

Air-stable Ir-(P-Phos) complex for highly enantioselective hydrogenation of quinolines and their immobilization in poly(ethylene glycol) dimethyl ether (DMPEG)

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An air-stable catalyst system Ir-(P-Phos) catalyst was found to be highly effective in the asymmetric hydrogenation of quinoline derivatives. The catalyst immobilized in DMPEG was efficiently recovered and reused eight times, retaining reactivity and enantioselectivity.

Asymmetric hydrogenation of heteroaromatic compounds provides an attractive and convenient approach to optically pure heterocycloalkanes and their derivatives.¹ However, a variety of chiral Rh, Ru and Ir complexes, which have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines, often failed to give good results.² So far only limited examples of the homogeneous asymmetric hydrogenation of heteroaromatic compounds have been reported.²⁻⁴

Optically pure tetrahydroquinoline derivatives are important organic synthetic intermediates and building blocks for the preparation of biologically active compounds.⁵ However, methods for the enantioselective formation of these chiral compounds are scarce. Recently, Zhou and co-workers found that the iridium complex generated *in situ* from [Ir(COD)Cl]₂ and (R)-MeO-Biphep or ferrocenyloxazoline-derived P,N-ligand worked efficiently in the enantioselective hydrogenation of quinoline derivatives at room temperature, providing optically active tetrahydroquinolines bearing a chiral carbon at 2-position with high enantioselectivities and yields.⁴

A frequently encountered problem associated with the use of transition metal phosphine catalyst is the air-sensitivity of the active catalyst. The existence of trace amount of air in the reaction system can lead to deactivation of the catalyst and irreproducible results. Therefore it is highly desirable to develop catalyst with high activity and good air-stability. We have recently prepared a new family of chiral dipyridylphosphane ligands and have shown their effectiveness in asymmetric hydrogenations of prochiral olefins and ketones.⁶ It is notable that the ruthenium complexes, [Ru(C₆H₆)(P-Phos)Cl₂] and [RuCl₂(P-Phos)(DPEN)] display good air-stability even in solution. Herein we report a highly effective and air-stable iridium catalyst generated *in situ* from P-Phos and [Ir(COD)Cl]₂, and its application in the enantioselective hydrogenation of a series of 2-substituted quinolines. The air-stability of the catalyst makes the experimental operations very convenient and shows good potential for industrial applications. Following our interest in the immobilization and recycling of chiral catalysts in asymmetric hydrogenation,⁷ we find this Ir-(P-Phos) catalyst to

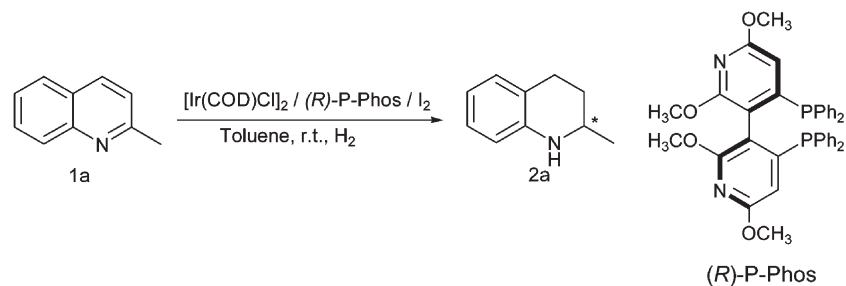
be effectively immobilized and reused in polyethylene glycol dimethyl ether (DMPEG), a low-cost and environmentally benign liquid polymer. To the best of our knowledge, immobilized catalyst for asymmetric hydrogenation of heteroaromatic compounds has not been previously reported. This also represents the first example of the immobilization of the new family of chiral dipyridylphosphane ligands and their organometallic complexes.

To assess the effectiveness and the air-stability of the Ir-(P-Phos) catalyst in asymmetric hydrogenation of quinolines, we chose 2-methyl quinoline **1a** as the model substrate. The catalyst was generated *in situ* from [Ir(COD)Cl]₂ and P-Phos in combination with I₂ as an additive and the hydrogenation was carried out for 20 h at room temperature under the conditions previously reported by Zhou and coworkers (Scheme 1).⁴ Initially 84% ee and 84% yield were achieved. A series of organic solvents were tested for the reaction and the corresponding results on the product ee and yield (in parenthesis) were found to be as follows: CH₂Cl₂, 88% (47%); 1, 2-dichloroethane, 89% (76%); THF, 91% (97%); benzene, 91% (55%); methanol, 48% (33%); and ethanol 18% (83%). THF was found to give the best results, and the use of alcoholic solvents resulted in lower enantioselectivity or catalytic activity. Most importantly, the Ir-(P-Phos) catalyst was found to be air-stable even after exposing the catalyst solution to air for 24 h. A ³¹P-NMR study of the solution showed no change of the spectrum even after two weeks in air. However, using MeO-BIPHEP as ligand under the same conditions, the enantioselectivity and the conversion of **2a** obtained dropped to 21% and 28%, respectively.

A series of 2-substituted quinoline derivatives were hydrogenated using Ir/P-Phos/I₂ catalyst in THF without degassing. The results are listed in Table 1. In general, all substituted quinolines studied were hydrogenated with high enantioselectivity (≥90% ee) and very good yields. The reaction is relatively insensitive to the length of side chain of 2-alkylated substituted quinolines, and good yields and enantioselectivities have been consistently obtained (entries 1–3). Good result was also achieved with 2-phenethyl quinoline (entry 4). The presence of substituted group on position 7 has no effect on either yield or enantioselectivity (entry 5). The tolerance of hydroxyl group is also demonstrated by the successful hydrogenation of substrates **1f–g** with excellent yields and high enantioselectivities (entries 6–7).



Having established the high efficiency and the air-stability of our Ir-(P-Phos) catalyst system, we started exploring the recyclability of this catalyst in the hydrogenation reaction. Since ionic liquids and polyethylene glycol (PEG) have attracted a great deal of recent interest because of their potential as displacements for conventional solvents and as a means to immobilize and recycle

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Scheme 1

Table 1 Asymmetric hydrogenation of quinolines catalyzed by Ir-(P-Phos)^d

Entry	R ₁ /R ₂	Yield (%)	ee ^b (%)	Config. ^c
1	Me/H (1a)	97(98) ^d (2a)	91(89) ^d	<i>R</i>
2	Et/H (1b)	99(99) ^d (2b)	92(90) ^d	<i>R</i>
3	n-Pentyl/H (1c)	97 (2c)	91	<i>R</i>
4	Phenethyl/H (1d)	99 (2d)	90	<i>R</i>
5	Me/F (1e)	90(90) ^d (2e)	90(88) ^d	<i>S</i>
6	 / H	99(99) ^d (2f)	91(88) ^d	<i>S</i>
7	 / H	98 (2g)	90	<i>S</i>

^a Reaction conditions: 1 mmol quinoline, [Ir(COD)Cl]₂ (0.005 mmol), (*R*)-P-Phos (0.011 mmol), I₂ (0.05 mmol), 5 mL THF, 700 psi H₂, rt, 20 h. ^b The enantioselectivities of products were determined by HPLC analysis with Chiralpak OJ-H (**2a–c**), As-H (**2d**) and OD-H (**2e–g**) columns. ^c The absolute configuration is assigned by comparison of the HPLC retention time with these reported in the literature data. ^d Data in parenthesis were obtained by using DMPEG/hexane (1/1) as solvent under otherwise the same reaction conditions.

transition-metal catalyst,^{8,9} we attempted the hydrogenation in the two kinds of reaction media with **1a** as model compound. However, ionic liquids and PEG all proved to be ineffective reaction media, giving either poor conversions and/or poor ees. For example, using ionic liquid 1-butyl 3-methyl imidazolium hexafluorophosphate as reaction medium only led to 5% conversion and 52% ee. When PEG-400 was used as solvent, complete conversion and 77% ee were obtained. It was quite likely that the Ir-(P-Phos) catalytic system favored a less polar reaction medium, and the hydrogenation reaction was retarded by the highly polar ionic liquids and alcoholic PEG. Similar observation has been reported by Burgess and coworkers in their Ir-catalyzed asymmetric hydrogenation of unfunctionalized aryl alkenes in ionic liquid.¹⁰ Considering the detrimental effect of the OH groups on PEG on the enantioselectivity, we switched to the less polar DMPEG. To our delight, hydrogenation of **1a** in pure DMPEG (*M* = 500) gave complete conversion and 85% ee. Most

importantly, the product could be easily separated by simple extraction with hexane while the catalyst was retained in the DMPEG phase (Scheme 2). In order to facilitate the separation of the product and the recycling of the catalyst, we also examined the DMPEG/hexane two-phase catalytic system for this reaction. Interestingly, higher enantioselectivity (up to 89% ee) and nearly quantitative yield (up to 98%) were achieved. A variety of substituted quinoline derivatives were also hydrogenated in DMPEG-500/hexane, and the results summarized in Table 1 (entries 1, 2, 5 and 6, data in parentheses) were comparable to those obtained in THF.

The recyclability of the Ir-catalyst in DMPEG was examined using **1a** as the model substrate. Upon completion of the reaction, the product was easily separated *via* simple decantation and the DMPEG layer was further extracted twice with hexane in air. The DMPEG phase was recharged with **1a** and hexane, and then subjected to hydrogenation again under the same conditions. The Ir-(P-Phos) catalyst was reused for eight times with the retention of reactivity and enantioselectivity (Table 2). These results further demonstrated the air-stability of the Ir-(P-Phos) catalyst system. ICP-AES analysis of the hexane extract showed leaching of less than 0.4% of the iridium complex during the extraction of the products.



Scheme 2 Immobilized Ir-(P-Phos) catalyst in hexane/DMPEG biphasic system (lower DMPEG phase).

Table 2 Recycling and reuse of Ir-(P-Phos) catalyst in asymmetric hydrogenation of **1a**^a

Run	1	2	3	4	5	6	7	8
Conv. (%)	98	98	99	98	99	98	99	99
ee (%)	89	88	87	88	86	87	87	88

^a Reaction conditions: 0.5 mmol **1a**, [Ir(COD)Cl]₂ (0.0025 mmol), (*R*)-P-Phos (0.0055 mmol), I₂ (0.025 mmol), 5 mL DMPEG/hexane (1/1), 700 psi H₂, rt, 20 h.

In summary, we have developed a highly effective and air-stable Ir-(P-Phos) catalyst for the asymmetric hydrogenation of quinolines. The catalyst has been effectively immobilized in DMPEG for the first time with retained reactivity and enantioselectivity in the eight catalytic runs. It is noteworthy that DMPEG has shown great potential as a low-cost, benign and recyclable solvent for catalytic reactions.

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