 10). We also tried the hydrogenation of other trisubstituted pyridines that are not fused to a cyclohexanone, such as **1x** and **1y**, but no reaction was observed.

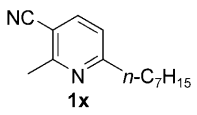
Table 6. Asymmetric hydrogenation of 2-substituted 7,8-dihydroquinolin-5(6*H*)-one derivatives catalyzed by Ir-(P-Phos).[a]

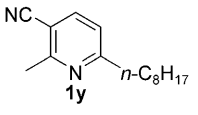


1n: R = methyl; **1o:** R = propyl; **1p** R = pentyl; **1q**: R = hexyl; **1r**: R = heptyl; **1s**: R = octyl; **1t**: R = decyl; **1u**: R = phenyl; **1v**: R = benzyl; **1w**: R = phenylethyl.

Entry	Substrate	Yield [%][b]	*ee* [%][c,d]
1	**1n**	98	95 (*S*)
2	**1o**	96	94 (*S*)
3	**1p**	97	95 (*S*)
4	**1q**	97	97 (*S*)
5	**1r**	96	93 (*S*)
6	**1s**	98	97 (*S*)
7	**1t**	98	99 (*S*)
8	**1u**	99	81 (*R*)
9	**1v**	98	92 (*R*)
10	**1w**	99	96 (*S*)

[a] *Reaction conditions:* 0.15 mmol substrate, $[Ir(COD)Cl]_2$ (0.5 mol%), (*S*)-P-Phos (1.1 mol%), I_2 (20 mol%), 0.6 mL degassed CH_2Cl_2, room temperature, 20 h.
[b] Isolated yield.
[c] The enantioselectivities were determined by HPLC analysis with OD-H (**2n–2t, 2v, 2w**) and AS-H (**2u**) columns.
[d] The absolute configurations were determined by comparison with the literature data.





Conclusions

In conclusion, the results presented in this paper indicated that the iridium complex generated *in situ* from $[Ir(COD)Cl]_2$, P-Phos and I_2 was an excellent catalyst for the asymmetric hydrogenation of a wide range of 2,6-substituted quinolines and trisubstituted pyridines [2-substituted 7,8-dihydroquinolin-5(6*H*)-one derivatives], affording high yields and enantioselectivities. In the asymmetric hydrogenation of quinolines, the catalyst performed efficiently at high S/C ratios of 2000–50000 to produce chiral 1,2,3,4-tetrahydroquino-

lines in excellent yields and up to 96% *ee*. Notably up to 4000 h^{-1} TOF and 43000 TON values were achieved. The amount of additive I_2 had a critical effect on the catalytic reactivity, and decreasing I_2 amount favored the hydrogenation at lower catalyst loadings. The effectiveness of this catalyst system was further demonstrated by the excellent yields and enantioselectivies observed in the hydrogenation of trisubstituted pyridines [2-substituted 7,8-dihydroquinolin-5(6*H*)-one derivatives]. In contrast to the hydrogenation of quinolines, increasing the amount of I_2 facilitated the reaction in the case of hydrogenation of pyridines. Owing to the extraordinary performance of this catalyst system, there is good potential for its practical applications in large-scale settings.

Experimental Section

General Methods

Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 106 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. Optical rotations were measured with PerkinElmer 341 polarimeter. All organic solvents were dried using standard, published methods and were distilled before use. All other chemicals were used as received from Aldrich or Acros without further purification.

Typical Procedure for Asymmetric Hydrogenation of 2,6-Substituted Quinolines

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and the ligand (*R*)-P-Phos (2.0 mg, 0.003 mmol) in THF (2.0 mL) was stirred at room temperature for 10 min in a glovebox. The catalyst was transferred by a syringe to a stainless steel autoclave, in which I_2 and a substrate (0.3–2.0 mmol) in 0.6–2 mL THF were placed beforehand. The hydrogenation was performed at room temperature under H_2 (700 psi) for 24 h. After carefully releasing the hydrogen, the reaction mixture was diluted with dichloromethane (5 mL) followed by the addition of saturated sodium carbonate aqueous solution (2.0 mL). After stirring for 15 min, the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuum to give the crude product. Purification on a silica gel column gave the pure product. The enantiomeric excess was determined by HPLC with a chiral column (OJ-H, OD-H, or AS-H). For details, see Supporting Information.

Typical Procedure for Asymmetric Hydrogenation of Trisubstituted Pyridine Derivatives

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and (*S*)-P-Phos (2.0 mg, 0.003 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 10 min in a glovebox. The catalyst was transferred by a syringe to a stainless steel autoclave, in which I_2 (15.2 mg, 0.06 mmol) and substrate (0.3 mmol) were placed before hand. The hydrogenation was performed at room temperature under H_2 (700 psi) for 20 h. After carefully releasing the hydrogen gas, the reaction mixture was diluted with dichloromethane (5 mL) followed by the addition of saturated sodium carbonate aqueous solution (2.0 mL). After stirring for 15 min, the aqueous layer was extracted with CH_2Cl_2 (1×3 mL). The combined organic layers were dried with sodium sulfate and concentrated under vacuum to give the crude product. Purification on an Al_2O_3 column gave the pure product. The enantiomeric excess was determined by HPLC with a chiral column (OD-H, or AS-H). For details, see Supporting Information

Acknowledgements

Financial supports from National Natural Science Foundation of China (20873179 and 20973178), the Ministry of Science and Technology under grant Nos. 2007CB935904 and 2010CB833305, Renmin University of China, the Hong Kong Research Grants Council (PolyU 5001/07P), the Hong Kong UGC AoE Scheme (AoE P/10-01) and the Hong Kong Polytechnic University Areas of Strategic Development Fund, are gratefully acknowledged.

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