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Asymmetric Hydrogenation of Quinoxalines with Diphosphinite Ligands: A Practical Synthesis of Enantioenriched, Substituted Tetrahydroquinoxalines**

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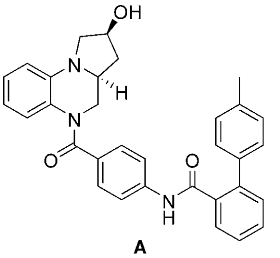
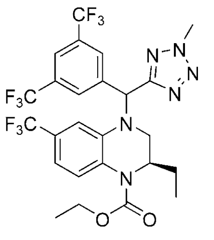
The 1,2,3,4-tetrahydroquinoxaline ring system is an important structural unit in many bioactive compounds.[1–3] Optically pure tetrahydroquinoxaline derivatives have shown great potential for pharmaceutical applications. For example, chiral compound **A** has been pursued as a potent vasopressin V2 receptor antagonists,[1d] and optically pure compound **B** is a promising inhibitor of cholesteryl ester transfer protein.[1e] In both cases, the chirality of the compounds was found to play a very important role in the relevant bioactivity of these compounds.



A



B

The most convenient and straightforward route to chiral tetrahydroquinoxalines is the asymmetric hydrogenation of quinoxalines. Although several kinds of heteroaromatic compounds,[4] such as quinolines,[5] indoles,[6] furans,[7] pyridines,[8] and pyrazines[9] have been successfully hydrogenated with good to excellent enantioselectivities and yields in the presence of chiral transition-metal catalysts, the enantioselective hydrogenation of substituted quinoxaline derivatives has been less extensively studied.[3] In 1987, Murata et al. first reported the rhodium-catalyzed asymmetric hydrogenation of 2-methylquinoxaline with only 3 % *ee*.[3a] Later Bianchini et al. enantioselectively hydrogenated 2-methylquinoxaline with an orthomelated dihydride iridium complex to produce the product with up to 90 % *ee*,[3b,c] but the reduction suffered from lower conversions. The performance of $[\mathrm{RuCl_2(diphosphine)(diamine)}]$ complexes[3d,e] and Ir/PQ-phos[3f] (PQ-phos = (*R*)-[6,6-(2*S*,3*S*-butadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl) was also investigated, but only gave medium to low *ee* values. Given the importance of chiral tetrahydroquinoxalines and in view of the lack of efficient methods for the preparation of these compounds,[2,3] the development of a practical and highly efficient catalytic asymmetric synthetic method appeared to be of great importance. Herein we describe the asymmetric hydrogenation of quinoxalines with an easily accessible Ir/diphosphinite catalyst. Good to excellent enantioselectivity (up to 98 % *ee*), unprecedented high catalytic activity (TOF up to 5620 h^{-1}), and productivity (TON up to 18140) were observed for a wide range of substrates.

Recently, the combination of transition metals and chiral phosphinite ligands has led to efficient catalysts for the asymmetric hydrogenation of prochiral olefins.[10] In comparison with diphosphines, diphosphinites offer the advantages of easy preparation and derivatization. Recently, we have demonstrated that the easily accessible chiral diphosphinite ligands derived from (*R*)-H_8-binol (binol = (1,1′-bi-2-naphthyl)) and (*R*)-1,1-spirobiindane-7,7-diol provided excellent catalytic activity and/or enantioselectivity in the Ir-catalyzed asymmetric hydrogenation of quinolines.[5f,g] Based on our previously optimized reaction conditions, we first investigated the performance of the $[\{\mathrm{IrCl(cod)}\}_2]$ (cod = 1,5-cyclooctadiene)/(*R*)-H_8-binapo or the (*R*)-sdpo/I_2 catalyst system in THF for the asymmetric hydrogenation of 2-methylquinoxaline (**1a**). To our delight, both catalysts worked efficiently with full conversions and good enantioselectivities (Table 1, entries 1 and 2), and (*R*)-H_8-binapo gave the desired product in somewhat better enantiomeric excess. In sharp contrast to

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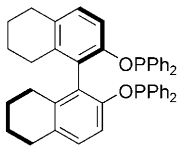
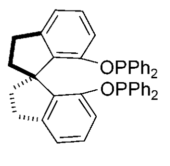
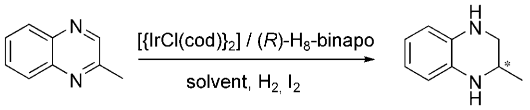


(R)-H_8-binapo (L*)



(R)-sdpo

Table 1: Optimization of the reaction conditions for asymmetric hydrogenation of 2-methyl-quinoxaline **1a**.[a]



1a **2a**

Entry	Solvent	H_2 [psi]; T [°C]; S/C	T [h]	Conv. [%][b]	*ee* [%][c]
1	THF	700; 20; 100	20	100	89(*S*)
2[d]	THF	700; 20; 100	20	100	83(*R*)
3	toluene	700; 20; 100	20	100	70(*S*)
4	CH_2Cl_2	700; 20; 100	20	100	80(*S*)
5	DCE	700; 20; 100	20	100	87(*S*)
6	MeOH	700; 20; 100	20	100	61(*S*)
7[e]	THF	700; 20; 100	20	28	38(*S*)
8	THF	1500; 20;100	1	100	89(*S*)
9	THF	300; 20; 100	1	100	83(*S*)
10	THF	700; 0; 100	1.5	100	91(*S*)
11	THF	700; −5; 100	1.5	100	93(*S*)
12	THF	700; −5; 1000	20	100	93(*S*)
13[f]	THF	700; −5; 5000	20	100	93(*S*)
14[f]	THF	700; −5; 10000	20	100	93(*S*)
15[g]	THF	700; −5; 20000	20	91	93(*S*)
16[g]	THF	700; −5; 20000	1	28	93(*S*)

[a] All reactions were carried out with 2-methylquinoxaline (0.15 mmol), I_2 (2 mol%), solvent (0.6 mL). [b] The conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] The enantiomeric excess was determined by HPLC on a chiral stationary phase according to previously reported methods.[3b] [d] (*R*)-SDPO was used as the ligand. [e] Without I_2 as an additive. [f] 0.3 mmol of 2-methylquinoxaline was used. [g] 0.6 mmol of 2-methylquinoxaline was used. DCE = 1,2-dichloroethane, S/C = substrate/catalyst molar ratio, THF = tetrahydrofuran.

the excellent performance of the commercially available chiral bidentate phosphine ligands in the iridium-catalyzed asymmetric hydrogenation of quinolines,[5] lower enantioselectivities of tetrahydroquinoxaline were observed when Ir/binap (18% *ee*; binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), Ir/MeO-biphep (59% *ee*; biphep = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl), Ir/P-Phos (49% *ee*; P-Phos = 2,2′,6,6′-4,4′-bis(diphenylphosphino)-3,3′-bipyridine), or Ir/synphos (77% *ee*; synphos = (5,6),-(5′,6′)-bis-(ethylenedioxy)-2,2′-bis(diphenylphosphino)-1,1′-biphenyl) were used. In addition, the other sterically demanding (*R*)-H_8-binapo derivatives bearing substituents on the 3- and 3′-positions of the ligand framework resulted in much lower enantioselectivities.[11]

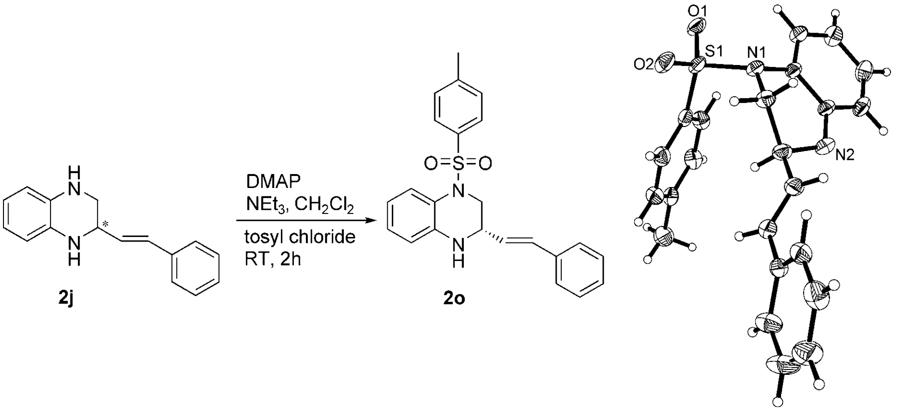
With the Ir/H_8-binapo catalyst in hand, a systematic study of the hydrogenation of **1a** was performed to establish the optimum reaction conditions. The solvent effect was examined, and changing the solvent from THF to other solvents led to similar catalytic activity but lower enantioselectivity (Table 1, entries 3–6). Considering the crucial role of the additive in the asymmetric hydrogenation of heteroaromatic compounds,[5] we also evaluated the effects of additives. For example, only 28% conversion and 32% *ee* were obtained in the absence of the iodine additive (Table 1, entry 7). Replacing iodine with other additives gave lower *ee* values or even racemic product.[11] With iodine as the additive and THF as the solvent, further investigations focused on the effect of hydrogen pressure and temperature. Increasing the hydrogen pressure had no effect on the reactivity and enantioselectivity (Table 1, entry 8), but decreasing the hydrogen pressure led to a lower *ee* value (83%; Table 1, entry 9). Lowering the reaction temperature resulted in a marked increase in enantioselectivity, and the best *ee* value of 93% was obtained at −5 °C (Table 1, entries 10 and 11). To the best of our knowledge, this *ee* value represents the highest enantioselectivity attained so far in the catalytic asymmetric hydrogenation of 2-methylquinoxaline.[3]

Having established a highly enantioselective hydrogenation of **1a**, we turned to examine the catalyst loading (Table 1, entries 12–16). Pleasingly, we were able to decrease the catalyst loading to 0.005 mol% without any loss in enantioselectivity. Even with 0.005 mol% of Ir catalyst, the reaction proceeded smoothly in only slightly lowered conversion and with the same enantioselectivity (Table 1, entry 15). Remarkably, under the same reaction conditions, **1a** was hydrogenated in 1 h to give 28% conversion, providing a TON of 18140 and a TOF of 5620 h^{-1} (Table 1, entry 16). Notably, this TOF value is the best result reported so far in the asymmetric hydrogenation of heteroaromatic compounds.[3–9]

Next, we explored the scope of the iridium-catalyzed asymmetric hydrogenation of substituted quinoxalines under the optimized reaction conditions. The results are listed in Table 2, which showed that all the substrates were smoothly reduced with good enantioselectivities and full conversions even at an S/C ratio of 5000. It was found that the reaction system was sensitive to steric effect, and the presence of a less sterically demanding alkyl group at the 2-position led to better enantioselectivities (compare Table 2, entries 1–4 with entry 5). The presence of substituents at the 6- and 7-positions of the quinoxaline framework slightly lowered the enantioselectivity (Table 2, entries 6 and 7). Lower *ee* values were also observed in the case of aryl-substituted quinoxalines (Table 2, entries 8 and 9). In the hydrogenation of 2-styryl-substituted quinoxalines, the substituents on the phenyl ring showed no influence on the catalytic activity, but slightly affected the enantioselectivity (Table 2, entries 10–14). The best results were obtained with substrates bearing phenyl or *p*-tolyl groups (Table 2, entries 10 and 13).

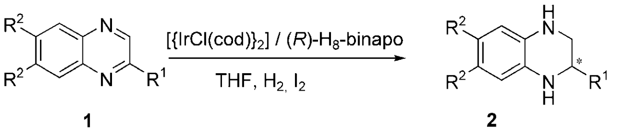
The absolute configuration of the 2-substituted styryl tetrahydroquinoxalines (**2j**) was determined to be *S* based on single-crystal X-ray analysis of 4-*N*-tosyl-2-styryl-tetrahydroquinoxaline (**2o**; Scheme 1).[11] The configurations of the other compounds are proposed by analogy.

Finally, we applied this new protocol to the synthesis of compound **2b**, an inhibitor of cholesteryl ester transfer protein,[1f] as an example of the quinoxaline class of biologically active compounds. Asymmetric hydrogenation of 2-



Scheme 1. Derivatization of **2j** and solid-state structure of **2o** showing the stereogenic center at C8 to have an *S* configuration. DMAP = 4-dimethylaminopyridine.

Table 2: Asymmetric hydrogenation of substituted quinoxalines **1**.[a]



Entry	**1**	R^1/R^2	Conv. [%][b,c]	*ee* [%][c,d,e]
1	**1a**	methyl/H	> 99 (> 99)	93 (93)
2	**1b**	ethyl/H	> 99 (> 99)	89 (89)
3	**1c**	*n*-butyl/H	> 99 (> 99)	93 (93)
4	**1d**	isobutyl/H	> 99 (> 99)	94 (94)
5	**1e**	*t*-butyl/H	> 99 (> 99)	85 (81)
6	**1f**	methyl/methyl	> 99	87
7	**1g**	ethyl/methyl	> 99 (> 99)	89 (91)
8	**1h**	phenyl/H	> 99 (> 99)	84 (85)
9	**1i**	*o'*-MeO-phenyl/H	> 99 (> 99)	84 (84)
10	**1j**	styryl/H	> 99 (> 99)	96 (97)
11	**1k**	3'-NO_2-styryl/H	> 99 (99)	92 (92)
12	**1l**	2'-Cl-styryl/H	> 99 (99)	92 (93)
13	**1m**	4'-CH_3-styryl/H	> 99 (99)	96 (98)
14	**1n**	2'-(naphth-1-yl)vinyl/H	> 99 (99)	93 (93)

[a] Reaction conditions: substrate (0.15 mmol), Ir/H_8-binapo catalyst (1 mol%), H_2 (700 psi), I_2 (2 mol%), THF (0.6 mL), stirred at −5 °C for 20 h. [b] The conversion was determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] The results in bracket were obtained at a substrate (0.3 mmol) to catalyst ratio of 5000. [d] The enantiomeric excess was determined by HPLC on a chiral stationary phase using a Chiralcel OD-H (**2a–2i**), AS-H (**2j**, **2m**), and OJ-H (**2k**, **2l**, **2n**) column. [e] The absolute configuration was assigned as *S* for all products according to a previously reported method[2f,3] (entries 1–4) or based on the optical rotation in comparison with a derivative of **2j**, which was characterized by single-crystal X-ray analysis (entries 5–13).

ethylquinoxaline (**1b**) was carried out on a gram scale (1.9 g) at a low catalyst loading (Ir/H_8-binapo (0.01 mol%)), thus providing tetrahydroquinoxaline **2b** in 95% yield with 89% *ee*. After transformation of **2b** into its N-tosylated derivative and recrystallization from Et_2O, up to 99.9% *ee* was obtained.[12]

In conclusion, we have developed a highly efficient iridium-catalyzed asymmetric hydrogenation of quinoxalines at low catalyst loading (as low as 0.005 mol%). This new method provides a practical synthetic approach to the preparation of optically active chiral tetrahydroquinoxaline derivatives.

Experimental Section

A mixture of [{IrCl(cod)}$_2$] and (*R*)-H_8-binapo (M/L* = 0.5/1.1) in THF was stirred at room temperature for 10 min in a glove box, the mixture was transferred by a syringe to a stainless steel autoclave, in which I_2 (2 mol%) and the substrate were already placed. The hydrogenation was performed at −5 °C under H_2 (700 psi) from 1–20 h. After carefully releasing the hydrogen gas, saturated sodium carbonate was added and the mixture was stirred for 10 min. The organic layer was separated and extracted with diethyl ether twice, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (eluent: CH_2Cl_2 or EtOAc) gave the pure products. The enantiomeric excess values were determined by HPLC on a chiral stationary phase using a Chiralcel OJ-H, OD-H, or AS-H column.

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[11] CCDC 748584 (**2o**) contains the supplementary crystallographic data for 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.

[12] For details, see the Supporting Information.