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# Iridium-Difluorphos-Catalyzed Asymmetric Hydrogenation of 2-Alkyl- and 2-Aryl-Substituted Quinoxalines: A General and Efficient Route into Tetrahydroquinoxalines

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**Abstract:** A highly efficient and general iridium-difluorphos-catalyzed asymmetric hydrogenation of diverse 2-alkyl- and 2-aryl-substituted quinoxalines into biologically and pharmaceutically relevant 2-substituted-1,2,3,4-tetrahydroquinoxaline units has been developed. High isolated yields and excellent enantioselectivities of up to 95% for 2-alkyl-substituted quinoxalines and of up to 94% for 2-aryl-substituted quinoxalines were obtained.

**Keywords:** asymmetric catalysis; difluorphos; hydrogenation; iridium; quinoxaline; tetrahydroquinoxalines

2-Substituted-1,2,3,4-tetrahydroquinoxalines are useful key structural units for drug development and have attracted significant attention over the years.[1] They exhibit a variety of biological activities and have found applications as cholesteryl ester transfer protein inhibitors **1** (CETP),[2] M2 acetylcholine receptor agonists **2**,[3] prostagladin D2 receptor antagonists **3**,[4] or therapeutic agents for increasing renal fluid flow[5] (Figure 1).

Therefore, a practical, convenient and atom-economical route to access tetrahydroquinoxaline core is highly desirable. Asymmetric hydrogenation constitutes one of the most direct and viable strategy for the synthesis of such compounds. Over the past few years, significant progress in the development of transition-metal catalyzed asymmetric hydrogenation of heteroaromatic compounds has been made.[6] However, despite the obvious biological potential of tetrahydroquinoxalines, few examples of asymmetric hydrogenation of the corresponding quinoxaline derivatives have been reported so far in the literature. Since the first report by Murata et al. in 1987 using Rh-DIOP catalyst (3% *ee*),[7] the substrate scope was mainly limited to 2-methylquinoxaline (MeQ) as a model substrate. Bianchini described in 1998 and 2001 the hydrogenation of MeQ using either *fac-exo*-(*R*)-{$IrH_2[C_6H_4C^*H(Me)N(CH_2CH_2\text{-}PPh_2)_2]$} (90% *ee*, 53.7% yield)[8] and iridium- or rhodium-[(*R*)-(*R*)-BPP-BzP] catalysts (11–23% *ee*, 40.7–93.2 yields).[9] In 2003, Henschke et al. used Noyori's $[RuCl_2(diphosphine)(diamine)]$ complexes with *ee* up to 73% and 99% conversion when HexaPHEMP de-

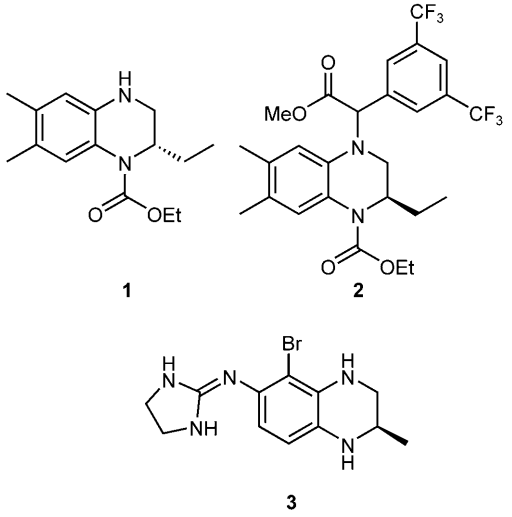



**Figure 1.** Representative bioactive compounds with the 2-substituted-1,2,3,4-tetrahydroquinoxaline framework.

rivatives were used as chiral ligands.[10,11] Chan et al. reported in 2006 the use of PQ-Phos ligands with *ee* up to 80% for asymmetric hydrogenation of MeQ,[12] and later, in 2009, an efficient Ir/$H_8$-binapo system for asymmetric hydrogenation of 2-alkyl-substituted quinoxalines derivatives with 85 to 96% *ee* at low catalyst loading.[13] Simultaneously, de Vries, Feringa and Minnaard described an iridium-based catalyzed hydrogenation of 2- and 2,6-substituted quinoxalines using the monodentate phosphoramidite PipPhos ligand and piperidine hydrochloride as an additive with *ee* ranging from 75 to 96%.[14] However, these catalytic systems are mostly limited to 2-alkyl-substituted quinoxalines. In sharp contrast, asymmetric hydrogenation of challenging 2-aryl-substituted quinoxalines has scarcely been explored. The rare examples reported so far are limited to 2-phenylquinoxaline, 2-benzo[1,3]dioxolequinoxaline and 2-*o*′-MeO-phenylquinoxaline with *ee* values up to 84% *ee* using (*R*)-$H_8$-Binapo,[13] up to 86% using (*S*)-PipPHOS,[14] and up to 65% *ee* using (*R*)-SegPhos.[15]

We were interested in pursuing a research program on the iridium-promoted asymmetric hydrogenation of heteroaromatic compounds, and report herein the first general, highly efficient, catalytic asymmetric hydrogenation of a broad range of 2-aryl-substituted quinoxalines. The hydrogenation of 2-alkyl-substituted quinoxalines is described as well. We previously reported the efficient asymmetric hydrogenation of 2-alkyl-substituted quinolines[16] and 2-aryl- and 2-alkyl-substituted quinolinium salts,[17] using various cationic dinuclear triply halogen-bridged iridium complexes of formula $[\{IrH((S)\text{-diphosphine})\}_2(\mu\text{-}X)_3]^+Y^-$.[18] We started our investigation by first identifying the most appropriate cationic iridium complexes bearing either (*S*)-Synphos[19] or (*S*)-Difluorphos[20] (Figure 2) for the asymmetric hydrogenation of 2-methylquinoxaline **5a** as a model substrate.

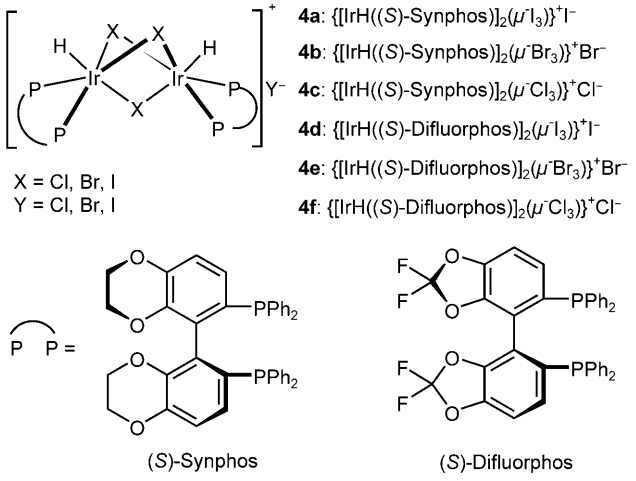
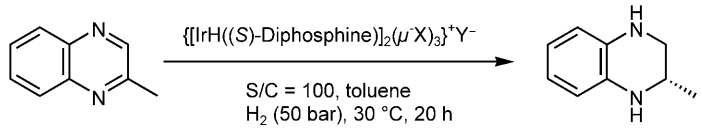



**Figure 2.** Cationic dinuclear triply halogen-bridged iridium complexes $[\{IrH((S)\text{-diphosphine})\}_2(\mu\text{-}X)_3]^+X^-$ **(4a–f).**

Complexes **4a–4f** used in this study were conveniently prepared by adding an excess of aqueous HX to a mixture of $[IrCl(COE)_2]_2$ and the required chiral diphosphine ligand in toluene at room temperature.[17,18] Initial experiments were performed under a standard set of reaction conditions (50 bar of $H_2$, 30 °C, toluene, S/C = 100). The results are summarized in Table 1. Hydrogenation of 2-methylquinoxaline **5a**, using $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}I)_3\}^+I^-$ **4a**, led to the desired product (*S*)-**6a** with complete conversion and a promising 72% *ee* (entry 1). Comparable results in terms of both conversion and enantioselectivity were obtained when catalysts $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}Br)_3\}^+Br^-$ **4b** and $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}Cl)_3\}^+Cl^-$ **4c**

**Table 1.** Catalyst screening.[a]

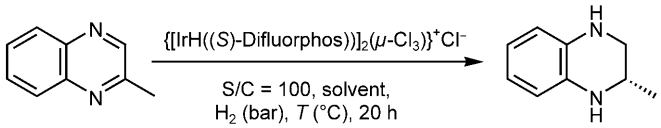



| Entry | | Catalysts | Conversion [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **4a** | $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}I)_3\}^+I^-$ | >99 | 72 |
| 2 | **4b** | $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}Br)_3\}^+Br^-$ | >99 | 75 |
| 3 | **4c** | $\{[IrH((S)\text{-Synphos})]_2(\mu\text{-}Cl)_3\}^+Cl^-$ | >99 | 75 |
| 4 | **4d** | $\{[IrH((S)\text{-Difluorphos})]_2(\mu\text{-}I)_3\}^+I^-$ | >99 | 69 |
| 5 | **4e** | $\{[IrH((S)\text{-Difluorphos})]_2(\mu\text{-}Br)_3\}^+Br^-$ | >99 | 87 |
| 6 | **4f** | $\{[IrH((S)\text{-Difluorphos})]_2(\mu\text{-}Cl)_3\}^+Cl^-$ | >99 | 92 |

[a] *Reaction conditions:* **5a** (1.0 mmol).
[b] Conversion was determined by $^1H$ NMR of the crude product.
[c] Enantiomeric excess was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column. Absolute configuration was determined by comparison of the specific rotation with reported data.

**Table 2.** Optimization of the reaction conditions.[a]




**5a** (*S*)-**6a**

| Entry | Solvent | $H_2$ [bar] | Temperature [°C] | Conversion [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | MeOH | 50 | 30 | >99 | (*R*) 19 |
| 2 | *i*-PrOH | 50 | 30 | >99 | (*S*) 53 |
| 3 | $CH_2Cl_2$ | 50 | 30 | >99 | (*S*) 88 |
| 4 | THF | 50 | 30 | >99 | (*S*) 85 |
| 5 | dioxane | 50 | 30 | >99 | (*S*) 85 |
| 6 | $Et_2O$ | 50 | 30 | >99 | (*S*) 90 |
| 7 | toluene | 50 | 30 | >99 | (*S*) 92 |
| 8 | toluene | 50 | 10 | >86 | (*S*) 93 |
| 9 | toluene | 50 | 50 | >99 | (*S*) 90 |
| 10 | toluene | 50 | 70 | >99 | (*S*) 90 |
| 11 | toluene | 70 | 30 | >99 | (*S*) 92 |
| 12 | toluene | 30 | 30 | >99 | (*S*) 94 |
| 13[d] | toluene | 30 | 30 | >99 | (*S*) 94 |

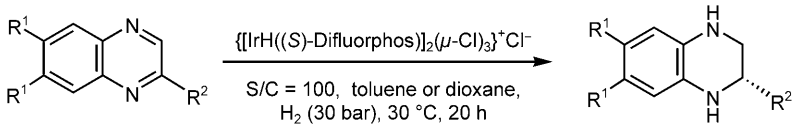
[a] *Reaction conditions:* **5a** (1.0 mmol).
[b] Conversion was determined by $^1$H NMR of the crude product.
[c] Enantiomeric excess was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column. Absolute configuration was determined by comparison of the specific rotation with reported data.
[d] S/C = 1000.

were used (entries 2 and 3, 99% conversion, 75% *ee*). Finally, we were pleased to find that switching from (*S*)-Synphos[19] to the electron-deficient ligand (*S*)-Difluorphos,[20] developed by our group, had a significant impact on the stereochemical outcome of the reaction. The high performance of the Difluorphos ligand has been previously demonstrated in the asymmetric hydrogenation of various 2-substituted quinoline derivatives.[16,17] Indeed, although the triply iodide-bridged catalyst {[IrH((*S*)-Difluorphos)]$_2$(μ-I)$_3$}$^+$I$^-$ **4d** gave (*S*)-**6a** with a moderate *ee* of 69%, the use of {[IrH((*S*)-Difluorphos)]$_2$(μ-Br)$_3$}$^+$Br$^-$ catalyst **4e** bearing a bromide instead of an iodide ligand led to a considerable improvement in the enantioselectivity, providing the reduced product (*S*)-**6a** with an *ee* of up to 87% and 99% conversion (entries 4 and 5). The best result regarding both conversion and enantioselectivity was reached with catalyst [{IrH((*S*)-Difluorphos)}$_2$(μ-Cl)$_3$]$^+$Cl$^-$ **4f** producing 2-methyl-1,2,3,4-tetrahydroquinoxaline (*S*)-**6a** with a full conversion and an excellent enantiomeric excess of 92% (entry 6). This unprecedented halide dependence is once again in agreement with our earlier observations on the asymmetric hydrogenation of 2-aryl- and 2-alkyl-substituted quinolinium salts, where chloro- and bromo-iridium catalysts gave superior catalytic performance over the corresponding iodo-iridium catalyst.[17]

To further improve the enantioselectivity of the reaction, the effects of solvent, temperature and hydrogen pressure were also investigated, using 1 mol% of the best catalyst {[IrH((*S*)-Difluorphos)]$_2$(μ-Cl)$_3$}$^+$Cl$^-$ **4f**. The results from these experiments are shown in Table 2. Excellent conversions were achieved in all examined solvents, either protic or aprotic, but the enantiomeric excesses of the products were highly solvent-dependent. While each catalytic hydrogenation was allowed to proceed in each considered solvent, the use of MeOH resulted in the formation of the hydrogenated product (*R*)-**6a**, with a low 19% *ee* and an opposite configuration; whereas running the reaction in *i*-PrOH provided (*S*)-**6a** in a moderate *ee* of 53% (entries 1 and 2). Tetrahydrofuran, ether, dioxane and dichloromethane gave significantly better enantioselectivities (entries 3–6, 85 to 90% *ee*), but the best *ee* (92%) was obtained when toluene was used as solvent (entry 7). Data in Table 2 also illustrate that variations of the temperature and hydrogen pressure influenced the catalytic activity in terms of both conversion and enantioselectivity. A temperature increase above 30 °C led to a decrease in selectivity giving **6a** with 90% *ee* whereas an excellent *ee* of up to 93%, was obtained when the reaction was conducted at 10 °C, albeit at a lower conversion of 86% (entries 8 *vs.* 9 and 10). A change in the hydrogen pressure from 30 to 70 bar had little effect on the stereochemical outcome of the reaction, since an excellent catalytic activity in terms of both conversion and enantioselectivity was still maintained with *ee*s ranging from 92

**Table 3.** Asymmetric hydrogenation of 2-alkyl- and 2-aryl-substituted quinoxalines.[a]




**5a – r** **6a – r**

| Entry | | Substrate $R^1$ | Substrate $R^2$ | Yield [%][b,c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | **5a** | H | Me | 99 | 94 (*S*) **6a** |
| 2 | **5b** | H | Et | 99 | 95 (*S*) **6b** |
| 3 | **5c** | H | *n*-Bu | 98 | 91 (*S*) **6c** |
| 4 | **5d** | H | *i*-Pr | 98 | 94 (*S*) **6d** |
| 5 | **5e** | H | $CH_2CH_2Ph$ | 97 | 91 (*S*) **6e** |
| 6 | **5f** | Me | Me | 98 | 90 (*S*) **6f** |
| 7 | **5g** | Me | Et | 98 | 91 (*S*) **6g** |
| 8 | **5h** | Me | *n*-Bu | 97 | 90 (*S*) **6h** |
| 9[e] | **5i** | H | $C_6H_5$ | 98 | 89 (*S*) **6i** |
| 10[e] | **5j** | H | *o*-Me-$C_6H_4$ | 97 | 91 (*S*) **6j** |
| 11[e] | **5k** | H | *m*-Me-$C_6H_4$ | 98 | 86 (*S*) **6k** |
| 12[e] | **5l** | H | *p*-Me-$C_6H_4$ | 99 | 91 (*S*) **6l** |
| 13[e] | **5m** | H | *m*-OMe-$C_6H_4$ | 97 | 87 (*S*) **6m** |
| 14[e] | **5n** | H | *p*-OMe-$C_6H_4$ | 97 | 90 (*S*) **6n** |
| 15[e] | **5o** | H | *p*-$NO_2$-$C_6H_4$ | 96 | 91 (*S*) **6o** |
| 16[e] | **5p** | H | *p*-F-$C_6H_4$ | 97 | 89 (*S*) **6p** |
| 17[e] | **5q** | H | *p*-Cl-$C_6H_4$ | 98 | 94 (*S*) **6q** |
| 18[e] | **5r** | H | *m*-Br-$C_6H_4$ | 98 | 88 (*S*) **6r** |

[a] *Reaction conditions:* **5** (1.0 mmol).
[b] Isolated yield after flash column chromatography on silica gel.
[c] In each case complete conversion was achieved.
[d] Enantiomeric excess was determined either by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on Chiralcel AD-H and OD-H columns for **6a-h**, or by HPLC on a Chiralcel OD-H column for **6i–r** (see Supporting Information). Absolute configuration was determined by comparison of the specific rotation with reported data.
[e] Dioxane was used as a solvent instead of toluene.

to 94% (entries 11 and 12). Moreover, the catalyst loading can even be lowered to 0.1 mol% without erosion of the enantioselectivity (entry 13).

Encouraged by the promising results obtained in the hydrogenation of 2-methylquinoxaline **5a**, a variety of 2-alkyl- and 2-aryl-substituted quinoxalines, easily prepared according to known procedures,[21,22] were reduced under the optimized reaction conditions. As illustrated in Table 3, all quinoxaline derivatives **5a–r** were successfully hydrogenated to afford their corresponding tetrahydroquinoxaline derivatives **6a–r** in excellent isolated yields and good to excellent enantioselectivities (entries 1–18, 96–99% yield and 86–95% *ee*).

For 2-alkyl-substituted quinoxalines, the length of the alkyl chain had a negligible impact on the enantioselectivity, since *ee* values ranging from 91% for the phenethyl substituent to 95% for the ethyl group were observed (entries 1–5). The absolute configuration of the 2-phenethyl-1,2,3,4-tetrahydroquinoxaline **6e** was determined to be *S* based on a single-crystal *X*-ray structure analysis[23] of the corresponding 4-*N*-tosyl-2-phenethyl-1,2,3,4-tetrahydroquinoxaline **7** (not shown). Comparable good selectivities were obtained with 2-alkyl-substituted quinoxalines bearing a methyl substituent at the 6- and 7-positions on the aromatic ring (entries 6–8, 90–91% *ee*). The data in Table 2 show that 2-aryl-substituted quinoxalines **5i–r**, with either electron-withdrawing or electron-donating substituents, can also be hydrogenated in high chemical yields and with good to excellent asymmetric inductions when the reactions were conducted in dioxane (entries 9–18, 96–99% yield and 86–94% *ee*). Indeed, hydrogenation of 2-phenylquinoxaline **5i** resulted in the formation of compound **6i** in 89% *ee*, which is the best enantioselectivity reported so far (entry 9), whereas *ortho*-substitution afforded **6j** in 91% *ee* (entry 10). Furthermore, high *ee* values were also reached with *meta*-substituted derivatives irrespective of the electronic nature of the substitution pattern (entries 11, 13, and 18, 86–88% *ee*). Finally, hydrogenation of 2-aryl-substituted quinoxalines containing either electron-donating or electron-withdrawing substituents at the *para* position of the aromatic moiety

led to excellent selectivities with *ee* up to 94% (entries 12, 14–17).

In conclusion, we have developed a general and efficient iridium-Difluorphos-catalyzed asymmetric hydrogenation of diverse 2-alkyl- and 2-aryl-substituted quinoxalines into biologically and pharmaceutically relevant 1,2,3,4-tetrahydroquinoxaline units, with high chemical yields and enantioselectivities ranging from 89% *ee* for 2-phenylquinoxaline to up to 95% *ee* which are, to the best of our knowledge, the highest *ee* values reported so far for the asymmetric hydrogenation reactions of 2-aryl-substituted quinoxaline derivatives.

## Experimental Section

### General Procedure

A glass tube was charged with **5** (0.42 mmol) and iridium dinuclear complex (2.1 μmol, S/C = 100). The tube was placed in a stainless steel autoclave, which was subjected to three vacuum/argon cycles. Anhydrous and degassed solvent (3.0 mL) was then added under argon. The hydrogenation was performed at 30 °C under an atmosphere of hydrogen (30 bar) for 20 h. After careful releasing of the hydrogen gas, the resulting mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. The conversion was determined by $^1$H NMR analysis of the crude product, and the enantiomeric excess by chiral CSP-SFC or HPLC analysis of the filtrate using a Chiralcel OD-H, or AD-H column.

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[23] See Supporting Information. CCDC 774501 contains the supplementary crystallographic data for compound (*S*)-**7** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

  