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# Asymmetric Hydrogenation of Quinoxalines Catalyzed by Iridium/PipPhos

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**Abstract:** A catalyst made *in situ* from the (cyclooctadiene)iridium chloride dimer, $[Ir(COD)Cl]_2$, and the monodentate phosphoramidite ligand (*S*)-PipPhos was used in the enantioselective hydrogenation of 2- and 2,6-substituted quinoxalines. In the presence of piperidine hydrochloride as additive full conversions and enantioselectivities of up to 96% are obtained.

**Keywords:** asymmetric catalysis; heterocycles; homogeneous catalysis; hydrogenation; iridium; phosphoramidites

Catalytic asymmetric hydrogenation of heteroaromatic compounds represents a valuable method for the synthesis of enantiopure saturated heterocyclic compounds.[1] Numerous chiral heterocyclic compounds, including quinoxalines, are prominent among various classes of pharmaceuticals.[2,3] Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid[4] as well as potent CETP (cholesteryl ester transfer protein) inhibitors for the treatment of atherosclerosis and obesity.[5] A synthetic approach to tetrahydroquinoxalines comprising catalytic asymmetric hydrogenation would be highly useful.

The first asymmetric hydrogenation of 2-methylquinoxaline (**1a**) was reported in 1987 using Rh-DIOP as a catalyst, however with only 3% *ee*.[6] In 1998 Bianchini reported an iridium-based catalyzed asymmetric hydrogenation of the same substrate with high enantioselectivity using an interesting *ortho*-metalated PPNC iridium dihydride complex (up to 90% *ee*).[7] In 2003 Henschke et al. reported the use of a diverse library of ruthenium Noyori-type precatalysts ($RuPPNNCl_2$) in the enantioselective hydrogenation of imines.[8] The highest enantioselectivity in the hydrogenation of 2-methylquinoxaline (73% *ee*) was obtained using (*S*)-Xyl-HexaPHEMP as ligand with the addition of (*S,S*)-cyclohexanediamine and potassium *tert*-butoxide as base. The use of a tethered BIPHEP-type ligand in combinatioin with $[Ir(COD)Cl]_2$ and $I_2$ was reported by Chan, who achieved up to 80% *ee* in the asymmetric hydrogenation of **1a**.[9]

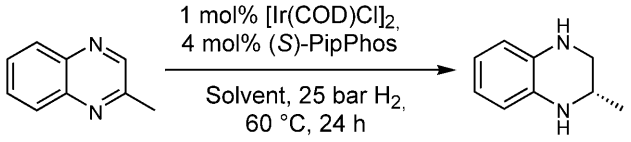
So far, only bidentate ligands were reported in the asymmetric hydrogenation of prochiral substituted quinoxalines. In the last decade, several papers have reported on the excellent results obtained with the use of chiral monodentate phosphines, phosphonites, phosphoramidites and phosphites in rhodium-catalyzed asymmetric hydrogenations.[10] We recently reported the asymmetric hydrogenation of quinolines[11] and *N*-arylimines[12] catalyzed by iridium compounds and monodentate phosphoramidite ligands with full conversion and excellent enantioselectivity. Notably, compared to bidentate ligands, monodentate phosphoramidites are readily accessible, structurally highly diverse, air-stable and inexpensive. They have found many applications in asymmetric hydrogenation.[13] In addition, they are amenable to parallel synthesis.[14]

Herein we report the highly enantioselective hydrogenation of 2- and 2,6-substituted quinoxalines using an iridium catalyst with the monodentate phosphoramidite (*S*)-PipPhos and piperidine hydrochloride as additive.

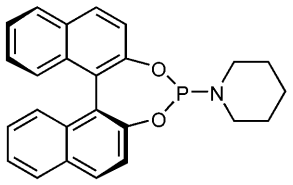
As a starting point, we used the best catalysts and conditions employed in the asymmetric hydrogenation of 2-substituted quinolines.[11] Optimization of the reaction conditions was achieved using the asymmetric hydrogenation of 2-methylquinoxaline **1a** as a test reaction. Our results are presented in Table 1. Employ-

**Table 1.** Asymmetric hydrogenation of 2-methylquinoxaline (**1a**)[a]




**1a** **1b**



(*S*)-PipPhos

| Entry | Solvent | 10 mol% piperidine·HCl | Time[b] [h] | *ee*[c] [%] | Config.[d] |
|---|---|---|---|---|---|
| 1 | MeOH | + | nd (<24) | 17 | (*S*) |
| 2 | TFE | + | nd (<24) | 10 | (*R*) |
| 3 | toluene | + | 4 | 55 | (*S*) |
| 4 | EtOAc | + | 6 | 70 | (*S*) |
| 5 | THF | + | 14 | 73 | (*S*) |
| 6 | DCM | – | 3 | 77 | (*S*) |
| 7 | DCM | + | 8 | 96 | (*S*) |
| 8 | DCM | + | 15 | 91[e] | (*S*) |

[a] *Reaction conditions:* 1 mmol scale, quinoxaline/$[Ir(COD)Cl]_2$/(*S*)-PipPhos/piperidine hydrochloride = 100/1/4/10, 4 mL of solvent, 60 °C, 25 bar $H_2$, 24 h.

[b] Time to achieve full conversion. Conversion was determined by $^1H$ NMR.

[c] Enantiomeric excess was determined by HPLC.

[d] The absolute configuration was determined by determining the optical rotation and comparing it with literature data.[15]

[e] 0.5 mol% $[Ir(COD)Cl]_2$ was used.

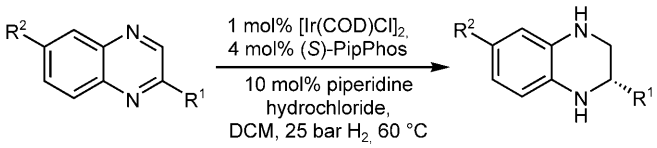
ing 1 mol% of the dimeric iridium precursor, 4 mol% of phosphoramidite ligand (*S*)-PipPhos and 10 mol% of piperidine hydrochloride at 60 °C and 25 bar of $H_2$ pressure, low enantioselectivities were obtained in a protic solvent such as methanol (Table 1, entry 1). It should be noted that the opposite configuration of the product, however with low *ee*, was obtained in 2,2,2-trifluoroethanol as solvent (entry 2). In aprotic solvents such as toluene and ethyl acetate higher enantioselectivities were obtained (55% and 70% *ee*, respectively) with a complete conversion within 6 h (entries 3 and 4). The use of THF slightly increased the enantioselectivity to 73% yet the reaction was slower (entry 5). Finally, the best results were obtained in dichloromethane with *ees* up to 96% (entries 6–8). It is clear that the presence of piperidine hydrochloride affects the enantioselectivity of this reaction in dichloromethane (entries 6 and 7). The addition of 10 mol% of the hydrochloride salt increased the *ee* by 19%, however the reaction was slower. We have shown previously that addition of chloride salts enhances the enantioselectivity of the iridium/phosphoramidite-catalyzed hydrogenation of quinolines.[11] In the previous work, we also showed that addition of tri-*o*-tolylphosphine increased the *ee* somewhat, but this effect was found to be negligible in the present case (result not shown in Table 1). Lowering the catalyst loading to 0.5 mol% influenced the reaction time but only a small effect was observed with respect to the enantioselectivity (entry 8).

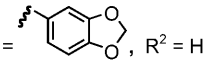
Various 2- and 2,6-disubstituted quinoxalines (**1a–12a**) were subjected to our best asymmetric hydrogenation conditions in order to study the scope of the reaction. The substrates were synthesized according to a known method by the iron-catalyzed Kumada reaction on the 2-chloroquinoxaline.[17] The results are presented in Table 2. All substrates were hydrogenated with high to excellent enantioselectivities, with 2-methylquinoxaline **1a** providing the product with the highest *ee* (96% *ee*, Table 2, entry 1). Changing from the methyl- to the ethyl-substituted quinoxaline substrate resulted in a decrease of enantioselectivity in the hydrogenation of 2-ethylquinoxaline (80% *ee*, entry 2). Similar enantioselectivities (80–85% *ee*) were obtained with all 2-alkylquinoxaline substrates (entries 3–7). 2-Phenyl-1,2,3,4-tetrahydroquinoxaline was obtained with 86% *ee* (entry 8). Low enantioselectivity was obtained with phenethyl-substituted substrate **9a** (75% *ee*, entry 9). The presence of a heteroatom in the structure such as oxygen did not have a significant effect on the enantioselectivity (80% *ee*, entry 10). A chloride substituent in the 6-position also did not influence the selectivity (entry 11). The product of this reaction can be further functionalized, for instance, *via* a Suzuki or a Sonogashira coupling. Unfortunately, attempted hydrogenation of the methyl ester of quinoxaline-2-carboxylic acid **12a** failed, which might be due to a strong bidentate coordination of the substrate to the metal (entry 12).

In conclusion, we have shown that using a combination of $[Ir(COD)Cl]_2$ as metal source, PipPhos as a ligand and piperidine hydrochloride as additive in the asymmetric hydrogenation of 2- and 2,6-substituted quinoxalines, full conversions and *ee*s from 75 to 96% were obtained. These results represent the highest selectivity reached for this class of heterocyclic compounds reported as yet. The highly enantioselective hydrogenation of imines and quinolines using this catalytic system is now extended to another class of heterocycles in high yields and *ee*s.

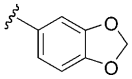
**Table 2.** Asymmetric hydrogenation of 2- and 2,6-substituted quinoxalines using (*S*)-PipPhos as a ligand and piperidine hydrochloride as an additive.[a]




**1a** $R^1$ = Me, $R^2$ = H
**2a** $R^1$ = Et, $R^2$ = H
**3a** $R^1$ = *i*-Bu, $R^2$ = H
**4a** $R^1$ = *n*-butyl, $R^2$ = H
**5a** $R^1$ = *n*-pentyl, $R^2$ = H
**6a** $R^1$ = 2-ethylhexyl, $R^2$ = H
**7a** $R^1$ = dodecyl, $R^2$ = H
**8a** $R^1$ = Ph, $R^2$ = H
**9a** $R^1$ = $CH_2CH_2Ph$, $R^2$ = H
**10a** $R^1$ =  , $R^2$ = H

**11a** $R^1$ = Me, $R^2$ = Cl
**12a** $R^1$ = COOMe, $R^2$ = H

**1b** – **12b**
full conversion
*ee* up to 96%

| Entry | $R^1$ | $R^2$ | Time[b] [h] | Yield [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | Me (**1b**) | H | 11 | 85 | 96 |
| 2 | Et (**2b**) | H | 5 | 71 | 80 |
| 3 | *i*-Bu (**3b**) | H | 10 | 74 | 80 |
| 4 | *n*-Bu (**4b**) | H | 8 | 83 | 82 |
| 5 | *n*-pentyl (**5b**) | H | 9 | (100)[d] | 85 |
| 6 | 2-ethylhexyl (**6b**) | H | 12 | 89 | 80 |
| 7 | dodecyl (**7b**) | H | 7 | 81 | 81 |
| 8 | Ph (**8b**) | H | 9 | 92 | 86 |
| 9 | $CH_2CH_2Ph$ (**9b**) | H | 8 | 81 | 75 |
| 10 |  (**10b**) | H | 14 | 83[d] | 80 |
| 11 | Me (**11b**) | Cl | 7 | 88 | 88 |
| 12 | COOMe (**12b**) | H | 16 | 0 | – |

[a] *Reaction conditions:* 1 mmol scale, quinoxaline/$[Ir(COD)Cl]_2$/(*S*)-PipPhos/piperidine hydrochloride = 100/1/4/10, 4 mL of DCM, 60 °C, 25 bar $H_2$.
[b] Time to achieve full conversion. Conversion was determined by $^1$H NMR.
[c] Enantiomeric excess was determined by HPLC.
[d] NMR yield.

# Experimental Section

## General Remarks

(*S*)-PipPhos was synthesized according to a literature procedure.[16] The catalyst was prepared *in situ* by mixing the iridium precursor, ligand and piperidine hydrochloride in 4 mL of solvent. Solvents were distilled before use. $^1$H and $^{13}$C NMR spectra were recorded on a Varian AMX400 (399.93 MHz for $^1$H, 100.59 MHz for $^{13}$C) spectrometer in $CDCl_3$. Chemical shifts are reported in $\delta$ values (ppm) relative to the residual solvent peak. Carbon assignments are based on APT experiments. HPLC analysis was performed on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. The enantiomeric excess values were determined by HPLC with an OD-H chiral column. High resolution mass spectra were recorded on an AEI-MS-902 mass spectrometer. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL).

## Preparation of Quinoxaline Substrates[17] (except 8a)

To a flame-dried, 3-necked flask 2-chloroquinoxaline (1.15 g, 6.99 mmol) and iron(II) acetylacetonate (125 mg, 0.35 mmol) were added. The mixture was dissolved in dry THF (50 mL) and *N*-methyl-2-pyrrolidone was added (4 mL). A Grignard solution (8.39 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred for 20 min, diluted with ether (50 mL) and quenched with 1 M aqueous HCl solution (15 mL). After 10 min water was added (50 mL). The ether layer was separated, washed with brine (50 mL), dried and the solvent was removed under vacuum. The crude product was purified by column chromatography on aluminum oxide (EtOAc/heptane = 1/6). 2-Methylquinoxaline was purchased from Aldrich and used directly in the hydrogenation reactions.

## General Experimental Procedure for Hydrogenation

A mixture of $[Ir(COD)Cl]_2$ (6.72 mg, 0.01 mmol), (*S*)-PipPhos (15.98 mg, 0.04 mmol), substrate (1 mmol) and piperidine hydrochloride (12.16 mg, 0.1 mmol) was dissolved in 4 mL of solvent, in a glass vial. The vial was placed in a stainless steel autoclave. Reaction vessels were filled under air and then flushed with nitrogen before hydrogen pressure was applied. Hydrogenation was performed at 60 °C under 25 bar of hydrogen pressure for the indicated time. After cooling the autoclave, the hydrogen pressure was carefully released. Solvent was removed under vacuum and conversion was determined by $^1$H NMR. The crude product was purified by chromatography (silica gel, heptane/EtOAc = 4/1). Although no side products were observed by $^1$H NMR, yields were ranging from 80 to 99%. It is assumed that in some cases the yield is lower due to the loss of product on the silica column.

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