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Air-Stable and Phosphine-Free Iridium Catalysts for Highly Enantioselective Hydrogenation of Quinoline Derivatives†

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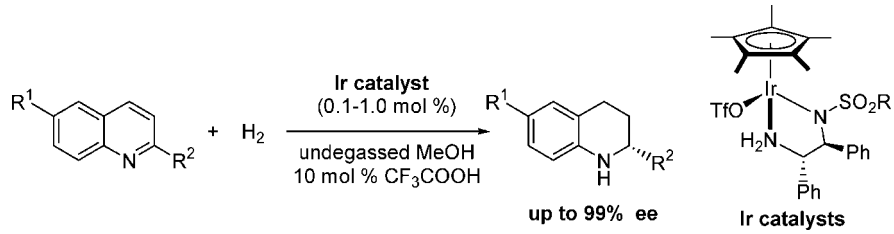
ABSTRACT



Enantioselective hydrogenation of quinoline derivatives catalyzed by phosphine-free chiral cationic Cp*Ir(OTf)(CF_3TsDPEN) complex (CF_3TsDPEN = *N*-(*p*-trifluoromethylbenzenesulfonyl)-1,2-diphenylethylene-diamine) afforded the 1,2,3,4-tetrahydroquinoline derivatives in up to 99% ee. The reaction could be carried out with a substrate-to-catalyst molar ratio as high as 1000 in undegassed methanol and with no need for inert gas protection.

Homogeneous asymmetric hydrogenation has been established as one of the most versatile and powerful tools for the preparation of a wide range of enantiomerically pure compounds in organic synthesis.[1] Transition metal complexes with chiral phosphorus ligands are the dominant choice of catalysts for asymmetric hydrogenation. To date, a number of efficient chiral phosphorus ligands with diverse structures have been developed, and their applications in asymmetric hydrogenation of prochiral olefins, ketones, and imines have been extensively utilized in both academic research and industry.[2] In contrast, transition-metal-catalyzed asymmetric hydrogenation of heteroaromatic compounds has achieved few successes,[3,4] probably due to the high resonance stability of these substrates and/or the potential poisoning of the catalysts by these heteroaromatic compounds. Recently, a number of iridium complexes that are effective in the asymmetric hydrogenation of quinolines have been reported since the first example reported by Zhou and co-workers.[4a] Although significant progress has been achieved in the area of asymmetric hydrogenation of 2-substituted quinolines,[4] several challenges still remain. For example, most of these reported catalytic systems suffered from low catalyst ef-

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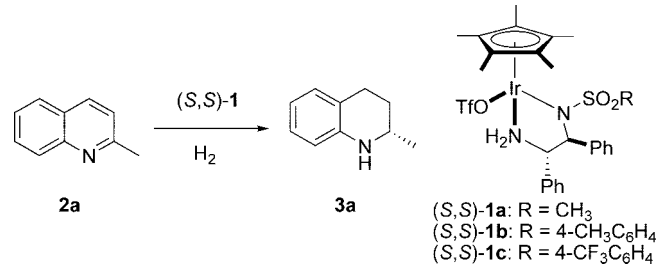
ficiency, as evidenced by the fact that good results could only be obtained at a low substrate/catalyst ratio of 100.[4d,e] Furthermore, all reported catalysts for such reactions have at least one phosphine ligand around the iridium center and are often air-sensitive.[5] From the viewpoints of both scientific interest and practical applications, it is highly desirable to develop easily available and air-stable chiral catalysts for the asymmetric hydrogenation of quinolines.

In comparison with the chiral phosphorus ligand-containing catalysts, the chiral diamine-based catalysts are more easily available and are expected to be more air-stable.[6] However, only a few of them were found to be capable of activating molecular hydrogen.[7,8] Recently, Noyori and Ohkuma reported that the chiral cationic phosphine-free Ru(OTf)(cymene)(TsDPEN) and Cp*Ir(OTf)(MsDPEN) complexes,[9] known as excellent catalysts for asymmetric transfer hydrogenation, could be used for the asymmetric hydrogenation of prochiral ketones in methanol.[8] A neutral to slightly acidic reaction condition fits the requirement of such reactions. In our recent study, we extended the application of this cationic Ru-catalyst to the enantioselective hydrogenation of quinolines at a substrate/catalyst molar ratio of 100 in neat ionic liquid, affording 1,2,3,4-tetrahydroquinolines with excellent enantioselectivity.[10] It was believed that the hydrogenation of quinoline occurred through a stepwise H^+/H^- transfer process, which was different from the concerted mechanism proposed for the reduction of ketone.[8b]

Many metal complexes that are reactive toward hydrogen, for example, the chiral diphosphine-containing catalysts, are known to be rapidly and irreversibly oxidized upon treatment with oxygen.[11] Therefore, asymmetric hydrogenation catalyzed by such complexes must be performed under extremely oxygen-free conditions. In contrast, Rauchfuss and coworkers recently reported that the iridium hydride complex, Cp*IrH(TsDPEN), could efficiently catalyze the hydrogenation of oxygen in the presence of Brønsted acid.[12] Similar observation was independently made by Ikariya at almost the same time.[13] Based on this finding, they developed an efficient protocol for the aerobic oxidative kinetic resolution of racemic secondary alcohols by using oxygen as a hydrogen acceptor.

Scheme 1. Asymmetric Hydrogenation of 2-Methylquinoline



Given the fact that the iridium hydride complexes could not be deactivated by oxygen, we wish to report here our continuing efforts on the investigation whether the chiral diamine-containing Ir complexes could be used as efficient and air-stable catalysts for the hydrogenation of quinolines (Scheme 1). It was found that the hydrogenation proceeded smoothly with a substrate-to-catalyst molar ratio as high as 1000 in undegassed methanol with no need for inert gas protection throughout the entire operation, affording a series of 2-substituted tetrahydroquinoline derivatives in up to 99% ee.

We started with the hydrogenation of 2-methylquinoline (**2a**) using Cp*Ir(OTf)(MsDPEN) (**1a**) as catalyst in undegassed methanol. The precatalyst was prepared from commercially available $[Cp^*IrCl_2]_2$ and (*S*,*S*)-MsDPEN ligand in two steps according to the published method with some modifications.[8d,14] With 1.0 mol % of **1a**, the reaction was carried out under 50 atm of hydrogen in undegassed methanol without using a glovebox (Table 1). To our delight, 69% conversion and 94% ee were obtained in 2 h (entry 1), which are comparable to those obtained under anaerobic conditions (with the use of degassed methanol and glovebox). Notably, the reaction rate increased significantly upon the addition of 10 mol % CF_3COOH as an additive (entry 2 vs entry 1).

To further test the stability of the catalyst to oxygen, the catalyst solution was stirred under oxygen atmosphere for 1 h prior to the introduction of hydrogen. Almost identical

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(9) TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine; TfO^- = trifluoromethanesulfonate; Cp* = pentamethylcyclopentadienyl; MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine.

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Table 1. Asymmetric Hydrogenation of 2-Methylquinoline (**2a**) Catalyzed by (*S*,*S*)-**1a**: Effects of the Oxygen and Acid[a]

entry	time (h)	TFA (mol %)	conv (%)[b]	ee (%)[c]
1	2		69 (71)[d]	94 (94)[d]
2	1	10	95	96
3[e]	1	10	71	95
4[f]	1	10	58	94
5[f,g]	24	10	10	93
6	1	2	42	95
7	1	5	63	95
8	1	25	>95	94

[a] Reaction conditions: 28.6 mg of substrate **2a** in 1 mL of undegassed MeOH, 1.0 mol % catalyst (*S*,*S*)-**1a**, 50 atm H_2, 25 °C. All manipulations were conducted in air, and the autoclave was purged with H_2 three times before reaction. [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC analysis. [d] Data in parentheses were obtained under nitrogen atmosphere. [e] The catalyst solution was stirred under oxygen atmosphere before hydrogenation. [f] Without purging the autoclave with H_2 before reaction. [g] Catalyst Ru(OTf)(cymene)(TsDPEN) was used.

enantioselectivity was observed, although the conversion decreased slightly (entry 3). *Even when the hydrogenation was carried out in undegassed solvent and in the presence of air, similar enantioselectivity was observed (entry 4).* These results indicated that both the Ir precatalyst and the catalytically active species were air-stable. In contrast, the reaction was found to be sluggish when Ru(OTf)(cymene)(TsDPEN) was used as catalyst under otherwise identical conditions, indicative of the decomposition and/or deactivation of the Ru-catalyst in the presence of air during the hydrogenation (entry 5).

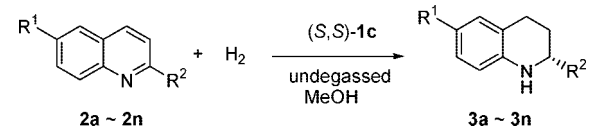
Considering the important impact of acid additive on reactivity, we then evaluated a number of organic and inorganic acids, such as CF_3SO_3H, CF_3COOH, CH_3COOH, *p*-toluenesulfonic acid, H_2SO_4, H_3PO_4, etc.[15] CF_3COOH (TFA) was found to be the best choice. Low conversions were observed by decreasing the amount of TFA (entries 6 and 7). In terms of both conversion and enantioselectivity, 10 mol % TFA was chosen for all following catalytic reactions.

Table 2. Optimization of Reaction Conditions[a]

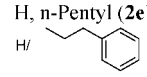
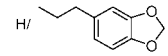
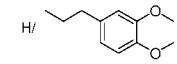
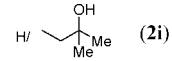
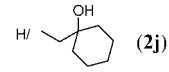
entry	catalyst	solvent	H_2 (atm); temp (°C)	conv (%)[b]	ee (%)[c]
1	(*S*,*S*)-**1a**	MeOH	50; 25	95	95
2	(*S*,*S*)-**1b**	MeOH	50; 25	66	91
3	(*S*,*S*)-**1c**	MeOH	50; 25	62	97
4	(*S*,*S*)-**1c**	EtOH	50; 25	77	95
5	(*S*,*S*)-**1c**	IPA	50; 25	74	75
6	(*S*,*S*)-**1c**	H_2O	50; 25	29	96
7	(*S*,*S*)-**1c**	CH_3CN	50; 25	23	92
8	(*S*,*S*)-**1c**	CH_2Cl_2	50; 25	27	85
9	(*S*,*S*)-**1c**	toluene	50; 25	62	46
10	(*S*,*S*)-**1c**	THF	50; 25	18	16
11	(*S*,*S*)-**1c**	MeOH	80; 25	70	97
12	(*S*,*S*)-**1c**	MeOH	20; 25	50	97
13	(*S*,*S*)-**1c**	MeOH	1; 25	25	94
14	(*S*,*S*)-**1c**	MeOH	50; 50	80	95
15	(*S*,*S*)-**1c**	MeOH	50; 0	32	98
16[d]	(*S*,*S*)-**1c**	MeOH	50; 15	99	98
17[e]	(*S*,*S*)-**1c**	MeOH	50; 15	90	98

[a] Reaction conditions: 28.6 mg of substrate **2a** in 1 mL of undegassed solvent, 1.0 mol % Ir-catalyst, 10 mol % TFA, 1 h. All manipulations were conducted in air, and the autoclave was purged with H_2 three times before reaction. [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC analysis. [d] Substrate/catalyst = 500 (143 mg substrate in 1 mL MeOH), 24 h. [e] Substrate/catalyst = 1000 (286 mg substrate in 1 mL MeOH), 24 h.

Table 3. Asymmetric Hydrogenation of 2-Substituted Quinoline Derivatives Catalyzed by (*S*,*S*)-**1c**[a]



2a ~ 2n **3a ~ 3n**

entry	R^1, R^2	yield (%)[b]	ee (%)[c]
1	H, Me (**2a**)	99	98
2	H, Et (**2b**)	98	98
3	H, n-Pr (**2c**)	98	96
4	H, n-Bu (**2d**)	97	97
5	H, n-Pentyl (**2e**)	98	96
6	 (**2f**)	97	97
7	 (**2g**)	97	97
8	 (**2h**)	96	96
9	 (**2i**)	97	99
10	 (**2j**)	97	99
11	MeO, Me (**2k**)	97	97
12	Me, Me (**2l**)	95	97
13	F, Me (**2m**)	98	94
14	H, Ph (**2n**)	90	79

[a] Reaction conditions: 0.75 mmol substrate in 1 mL of undegassed MeOH, 0.2 mol % (*S*,*S*)-**1c**, 10 mol % TFA, 50 atm H_2, 15 °C, 24−48 h. All manipulations were conducted in air, and the autoclave was purged with H_2 three times before reaction. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Next, the effects of chiral ligands, solvents, H_2 pressure, and reaction temperature on catalytic activity and enantioselectivity were examined by using **2a** as a standard substrate. The results, in Table 2, showed the influence of the sulfonyl group on the performance of catalysts (entries 1−3). Catalyst **1c**, which gave the highest enantioselectivity (97% ee, entry 3), was thus selected as the catalyst for the optimization of other factors.

As shown in Table 2, a strong solvent-dependent effect was observed (entries 3−10). The hydrogenation in alcoholic solvent, such as methanol, ethanol, and isopropanol, proceeded well to give 2-methyl-1,2,3,4-tetrahydroquinoline (**3a**) in good conversion and good to excellent enantioselectivity (entries 3−5). Notably, the reaction could be carried out in H_2O and CH_3CN, affording **3a** with very good enantioselectivity but low conversion (entries 6 and 7). In contrast, aprotic solvents, such as CH_2Cl_2, toluene and THF gave much lower conversions and enantioselectivities (entries 8−10). It was noted that the enantioselectivity is insensitive

to the hydrogen pressure in the range of 20−80 atm, while much lower conversion and slightly low enantioselectivity were observed under atmosphere hydrogenation pressure (entries 11−13). Increasing reaction temperature led to higher conversion but at a cost of slightly low enantioselectivity (entries 14 and 15). *Most importantly, the reaction proceeded smoothly at low catalyst loading (0.1 mol %) in high conversion with excellent enantioselectivity upon prolonged reaction time* (entries 16 and 17).

Under the optimized reaction conditions, a series of 2-substituted and 2,6-disubstituted quinoline derivatives were then hydrogenated with catalyst **1c** in undegassed methanol.[16] The results are listed in Table 3. In general, all 2-alkyl-substituted quinolines were hydrogenated with good reactivity and excellent enantioselectivity (96−98% ee). The reaction was relatively insensitive to the length of the side chain of 2-alkylated quinolines (entries 1−5). Excellent results were also achieved with 2-phenethyl quinolines (entries 6−8). Notably, the quinolines with a hydroxyl group at the side chain provided the highest enantioselectivity of 99% ee (entries 9 and 10). The presence of a substituted group on the 6-position had no obvious effect on either yield or enantioselectivity (entries 11−13). The hydrogenation of 2-phenyl-substituted quinoline also proceeded smoothly but gave a lower enantioselectivity than those of 2-alkylated quinolines (entry 14).

In summary, we have developed a new kind of highly effective phosphine-free Ir-catalysts for the asymmetric hydrogenation of quinolines with up to 99% ee. The reaction proceeded smoothly in undegassed solvent with no need for inert gas protection throughout the entire operation. Thus, this method provides an efficient and practical tool for the synthesis of a variety of optically active 1,2,3,4-tetrahydroquinoline derivatives.

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Supporting Information Available: Experimental procedures and characterization data for the Ir catalysts and the reduced products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For details, see Supporting Information.

(16) 3-Methylquinoline could also be completely hydrogenated with catalyst **1c**, but racemic product was obtained.