Novel Ir–SYNPHOS® and Ir–DIFLUORPHOS® Catalysts for Asymmetric Hydrogenation of Quinolines

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Abstract: Novel Ir–SYNPHOS and Ir–DIFLUORPHOS catalysts were synthesized and used for the synthesis of tetrahydroquinolines via asymmetric hydrogenation of the corresponding quinoline derivatives.

Key words: catalysts, iridium, hydrogenation, enantioselectivity

Over the last few years, tetrahydroquinoline derivatives **1** have stimulated greatest interest due to their biological activities. Many simple synthetic 1,2,3,4-tetrahydroquinolines are used as potential drugs.[1] Among them, the 2,4,6-trisubstituted tetrahydroquinoline **2**[2] exhibited activity as a bradykinin antagonist with muscarinic receptors, L-689,560 (**3**)[3] is a potent NMDA antagonist and (–)-galipeine (**4**)[4] can be used against fevers (Figure 1). Because the synthetic utility of this family of compounds is well established, synthetic methods for the enantioselective synthesis of 2-substituted tetrahydroquinolines were reported[1] including intramolecular aza-Diels–Alder reactions.[5]

The direct asymmetric hydrogenation of aromatic compounds[6] and more particularly of 2-substituted quinolines derivatives is a convenient route to synthesize optically active 2-substituted tetrahydroquinoline derivatives **1**. Recently, Zhou and co-workers reported the first catalytic asymmetric hydrogenation of quinolines using $[IrCl(cod)]_2$/MeO-Biphep/I_2[7a] and chiral ferrocenyloxazoline-derived N,P ligands[7b] as catalysts with good yields and high enantioselectivities. They described a new strategy for the asymmetric hydrogenation of quinolines by using chloroformate[7c] as an activating reagent. Good results were also obtained with the air-stable Ir(P-PHOS) complex and their immobilization in poly(ethyleneglycol)dimethyl ether (DMPEG)[8a] together with chiral phosphinite H8-BINAPO[8b] and chiral diphosphinite ligand derived from (*R*)-1,1′spirobiindane-7,7′-diol at a high substrate/catalyst ratio.[8c] A chiral diphosphonite, derived from BINOL with an achiral diphenylether backbone[9a] and Ir(BINAP)-cored dendrimers[9b] were also used.

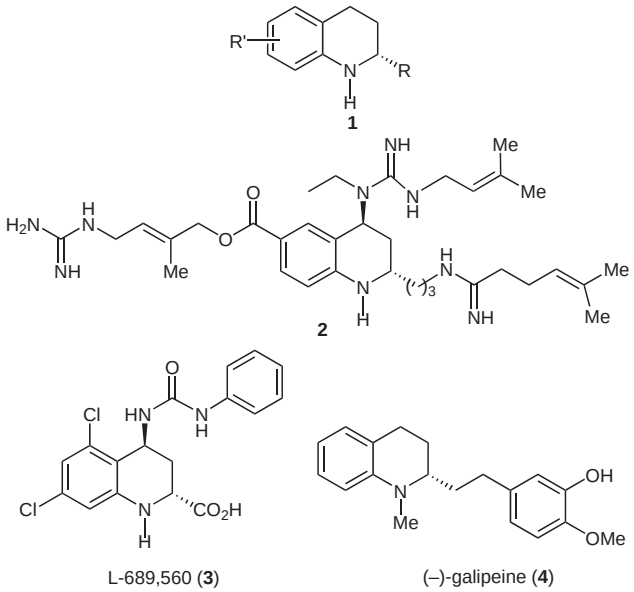

Figure 1

In previous communications, we have described the synthesis of new atropisomeric diphosphines (Figure 2) named SYNPHOS[10] and DIFLUORPHOS.[11]

Our studies have demonstrated both their relevant steric and electronic properties and their catalytic performance[12] in ruthenium-promoted hydrogenation reactions.[13] We have recently reported the preparation of a new generation of Ir–SYNPHOS catalysts[14a] which were fully characterized. Since the tetrahydroquinoline is an extremely important unit that can be found in many synthetic and bioactive compounds and as part of our continuing interest in expanding the catalytic properties of our ligands in homogeneous hydrogenation reactions,[13] we wish to report the synthesis and a new application of novel chiral Ir–

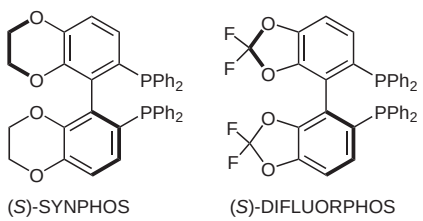

Figure 2

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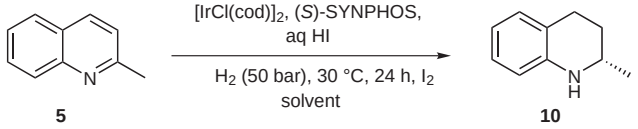
SYNPHOS and Ir–DIFLUORPHOS catalysts for the asymmetric hydrogenation of quinoline derivatives.

We first examined the Ir–SYNPHOS-promoted hydrogenation reaction of 2-methylquinoline (**5**, Scheme 1). Chiral iridium complexes were prepared in situ by stirring the $[IrCl(cod)]_2$ together with (*S*)-SYNPHOS at room temperature in toluene for 1 hour followed by the addition of 10 equivalents of aqueous HI for 45 minutes. The catalytic tests were performed at 30 °C under 50 bar of hydrogen pressure with a substrate/catalyst ratio (S/C) of 100 (Scheme 1) in the presence of a catalytic amount of iodine. Preliminary studies were carried out by varying both the solvent of the hydrogenation reaction and the hydrogen pressure (Table 1). Under these experimental conditions, the hydrogenation of 2-methylquinoline (**5**) to **10** demonstrated to be highly solvent dependent. In alcoholic solvents such as MeOH and *i*-PrOH, 2-methyl-1,2,3,4-tetrahydroquinoline **10** was obtained with both moderate conversions and enantioselectivities (entries 1 and 2, 40% and 20% conv., 27% and 47% ee, respectively). When an aprotic solvent such as CH_2Cl_2 was used (entry 3), an increased conversion and selectivity were reached (entry 3, 70% conv., 87% ee). Using a mixture of THF–MeOH (9:1) led to the formation of **10** with excellent conversion and good enantioselectivity (entry 4, 98% conv., 87% ee). Similar results were achieved when the hydrogenation of **5** was performed in toluene–THF (9:1, entry 5, 100% conv., 86% ee). Finally, the optimal conditions were achieved when 2-methylquinoline (**5**) was hydrogenated in THF with quantitative conversion and 90% of enantioselectivity (entry 6) although no improvement was observed in lowering either the temperature to 10 °C (entry 7) or the pressure from 30 to 5 bar which resulted in decreased conversions and ee (entries 8 and 9).



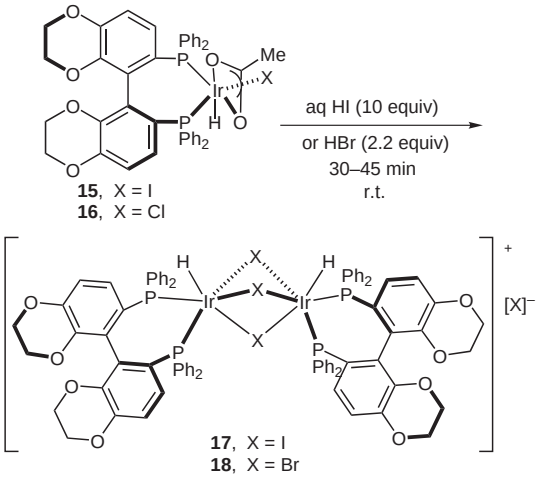
Scheme 1

Next, a comparative study was carried out using these optimized conditions with a new generation of Ir–(*S*)-SYNPHOS catalysts (Scheme 2) recently synthesized[14a] in our group and this study was extended to a series of quinoline derivatives **5**–**9** (Scheme 3). The mononuclear Ir catalysts IrI(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**15**] and IrCl(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**16**] were prepared from $[IrX(cod)]_2$ (X = I, Cl) according to our convenient one-pot procedure[14a] (Scheme 2). The effect of halide variation was studied by adding either aqueous HI or methanolic HBr to the mononuclear catalysts (*S*)-**15** and (*S*)-**16** to generate the corresponding cationic triply halogen-bridged dinuclear iridium(III) complexes of SYNPHOS (*S*)-**17** and (*S*)-**18** which were tested as catalysts for the asymmetric hydrogenation of quinolines **5**–**9** (Table 2).

Table 1 Optimization of the Asymmetric Hydrogenation of 2-Methylquinoline (**5**)

Entry	P (bar)	Solvent	Conv. (%)[a]	ee (%)[b]
1	50	MeOH	40	27
2	50	*i*-PrOH	20	47
3	50	CH_2Cl_2	70	87
4	50	THF–MeOH (9:1)	98	87
5	50	Toluene–THF (9:1)	100	86
6	50	THF	100	90
7	50	THF/10 °C	100	88
8	30	THF	97	73
9	5	THF	96	64

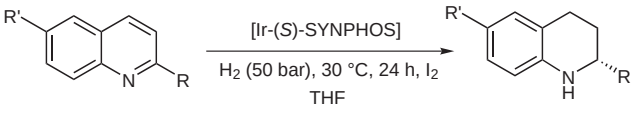
[a] Conversions were determined by ^{1}H NMR analysis of the crude product.
[b] The ee values were determined by HPLC analysis (chiralcel OD-H column).



Scheme 2

The screening tests were carried out on a 1 mmol scale in THF under 50 bar of hydrogen pressure at 30 °C by using both 1 mol% of the Ir–SYNPHOS complexes $[Ir_2I_3H_2$(*S*)-synphos$_2]^+I^-$ [(*S*)-**17**], $[Ir_2Br_3H_2$(*S*)-synphos$_2]^+Br^-$ [(*S*)-**18**] (Scheme 2) and the in situ generated Ir catalyst $[IrCl(cod)]_2$/(*S*)-SYNPHOS/HI. As illustrated in Table 2, all hydrogenations exhibited good levels of both conversion (up to 100%) and enantioselectivity (up to 91%). The hydrogenation of 2-methylquinoline (**5**) to **10** proceeded smoothly with quantitative conversion and 85% ee with IrI(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**15**] and 10 equivalents of aqueous HI (entry 1) although a better 91% ee was reached using IrI(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**15**] with 2.2 equivalents of methanolic HBr (entry 2). Fully comparable conversions and enantioselectivities were obtained with both IrCl(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**16**] with 2.2 equivalents of methanolic HBr and the in situ generated $[IrCl(cod)]_2$/(*S*)-SYNPHOS/HI (entries 3 and 4, 90% ee).

These results compare favorably with the asymmetric hydrogenation of 2-methylquinoline (**5**) with benzylchloroformate as an activating agent (83% ee).[7c] Afterwards, 2-substituted quinolines **6**–**9** were hydrogenated with the Ir–SYNPHOS-based catalytic systems. As previously outlined for **5**, the best results for asymmetric hydrogenation of **6** to **11** were obtained by using IrCl(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**16**] with 2.2 equivalents of methanolic HBr and the in situ generated [IrCl(cod)]$_2$/(*S*)-SYNPHOS/HI with ee up to 88% (entries 7 and 8) although a lower ee was attained by using IrI(H)(O_2CMe)[(*S*)-synphos] [(*S*)-**15**] with 2.2 equivalents HBr (entries 5 and 6, 80% ee). Iridium-promoted hydrogenation reaction of **7** with (*S*)-**15** and 2.2 equivalens HBr and with (*S*)-**16** and 2.2 equivalents HBr furnished the corresponding tetrahydroquinoline **12**, respectively, with 87% and 80% ee (entries 9 and 10). Comparable ee were observed for the asymmetric hydrogenation of **8** to **13** both with (*S*)-**15** and 2.2 equivalents HBr and (*S*)-**16** and 2.2 equivalents HBr (entries 11 and 12, up to 88% ee). Finally, the Ir-catalyzed hydrogenation of 2-phenylquinoline **9** to **14** was performed with lower conversions and ee values up to 66% (entries 13–15, conv. 70–92%, ee 56–66%, respectively).



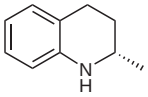
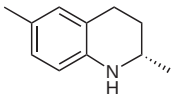
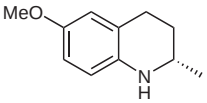
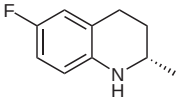
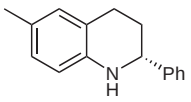
5, R = Me, R' = H
6, R = Me, R' = Me
7, R = Me, R' = OMe
8, R = Me, R' = F
9, R = Ph, R' = H

10, R = Me, R' = H
11, R = Me, R' = Me
12, R = Me, R' = OMe
13, R = Me, R' = F
14, R = Ph, R' = H

Scheme 3

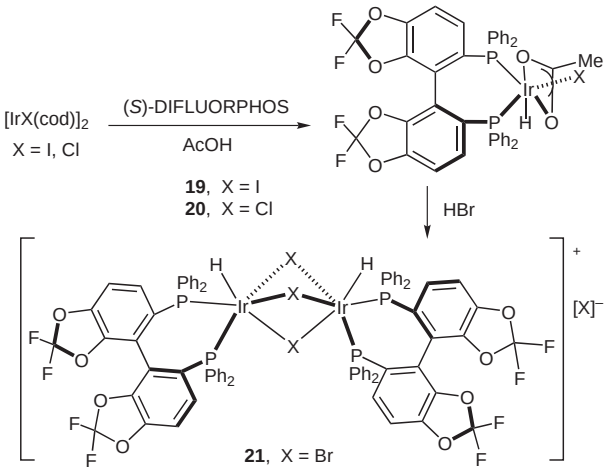
Afterwards, this study was extended to novel iridium catalysts based upon DIFLUORPHOS ligand. The Ir–DIFLUORPHOS complexes were prepared in situ by mixing [IrCl(cod)]$_2$ with (*S*)-DIFLUORPHOS and in a simple

Table 2 Asymmetric Hydrogenation of Quinolines **5**–**9** with Ir–(*S*)-SYNPHOS Catalysts

Entry	Substrate	[Ir–(*S*)-SYNPHOS] catalyst	Conv. (%)[a]	Product	ee (%, conf.)[b]
1	**5**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HI	100		85 (*S*)
2	**5**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HBr	100	**10**	91 (*S*)
3	**5**	IrCl(H)(O_2CMe)[(*S*)-synphos] (**16**)/HBr	100	**10**	90 (*S*)
4	**5**	in situ [IrCl(cod)]$_2$/(*S*)-synphos/HI	100	**10**	90 (*S*)
5	**6**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HI	>95		80 (*S*)
6	**6**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HBr	100	**11**	80 (*S*)
7	**6**	IrCl(H)(O_2CMe)[(*S*)-synphos] (**16**)/HBr	100	**11**	88 (*S*)
8	**6**	in situ [IrCl(cod)]$_2$/(*S*)-synphos/HI	100	**11**	88 (*S*)
9	**7**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HBr	92		87 (*S*)
10	**7**	IrCl(H)(O_2CMe)[(*S*)-synphos] (**16**)/HBr	100	**12**	80 (*S*)
11	**8**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HBr	100		88 (*S*)
12	**8**	IrCl(H)(O_2CMe[(*S*)-synphos] (**16**)/HBr	99	**13**	82 (*S*)
13	**9**	IrI(H)(O_2CMe)[(*S*)-synphos] (**15**)/HBr	70		58 (*R*)
14	**9**	IrCl(H)(O_2CMe)[(*S*)-synphos] (**16**)/HBr	80	**14**	56 (*R*)
15	**9**	in situ [IrCl(cod)]$_2$/(*S*)-synphos[c]	92	**14**	66 (*R*)

[a] Conversions were determined by ^{1}H NMR analysis of the crude product.
[b] The ee values were determined by HPLC analysis using Chiralcel OD-H or Chiralcel OJ column.
[c] Hydrogenation was carried out in toluene.

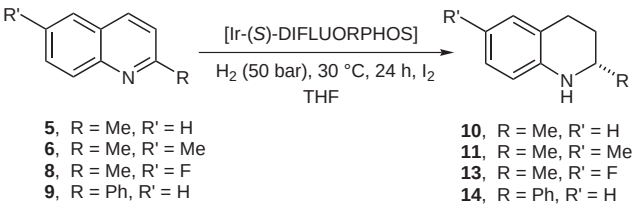
one-pot reaction of $[IrX(cod)]_2$ (X = I, Cl) with 2 equivalents of (*S*)-DIFLUORPHOS and 10 equivalents of acetic acid affording mononuclear complexes IrI(H)(O_2CMe)[(*S*)-difluorphos] [(*S*)-**19**] and IrCl(H)(O_2CMe)[(*S*)-difluorphos] [(*S*)-**20**]. The corresponding cationic complex (*S*)-**21** was synthesized by adding 2.2 equivalents of methanolic HBr to (*S*)-**19** and (*S*)-**20** (Scheme 4).



Scheme 4

Once prepared, these Ir catalysts were screened for the asymmetric hydrogenation of quinolines derivatives **5**, **6**, **8**, and **9**. The catalytic tests were performed on a 1 mmol scale in THF under 50 bar of hydrogen pressure at 30 °C by using 1 mol% of the Ir–DIFLUORPHOS complexes (Scheme 5). We were pleased to find that homogeneous systems based on Ir–DIFLUORPHOS catalysts gave good results with excellent conversions up to 100% and ee up to 92% (Table 3). Asymmetric hydrogenation of 2-methylquinoline (**5**) conducted with both IrI(H)(O_2CMe)[(*S*)-difluorphos] [(*S*)-**19**] and IrCl(H)(O_2CMe)[(*S*)-difluorphos] [(*S*)-**20**] treated, respectively, with 2.2 equivalents of methanolic HBr together with $[IrCl(cod)]_2$/(*S*)-difluorphos led to the formation of **10** with complete conversion and up to 91% ee (entries 1–3). In most cases, comparable conversions (up to 100%) and enantioselectivities were achieved, respectively, for the formation of tetrahydroquinolines derivatives **11** (entries 4 and 5, up to 88% ee), **13** (entries 6–8, up to 92% ee), and **14** (entries 9 and 10, up to 58%) and thus whatever the Ir–DIFLUORPHOS complexes considered.

The absolute configurations of the chiral tetrahydroquinoline derivatives **11**–**14** were assigned from $[\alpha]_D$ value by comparison with known compounds.[7a]



5, R = Me, R' = H
6, R = Me, R' = Me
8, R = Me, R' = F
9, R = Ph, R' = H

10, R = Me, R' = H
11, R = Me, R' = Me
13, R = Me, R' = F
14, R = Ph, R' = H

Scheme 5

Table 3 Asymmetric Hydrogenation of Quinolines **5**, **6**, **8**, and **9** with Ir–(*S*)-DIFLUORPHOS Catalysts

No	Ir–(*S*)-DIFLUORPHOS catalyst	Conv. (%)[a]	Product	ee (%)[b]
1	IrI(H)(O_2CMe)[(*S*)-difluorphos] (**19**)/HBr	100	**10**	90
2	IrCl(H)(O_2CMe)[(*S*)-difluorphos] (**20**)/HBr	100	**10**	90
3	$[IrCl(cod)]_2$/(*S*)-difluorphos[c]	90	**10**	91
4	IrI(H)(O_2CMe)[(*S*)-difluorphos] (**19**)/HBr	100	**11**	88
5	IrCl(H)(O_2CMe)[(*S*)-difluorphos] (**20**)/HBr	100	**11**	85
6	IrI(H)(O_2CMe)[(*S*)-difluorphos] (**19**)/HBr	100	**13**	90
7	IrCl(H)(O_2CMe)[(*S*)-difluorphos] (**20**)/HBr	100	**13**	88
8	$[IrCl(cod)]_2$/(*S*)-difluorphos[c]	95	**13**	92
9	IrI(H)(O_2CMe)[(*S*)-difluorphos] (**19**)/HBr	100	**14**	58
10	IrCl(H)(O_2CMe)[(*S*)-difluorphos] (**20**)/HBr	100	**14**	57

[a] Conversions were determined by ^{1}H NMR analysis of the crude product.
[b] The ee values were determined by HPLC analysis (chiralcel OD-H or chiralcel OJ).
[c] Hydrogenation was carried out in toluene.

In conclusion, we have synthesized novel Ir catalysts based upon SYNPHOS and DIFLUORPHOS that are useful for producing enantiomerically enriched tetrahydroquinoline derivatives. In this work, we have demonstrated that the new Ir–SYNPHOS and Ir–DIFLUORPHOS complexes can be efficiently used in these transformations[15] with good conversions (up to 100%) and enantioselectivities (up to 92%) by using different counterions. We are currently investigating the scope of these new Ir–SYNPHOS and Ir–DIFLUORPHOS complexes for transition-metal catalysis.

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(15) **General Hydrogenation Procedure**
The Ir complex (0.01 mmol) was placed in a dry 10 mL Schlenk tube which was equipped with a magnetic bar, a stopper, and connected to a supply of vacuum/argon. Degassed anhydrous acetone (2 mL) was introduced via a syringe under a stream of argon. The mixture was degassed with three vacuum/argon cycles. Methanolic HBr (2.2 equiv) was added dropwise to the solution and stirred for 30 min at r.t. The precipitate was concentrated under vacuum and anhydrous THF (2 mL) was introduced via syringe under a stream of argon. Then, the solution was degassed again with three vacuum/argon cycles. The mixture was transferred by a syringe to a dry 10 mL Schlenk tube, in which I_2 (0.1 mmol) and quinoline (1 mmol) were placed beforehand. This Schlenk tube was equipped with a magnetic bar, a stopper, and connected to a supply of vacuum/argon. The mixture was degassed with three vacuum/argon cycles. The hydrogenation was performed under H_2 (50 bar) at 30 °C for 24 h. After releasing the hydrogen, the reaction mixture was concentrated and the crude product was purified by a short silica gel column eluted with cyclohexane–EtOAc.