




## Article

# Asymmetric Hydrogenation of 1-aryl substituted-3,4-Dihydroisoquinolines with Iridium Catalysts Bearing Different Phosphorus-Based Ligands

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Received: 24 July 2020; Accepted: 4 August 2020; Published: 10 August 2020



**Abstract:** Starting from the chiral 5,6,7,8-tetrahydroquinolin-8-ol core, a series of amino-phosphorus-based ligands was realized. The so-obtained amino-phosphine ligand (**L1**), amino-phosphinite (**L2**) and amino-phosphite (**L3**) were evaluated in iridium complexes together with the heterobiaryl diphosphines tetraMe-BITOP (**L4**), Diophop (**L5**) and **L6** and **L7** ligands, characterized by mixed chirality. Their catalytic performance in the asymmetric hydrogenation (AH) of the model substrate 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline **1a** led us to identify Ir-**L4** and Ir-**L5** catalysts as the most effective. The application of these catalytic systems to a library of differently substituted 1-aryl-3,4-dihydroisoquinolines afforded the corresponding products with variable enantioselective levels. The 4-nitrophenyl derivative **3b** was obtained in a complete conversion and with an excellent 94% e.e. using Ir-**L4**, and a good 76% e.e. was achieved in the reduction of 2-nitrophenyl derivative **6a** using Ir-**L5**.

**Keywords:** atropoisomeric chirality; chiral diphosphines; amino phosphine; imines reduction; iridium complexes

## 1. Introduction

Many pharmaceutically active compounds owe their physiological activity to the presence of an aminic group in their structure. In particular, 1,2,3,4-tetrahydroquinolines and their analogs are very important building blocks for the synthesis of biologically active compounds [1–3] such as salsolidine [4–7] and carnegine [8], solifenacin [9], cryptostyline [10], complex alkaloids [11–14] and new derivatives active as anti-HIV agents [15] and as anticonvulsants (as an inhibitor of carbonic anhydrase [16] or as a non-competitive antagonist via interaction with the glutamate ionotropic AMPA receptor complex) [17] (Figure 1).

The traditional organic methods for the synthesis of tetrahydroquinoline are based on condensation, the cyclization/reduction sequence and intramolecular nucleophilic addition [18–23]. Many efforts have been made to improve the synthetic approach via catalytic methods [7,24–31]. Considering the convenience in terms of efficiency and atom economy, asymmetric hydrogenation (AH) of prochiral imines, using phosphine-based metal complexes as catalysts, was evinced as the most practical application. It is well known that the steric hindrance of the ligands plays an important role in the

asymmetric reduction of this substrate, and matching the hindrance of both catalyst and substrate could enhance the performance of the asymmetric reduction. Among the very first works in the asymmetric hydrogenation of such a class of substrates [32,33], Zhang's group [28] and Ratovelomanana-Vidal's group [34,35] have made a breakthrough, setting up an innovative strategy for the reduction of dihydroisoquinolines. The atropoisomerism, stemming from a restricted rotation around aryl–aryl bonds, constitutes the structural feature accounting for the selectivity in many diphosphine ligands, both as binaphane-type ligands and as classic chiral ones [36,37]. On the contrary, the amino-monophosphine ligands bearing a 1,1'-bi-2-naphthol as an additional source of chirality have been less studied. In this work, we compared three different types of phosphine ligands bearing an atropisomeric chirality in iridium (III) complexes for the reduction of substituted cyclic aromatic 1-aryl imines.

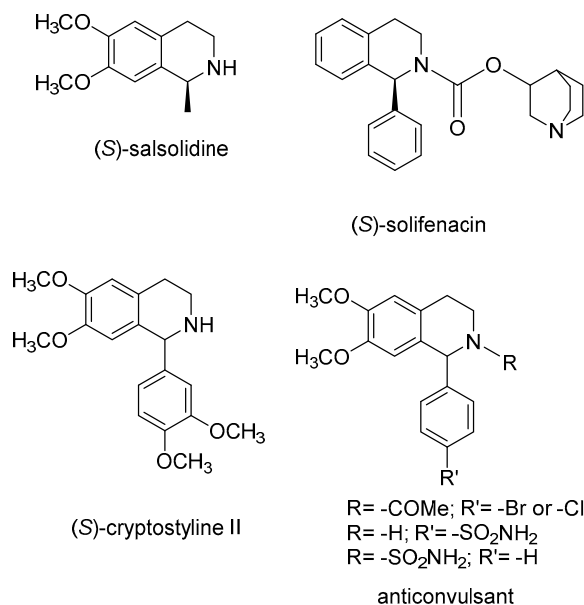


Figure 1. Representative bioactive compounds based on tetrahydroquinolines

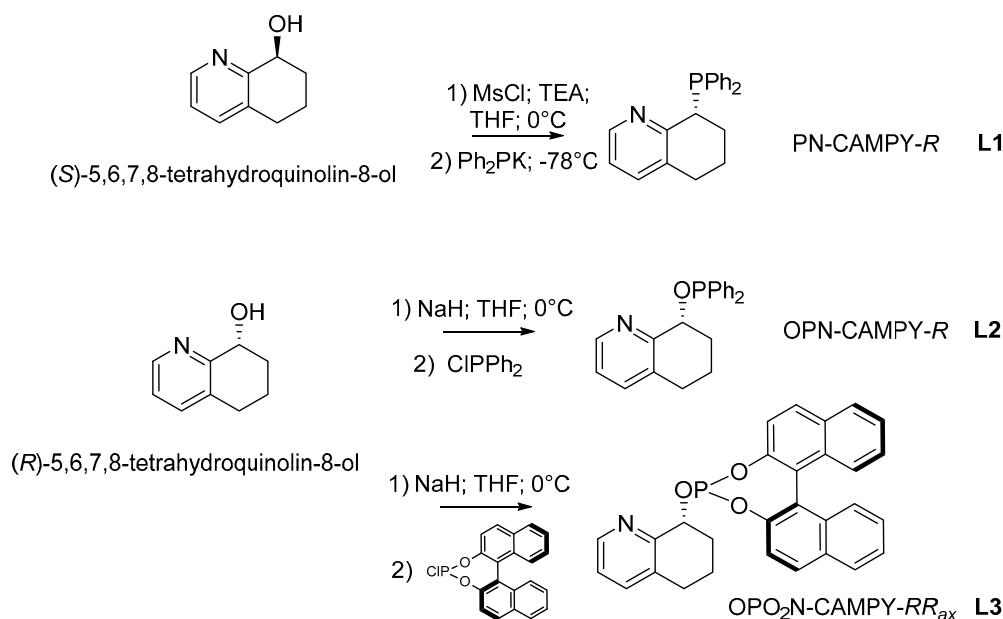
## 2. Results and Discussion

Atropoisomerism is a special characteristic that, based on the 1,1'-bi-2-naphthol moiety, furnishes one of the most common and efficient sources of chirality in the pool of phosphine ligands.

Based on our experience in the use of the chiral 8-amino-5,6,7,8-tetrahydroquinoline scaffold and its derivatives as ligands in transition metal complexes, and considering their employment as sources of chirality in organometallic catalysts for asymmetric reduction or for C–B bond formation reactions [38–40], we decided to focus our attention on the synthesis of three amino monophosphine ligands: amino-phosphine (L1), -phosphinite (L2) [41,42] and -phosphite (L3). For the synthesis of amino monophosphines, we started from the chiral 5,6,7,8-tetrahydroquinolin-ol, the enantiomers of which were successfully separated through enzymatic DKR by *Candida antarctica* lipase B with high yield and purity [43]. The synthesis of the three different types of amino monophosphines proceeded as reported in Scheme 1. These ligands were synthesized with the aim of evaluating the importance of the atropisomeric scaffold when starting from an amino-phosphine in order to afford ligand L3, in which the 1,1'-bi-2-naphthol moiety resulted in an additional source of chirality or/and of additional steric hindrance.

In the case of the monophosphine L1, the synthesis proceeded without racemization at the chiral center at position 8 of the tetrahydroquinoline, as evinced by chiral HPLC analysis (see SI). These monophosphines were used in comparison with other atropisomeric phosphines known from the literature, in each of which atropoisomerism assumed peculiar features: in L4 [44,45] and L5 [46], the heterobiaryl moiety afforded the core of the diphosphines, introducing an axial chirality element comparable to the one arising from a 1,1'-bi-2-naphthol, although with a different steric hindrance.

Moreover, **L5** provided mixed stereogenic elements similar to **L6** and **L7** [47] in which the ligands comprise one stereogenic  $sp^3$  carbon atom backbone and the stereogenic axis of the biaryl moiety (Table 1).



**Scheme 1.** Synthesis of 8-(diphenylphosphanyl)-5,6,7,8-tetrahydroquinoline, PN-CAMPY-R **L1**, (R)-8-((diphenylphosphanyl)oxy)-5,6,7,8-tetrahydroquinoline, OPN-CAMPY-R **L2** and (8R)-8-(((4R)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)-5,6,7,8-tetrahydroquinoline, OPO<sub>2</sub>N-CAMPY-RR<sub>ax</sub> **L3**.

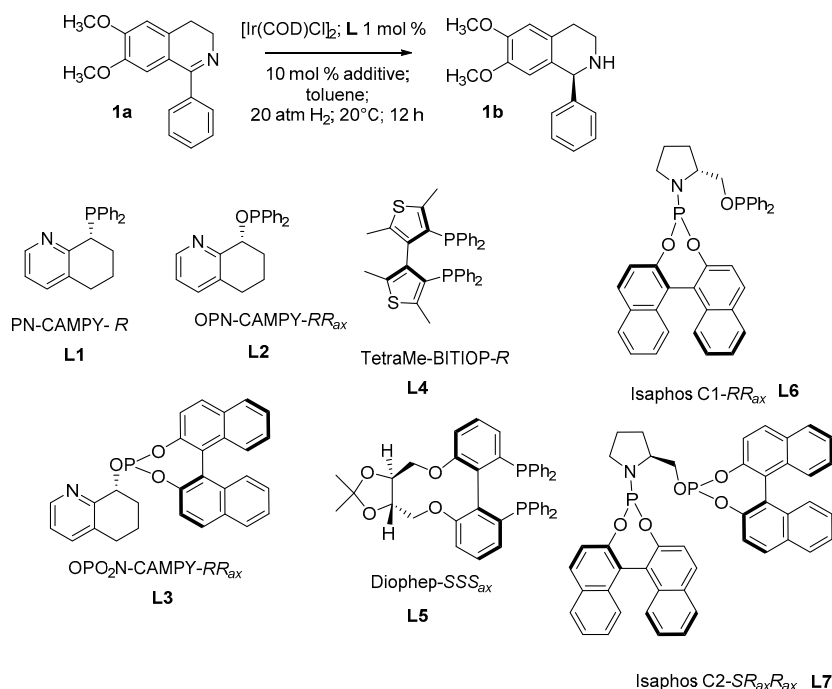
The catalytic investigation was applied to the asymmetric hydrogenation of a series of synthesized cyclic aromatic 1-aryl imines under different reaction conditions, employing Ir-precatalysts generated in situ. For a preliminary screening, the commercially available 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline **1a** was used as a model substrate in order to set up the reaction.

Among the variables of the conditions taken into consideration, the ones able to impact the outcome of the reaction included the use of different types of additives (1,3-dichloro-5,5-dimethylhydantoin, DCDMH [48],  $FeCl_3$ , *N*-bromosuccinimide, NBS, *N*-chlorosuccinimide [32] or  $H_3PO_4$  [9]) and of the solvent employed (THF, toluene,  $CH_2Cl_2$ ) [49] (see SI, Table S1; data refer to substrate **1a**). In the reactions in which **L1**, **L2**, **L3** and **L7** were used as ligands, the presence of an additive proved mandatory (Table 1, entries 1, 3, 5 and 17). From the obtained results, the optimized protocol for the AH reaction comprised a 100/1 substrate/catalyst ratio in toluene under 20 atm of molecular hydrogen in the presence of 10% molar of additive at 20°C for 12 h. Neither the increase in temperature nor a higher hydrogen pressure allowed significant variations to be obtained in terms of enantioselectivity.

The obtained data underlined that the best results in terms of conversion and enantioselectivity were achieved by using NBS as an additive for all ligands (Table 1, entries 2, 4, 6, 9, 11, 13, 16 and 18). Regarding the phosphorous ligands, the amino-monophosphines **L1**–**L3** proved less active, and only modest enantiomeric excesses accompanied the reaction (20–39% e.e., Table 1, entries 2, 4 and 6), although the addition of the 1,1'-bi-2-naphthol moiety in the ligand slightly increased the enantioselectivity (Table 1, entry 6). The same results were obtained in the presence of ligands **L6** and **L7**, in which the mixed types of chirality ( $sp^3$  and axial) did not match (Table 1, entries 16 and 18). The best results were obtained by the classical atropoisomeric diphosphines **L4** and **L5** (Table 1, entries 9 and 13). In particular, in the presence of tetraMe-BITIOP as the ligand, good enantioselectivity was achieved with either NBS or DCDMH as the additive, although the conversion was completed only in the presence of NBS within 12 h (Table 1, entry 7 vs. entry 9). An increase in the substrate/catalyst ratio

to 250/1 did not affect the enantioselectivity of the reaction, with only a minimum erosion in terms of conversion within the settled reaction time (12 h) (Table 1, entry 11).

**Table 1.** Screening of different iridium complexes bearing L1–7.



Entry	Ligand	Additive	Conversion % <sup>[b]</sup>	e.e. (S %) <sup>[b]</sup>
1	L1-R	-	-	-
2	L1-R	NBS	50	20
3	L2-R	-	-	-
4	L2-R	NBS	27	32
5	L3-RR <sub>ax</sub>	-	-	-
6	L3-RR <sub>ax</sub>	NBS	41	39
7	L4-R	DCDMH <sup>[c]</sup>	83	73
8	L4-R	-	85	50
9	L4-R	NBS	>99	72
10	L4-R	FeCl <sub>3</sub>	85	72
11	L4-R <sup>[a]</sup>	NBS	90	71
12	L5-SSS <sub>ax</sub>	-	10	38
13	L5-SSS <sub>ax</sub>	NBS	69	55
14	L6-RR <sub>ax</sub>	-	21	27
15	L6-RR <sub>ax</sub>	DCDMH	5	25
16	L6-RR <sub>ax</sub>	NBS	50	25
17	L7-SR <sub>ax</sub> R <sub>ax</sub>	-	-	-
18	L7-SR <sub>ax</sub> R <sub>ax</sub>	NBS	25	25

Reactions were conducted using 1 mol % iridium complex in toluene with or without an additive (catalyst:additive = 1:10) at 20 °C and 20 atm of H<sub>2</sub> pressure for 12 h. [a] The reaction was conducted using 0.4 mol % iridium complex. [b] Conversion was determined by <sup>1</sup>H-NMR, while enantiomeric excess was determined by HPLC equipped with a chiral column (Chiralcel OD-H). [c] DCDMH = 1,3-dichloro-5,5-dimethyl-hydantoin.

The synthesis of differently substituted derivatives of the standard substrate **1a** was accomplished following the well-known Bischler–Napieralski cyclodehydration [50]. All the obtained products were fully characterized by NMR and MS analysis results in accordance with the data reported in the literature, with the exception of 1-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline, **11a**, here reported for the first time to the best of our knowledge. Considering that the best performances were obtained using atropoisomeric diphosphines **L4** and **L5** in situ coordinated with the iridium(III)

metal center (see Table S1 in SI for comparison), the asymmetric hydrogenation of the substrates reported below was carried out under the following optimized reaction conditions established for the standard substrate **1a**: substrate/catalyst ratio of 100/1 (final substrate concentration of 10 mM) in toluene in the presence of 10% molar of NBS as an additive under 20 atm of hydrogen pressure at 20 °C for 12 h. This allowed a comparison of the reactivity of the catalytic systems to be made relative to the structural and electronic differences of the substrates.

As evinced by the data reported in Figure 2, for all the 1-aryl imines, the best results in terms of enantioselectivity and conversion were afforded by using the **L4** ligand, providing an e.e. of up to 94% along with 99% conversion for the substrate **3a**. The only exceptions were obtained in the reduction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline, **8a**, for which **L5** raised the enantiomeric excess to 75% with a good conversion of 86%, and in the reduction of the substrate **6a**, for which a 76% e.e. was reached, although with a modest conversion of 45%. Indeed, the reduction of the substrates **8a–11a**, characterized by the absence of the two methoxy groups on the quinoline ring, confirmed the pivotal role of the *p*-NO<sub>2</sub> group in furnishing enantiodiscrimination in the reaction when Ir-**L4** was used as the catalyst, allowing it to obtain **10b** with 81% e.e. The differences in both enantioselectivity and conversion rate between the two diphosphines could be due to the basicity and, consequently, to the more electron-rich properties of **L4** compared with **L5** and, conversely, to the steric hindrance of **L5**, which is greater than that of **L4**.

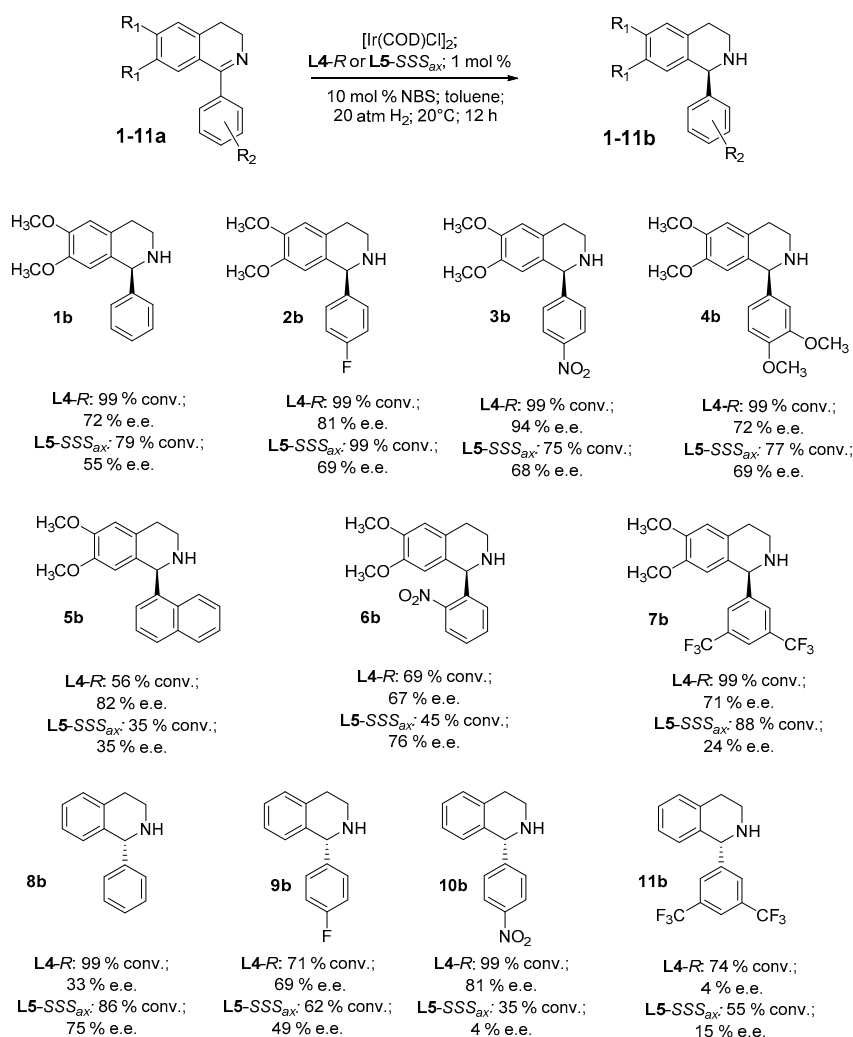


Figure 2. Asymmetric hydrogenation of different 1-aryl imines using **L4** and **L5** as ligands.

### 3. Experimental

**General:**  $^1\text{H}$ -,  $^{13}\text{C}$ - and  $^{31}\text{P}$ -NMR spectra were recorded in  $\text{CDCl}_3$  or  $\text{C}_6\text{D}_6$  on Bruker DRX Avance 400 and 300 MHz equipped with a non-reverse probe. Chemical shifts (in ppm) were referenced to the residual solvent proton/phosphorous peak. MS analyses were performed by using a Thermo Finnigan (MA, USA) LCQ Advantage system MS spectrometer with an electrospray ionization source and an 'Ion Trap' mass analyzer. The MS spectra were obtained by direct infusion of a sample solution in MeOH under ionization, ESI positive. Catalytic reactions were monitored by HPLC analysis with Merck-Hitachi L-7100 equipped with Detector UV6000LP and a chiral column (Chiralcel OD-H, Chiralpak AD, Lux Cellulose-2 or Lux Amylose-2).

#### 3.1. General Procedure for Synthesis of Substrates

The synthesis of substrates was conducted as reported in the literature. To a solution of 2-arylethylamine (1.0 eq.) and triethylamine (1.5 eq.) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at  $0^\circ\text{C}$ , carbonyl chloride (1.0 eq.) was slowly added. The mixture was stirred at room temperature overnight, and then it was concentrated in vacuo. EtOAc (30 mL) was added, and the solution was washed with saturated  $\text{NH}_4\text{Cl}$  solution (30 mL). The aqueous layer was extracted with EtOAc ( $3 \times 20$  mL), and the combined organic layers were washed with brine (50 mL) and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated, and the residue was used without further purification. To a solution of N-acyl-2-arylethylamine (1.0 eq.) and 2-chloropyridine (1.2 eq.) in  $\text{CH}_2\text{Cl}_2$  (25 mL) cooled at  $-78^\circ\text{C}$ , trifluoromethanesulfonic anhydride (1.1 eq.) was added dropwise. Then, the mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with saturated  $\text{NaHCO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic layers were washed with brine and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . After that, the solvent was reduced in vacuo, and the obtained product was purified by flash chromatography (yield: 50–85%). All the obtained substrates were characterized, and the analytical results matched those reported in the literature [25,50–54].

1-(3,5-Bis(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline, (**11a**): pale yellow oil, yield 53%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (s, 2H), 7.97 (s, 1H), 7.44 (dt,  $J = 7.5$  Hz  $J = 1.2$  Hz, 1H), 7.33–7.27 (m, 2H), 7.15 (d,  $J = 7.5$  Hz, 1H), 3.94–3.89 (m, 2H), 2.87–82 (m, 2H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 164.9, 141.0, 138.8, 131.6 (q,  $^2J_{\text{CF}} = 33$  Hz, 2C), 131.4, 129.0 (q,  $^3J_{\text{CF}} = 3.0$  Hz, 2C), 127.9, 127.7, 127.0, 126.9, 126.8 (q,  $^1J_{\text{CF}} = 273$  Hz, 2C), 123.0 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 47.9, 26.0 ppm. FTIR (NaCl)  $\nu = 3072.04$ , 2941.10, 1624.11, 1609.56, 1389.17, 1278.13, 1183.71, 1128.18, 890.92, 745.80  $\text{cm}^{-1}$ ; MS (ESI) for  $\text{C}_{17}\text{H}_{11}\text{F}_6\text{N}$ :  $m/z$  344.01  $[\text{M}+\text{H}]^+$ .

#### 3.2. Synthesis of (R)-8-(Diphenylphosphanyl)-5,6,7,8-Tetrahydroquinoline, L1

The chiral 5,6,7,8-tetrahydroquinoline-8-ol was obtained as previously reported with a yield of 89% for the (R)-enantiomer (99% e.e.) and 87% for the (S)-enantiomer (96% e.e.) [43]. To a solution of (S)-5,6,7,8-tetrahydroquinoline-8-ol (1 mmol) in 5 mL of anhydrous THF at  $0^\circ\text{C}$ , TEA (2.5 eq.) was added. Methanesulfonyl chloride (1.5 eq.) was added dropwise, and the mixture was stirred at  $0^\circ\text{C}$  for 10 min. The temperature was decreased to  $-78^\circ\text{C}$ , and potassium diphenylphosphide solution (0.5 M) in THF (1.7 eq.) was added within 15 min. The mixture was stirred for 6 h, and the temperature was warmed to room temperature. At the end of the reaction, 5 mL of diethyl ether and HCl (2M) was added until the solution reached an acid pH. The organic phase was extracted with  $3 \times 5$  mL of diethyl ether and washed with a saturated solution of  $\text{Na}_2\text{CO}_3$  until it reached a basic pH. The aqueous phase was extracted with dichloromethane ( $3 \times 5$  mL). Combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated. The obtained product did not need further purification.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 8.23 (d,  $J = 3.9$  Hz, 1H), 7.53–7.21 (m, 11H), 6.99–6.95 (m, 1H), 3.93–3.88 (m, 1H), 2.75 (t,  $J = 6.0$  Hz, 2H), 2.08–1.98 (m, 1H), 1.90–1.77 (m, 2H), 1.73–1.62 (m, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.6, 147.3, 137.0, 135.1, 134.8, 134.2 (2C), 133.9 (2C), 129.4, 129.0 (2C), 128.9 (2C), 128.4



(2C), 121.6, 41.7, 29.1, 26.8, 22.2 ppm;  $^{31}\text{P}$ -NMR ( $\text{CDCl}_3$ , 160 MHz):  $\delta$  2.76 ppm; MS (ESI) for  $\text{C}_{21}\text{H}_{20}\text{NP}$ :  $m/z$  318.23  $[\text{M}+\text{H}]^+$ .

### 3.3. Synthesis of (R)-8-((Diphenylphosphanyl)oxy)-5,6,7,8-Tetrahydroquinoline and (8R)-8-(((4R)-Dinaphtho[2,1-d:1',2'-f][1,3,2]Dioxaphosphepin-4-yl)oxy)-5,6,7,8-Tetrahydroquinoline, L2 and L3

The chiral 5,6,7,8-tetrahydroquinolin-8-ol and (R)-(+)-1,1'-binaphthyl-2,2'-diylphosphite chloride were obtained as previously reported. To a solution of NaH (1.1 eq.) in 5 mL of anhydrous THF at 0 °C was added (S)-5,6,7,8-tetrahydroquinolin-8-ol (1 mmol). The suspension was stirred for 30 min, and chlorodiphenylphosphine or (R)-(+)-1,1'-binaphthyl-2,2'-diylphosphite chloride (1.1 eq.) was added. The mixture was then stirred at room temperature for 1 h. Then, 10 mL of diisopropyl ether was added, and the formed precipitate, containing the inorganic salts, was filtered off. The solvent was evaporated, and the obtained white solid did not need further purification.

**L2:**  $^1\text{H}$ -NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 8.30 (d,  $J$  = 4.4 Hz, 1H), 7.78–7.63 (m, 2H), 7.50–7.10 (m, 10H), 4.74 (t,  $J$  = 5.2 Hz, 1H), 2.76–2.65 (m, 2H), 2.16–1.68 (m, 4H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.6, 146.3, 137.0, 133.4, 132.8, 134.6, 131.8 (4C), 131.2 (2C), 128.7 (2C), 127.8 (2C), 121.9, 43.2, 28.4, 23.8, 20.7 ppm;  $^{31}\text{P}$ -NMR ( $\text{C}_6\text{D}_6$ , 160 MHz):  $\delta$  111.4 ppm; MS (ESI) for  $\text{C}_{21}\text{H}_{20}\text{NOP}$   $m/z$  334.43  $[\text{M}+\text{H}]^+$ .

**L3:**  $^1\text{H}$ -NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 7.96–7.02 (m, 14H), 6.84 (d,  $J$  = 8.4 Hz, 1H), 4.92 (m, 1H), 2.72–2.61 (m, 3H), 2.28–2.23 (m, 1H), 1.92–1.89 (m, 2H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 150.1 (2C), 145.3, 137.6, 134.6, 134.1, 133.7, 132.8, 131.8, 128.8 (2C), 128.4 (2C), 128.0 (2C), 127.7 (2C), 124.1 (2C), 123.2 (2C), 121.7, 117.9 (2C), 43.3, 28.8, 24.1, 20.8 ppm;  $^{31}\text{P}$ -NMR ( $\text{C}_6\text{D}_6$ , 160 MHz):  $\delta$  145.3 ppm; MS (ESI) for  $\text{C}_{29}\text{H}_{22}\text{NO}_3\text{P}$ :  $m/z$  464.57  $[\text{M}+\text{H}]^+$ .

### 3.4. General Procedure for Asymmetric Hydrogenation

$[\text{Ir}(\text{COD})\text{Cl}]_2$  (0.5 eq.) was added to a solution of phosphine (1 eq.) in 5 mL of solvent, and the mixture was stirred at room temperature for 15 min. The additive (10 eq.) was added and, after stirring for an additional 15 min, the imine (100 eq.) was added to the reaction mixture. The solution was transferred to a stainless-steel autoclave (50 mL) with a cannula. The autoclave, equipped with temperature control and magnetic stirrer, was purged five times with hydrogen and then pressurized at 20 atm, and the temperature was set to 20 °C. At the end, the autoclave was vented, and the mixture was analyzed by HPLC equipped with a chiral column (for analytical conditions, see below).

### 3.5. Analytical Conditions

The products were analyzed by  $^1\text{H}$  NMR to determine the molar conversion, whereas the enantiomeric excess was evaluated by HPLC analysis, and the absolute configuration was assigned by comparison with literature references [25,55].

**6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 1b** [25]: R-isomer: 12.1 min (*min*); S-isomer: 17.3 min (*maj*); column: Chiralcel OD-H, eluent: 2-propanol/hexane = 30/70 (0.01% DEA), flow = 0.7 mL/min,  $\lambda$  = 220 nm.

**1-(4-Fluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2b** [25]: R-isomer: 21.0 min (*min*); S-isomer: 23.9 min (*maj*); column: Chiralpak AD, eluent: 2-propanol/hexane = 10/90, flow = 0.8 mL/min,  $\lambda$  = 220 nm.

**6,7-Dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline 3b** [54]: R-isomer: 25.7 min (*min*); S-isomer: 32.5 min (*maj*); column: Chiralcel OD-H, eluent: 2-propanol/hexane = 30/70 (0.01% DEA), flow = 0.7 mL/min,  $\lambda$  = 285 nm.

**1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 4b** [25]: R-isomer: 23.7 min (*min*); S-isomer: 33.0 min (*maj*); column: Chiralcel OD-H, eluent: 2-propanol/hexane = 30/70 (0.01% DEA), flow = 0.7 mL/min,  $\lambda$  = 285 nm.

**6,7-Dimethoxy-1-(naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline 5b** [35]: 1 isomer: 14.7 min (*min*); 2 isomer: 16.4 min (*maj*); column: Chiralcel OD-H, eluent: 2-propanol/hexane = 30/70 (0.01% DEA), flow = 0.7 mL/min,  $\lambda$  = 285 nm.

6,7-Dimethoxy-1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **6b** [24]: 1 isomer: 8.6 min (*min*); 2 isomer: 15.0 min (*maj*); column: Chiralcel OD-H, eluent: 2-propanol/hexane = 30/70 (0.01% DEA), flow = 0.7 mL/min,  $\lambda$  = 240 nm.

1-(3,5-Bis(trifluoromethyl)phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **7b** [56]: 1 isomer: 7.5 min (*maj*); 2 isomer: 8.5 min (*min*); column: Lux Amylose-2, eluent: 2-propanol/hexane = 10/90 (0.01% DEA), flow = 0.8 mL/min,  $\lambda$  = 220 nm.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline **8b** [25]: S-isomer: 13.1 (*min*); R-isomer: 15.4 (*maj*); column: Chiralpak AD, eluent: 2-propanol/hexane = 4/96, flow = 0.8 mL/min,  $\lambda$  = 240 nm.

1-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline **9b** [25]: S-isomer: 5.5 (*min*); R-isomer: 7.1 (*maj*); column: Lux Amylose-2, eluent: 2-propanol/hexane = 10/90, flow = 1.0 mL/min,  $\lambda$  = 220 nm.

1-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **10b** [26]: S-isomer: 15.9 (*min*); R-isomer: 20.9 (*maj*); column: Lux Amylose-2, eluent: 2-propanol/hexane = 10/90 (0.01% DEA), flow = 0.8 mL/min,  $\lambda$  = 254 nm.

1-(3,5-Bis(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**11b**): yellow solid, yield 61 %;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.84 (s, 1H), 7.80 (s, 2H), 7.36–7.32 (m, 1H), 7.20–7.21 (m, 2H), 7.12–07 (m, 1H), 5.25 (s, 1H), 3.20–3.13 (m, 2H), 2.91–2.82 (m, 2H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 147.9, 136.8, 135.9, 132.0 (q,  $^2J_{\text{CF}}$  = 33 Hz, 2C), 129.9, 129.6 (q,  $^3J_{\text{CF}}$  = 3.3 Hz, 2C), 128.1, 127.4, 126.4, 123.3 (q,  $^1J_{\text{CF}}$  = 273 Hz, 2C), 121.9 (q,  $^3J_{\text{CF}}$  = 3.8 Hz), 61.8, 42.7, 29.9 ppm. FTIR (NaCl)  $\nu$  = 3035.13, 2901.08, 1571.24, 1350.12, 1228.89, 1165.04, 1153.73, 873.20, 778.63  $\text{cm}^{-1}$ ; MS (ESI) for  $\text{C}_{17}\text{H}_{13}\text{F}_6\text{N}$ :  $m/z$  346.21  $[\text{M}+\text{H}]^+$ . HPLC: 1 isomer: 8.2 (*min*); 2 isomer: 12.0 (*maj*); column: Lux Cellulose-2, eluent: 2-propanol/hexane = 5/110, flow = 0.6 mL/min,  $\lambda$  = 220 nm.

#### 4. Conclusions

Different types of chiral phosphines serving as a source of chirality in an atropoisomeric moiety due to the presence of axial biaryl asymmetry were evaluated in the reduction of a standard cyclic imine, 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline **1a**. By this preliminary screening, the classical atropoisomeric diphosphines, **L4** and **L5**, proved the most effective ligands in iridium complexes for the asymmetric hydrogenation of this substrate, while the amino-monophosphines **L1**, **L2** and **L3** were less stereoselective as ligands despite the presence of the additional 1,1'-bi-2-naphthol moiety. The ligands **L6** and **L7**, comprising both the stereogenic  $\text{sp}^3$  carbon atom backbone and the stereogenic axis of the biaryl moiety, resulted in poor enantioselectivity. With the optimal reaction conditions in hand, we were able to extend the scope of the reaction to a series of 1-aryl cyclic imines, different from an electronic point of view for the presence of electron-withdrawing or electron-donor groups on the 1-phenyl substituent. An excellent 94% e.e. was achieved in the AH of the substrate **3a** using the Ir-**L4** complex, with a complete conversion for substrate **7a**, although with a lower but still good 71% e.e. A remarkable point is the 82% e.e. reached in the reduction of the steric-hindered imine **5a**. The Ir-catalytic system,  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and the **L5** ligand, afforded the best results in the AH of the 1-(2-nitro)phenyl-substituted substrate **6a** with a 76% e.e. and in the AH of the simple but demanding substrate **8a**, affording the product with a good e.e. of 75% and with 86% conversion.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2073-4344/10/8/914/s1>, Table S1: Preliminary screening with L1-L7.

**Author Contributions:** These authors contributed equally. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** authors declare no conflict of interest.

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