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Asymmetric hydrogenation of quinolines with recyclable and air-stable iridium catalyst systems

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Abstract—The iridium complex-catalyzed asymmetric hydrogenation of quinolines in a DMPEG/hexane biphasic system was studied. Catalysts with C_2-symmetric ligands such as Xyl-P-Phos, Cl–MeO–BIPHEP, SYNPHOS, and DifluorPhos are highly effective for this type of reaction. Most of the catalysts tested can be retained in DMPEG ($M_n = 500$), and the asymmetric hydrogenation of various quinoline substrates can be carried out in DMPEG/hexane biphasic system with up to 92% ee. The catalysts and the products can be separated via simple phase separation, and the reactivity/stereoselectivity of the catalysts can be retained for at least three reaction cycles.

1. Introduction

Despite the fact that transition metal-catalyzed asymmetric hydrogenation has been extensively studied and over a thousand new ligands have been developed, examples of successful industrial application of this type of important reaction are still very much limited. This is partially due to the difficulties in separation and reusability of the generally very expensive chiral catalysts. For these reasons, reactions under conditions, which would facilitate the separation of products from the reaction media are of high interest. Moreover, environmental problems are calling for greener and more environmentally friendly reaction media for chemical processes.[1] Among the various approaches studied, liquid biphasic systems have been proven to be effective by providing easy catalyst-product separation.[2] Herein, we report our recent progress in the asymmetric hydrogenation in liquid biphasic systems, and the recycle and re-use of the air-stable iridium catalyst systems.

Chiral tetrahydroquinolines are important structural units of alkaloids,[3] and asymmetric hydrogenation of quinolines would provide an effective route to this type of compounds. Prior to the works by Zhou,[4] ourselves,[5] and Reetz,[6] only limited systems were known for the successful asymmetric hydrogenation of heteroaromatic compounds such as quinolines under homogeneous conditions.[7] Chiral ligands, which have been tested in the iridium-catalyzed asymmetric hydrogenation of quinolines, include MeO–BIPHEP,[4a] ferrocenyl-oxazoline derived ligand,[4b] P-Phos,[5a] H_8-BINAPO,[5b] a BINOL-derived diphosphonite[6a] and BINAP-cored dendrimers.[6b] We have reported an air-stable Ir/(*R*)-P-Phos/DMPEG/hexane catalyst system for the asymmetric hydrogenation of quinolines with up to 89% ee and nearly quantitative conversion.[5] As part of our continuing effort in this area, we sought to improve both the enantioselectivity and catalyst recyclability for this reaction.

2. Results and discussion

At first, some readily available chiral ligands were examined in the asymmetric hydrogenation of 2-methylquinoline **1a** (Scheme 1). All catalysts were prepared via in situ reaction of $[Ir(COD)Cl]_2$ with a chiral ligand in THF (unless otherwise specified) with I_2 as an additive, and the reactions were carried out for 20 h at room temperature.

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From Table 1, classical ligands, such as BINAP **7**, DIOP **8** and CHIRAPHOS **13** exhibited high conversions; however, only moderate enantioselectivities were obtained. The ferrocenyl N–P/S ligand **10**[9f] showed nearly zero enantioselectivity. Ligands with special structural features **11** and**12** did not offer any special advantages in improving the enantioselectivities also. The O–P **9** and **16**, N–P **17**, and P/N **14** and **15** ligands only showed poor enantioselectivities here. After screening, we found that some axially chiral bidendate phosphines, especially those with electron-donating groups attached to the backbones (Fig. 1) showed good enantioselectivity and conversion. P-Phos **3a**, Xyl-P-Phos **3b**, and Cl–MeO–BIPHEP **4a** exhibited an additional advantage of air-stability under the reaction conditions and were chosen for further studies.

As can be seen from Table 2, the solvent had a significant effect on both the enantioselectivities and conversions. The use of protic solvents led to poor conversion and enantioselectivities (entries 3–4, 8–9 and 15–16). The best results were obtained when mixed THF and DCM (dichloromethane) (v/v = 1:1) was used as the reaction solvent with 89% enantioselectivity and 99% conversion for both SYNPHOS

Table 1. Ligand screening for Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline (**1a**)[a]

Entry	Ligand	ee[b] (%)	Conv.[c] (%)
1	**7a**	52	>99
2	**7b**	69	>99
3	**7c**	77	99
4	**8**	31	>99
5	**9**	1	>99
6	**10**	1	>99
7	**11**	2	84
8	**12**	1	>99
9	**13**	51	>99
10	**14**	15	3
11	**15**	13	>99
12	**16**	14	>99
13	**17**	9	35

[a] Reaction conditions: 0.15 mmol **1a**, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 1.5 ml THF, 700 psi H_2 pressure at rt for 20 h.

[b] The ee values were determined by HPLC using Chiralpak OJ-H column with mobile phase of IPA/hexane (5:95) at 0.5 ml/min.

[c] The conversions were determined by ^1H NMR spectroscopy of the crude product.

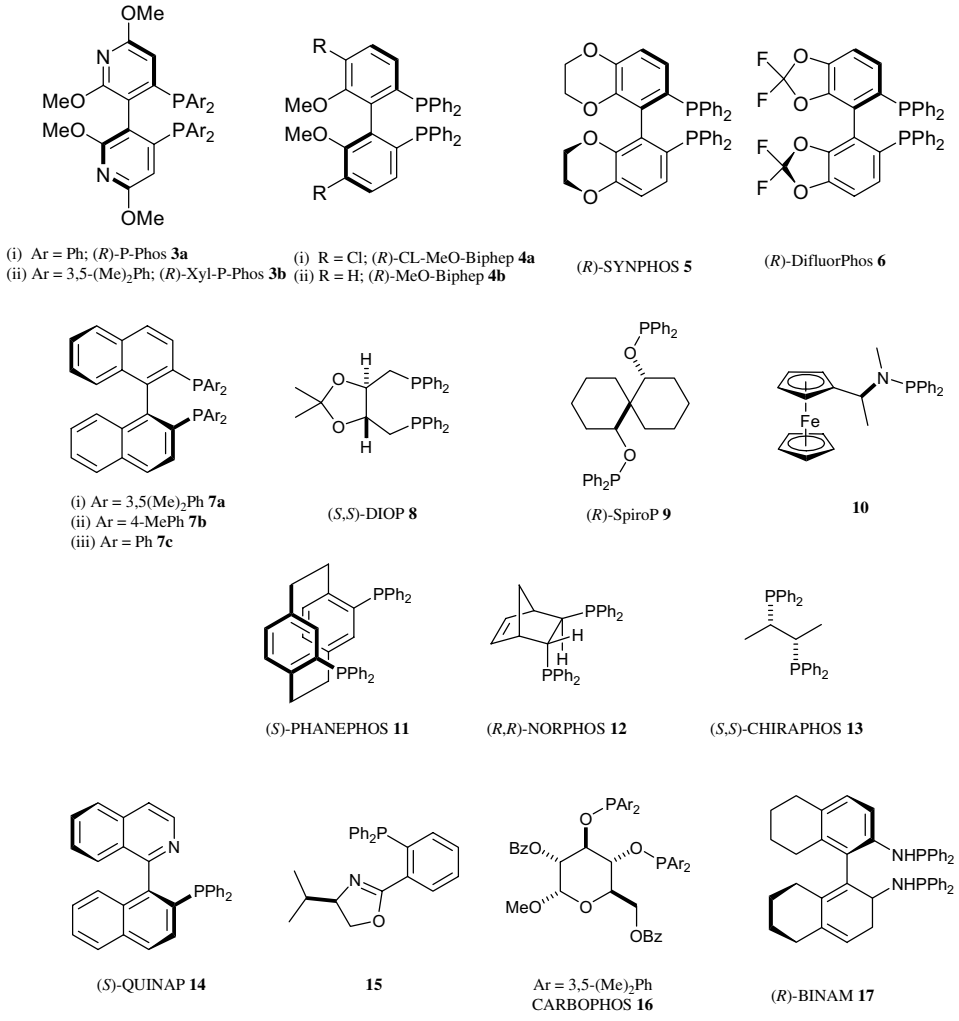


Figure 1. Structures of chiral ligands[8] **3**–**17**.

Table 2. Ir Complex-catalyzed asymmetric hydrogenation of 2-methylquinoline **1a**[a]

Entry	Ligand	Solvent	ee[b] (%)	Conv.[c] (%)	Config.
1	**3a**	THF	91	97	(*R*)
2	**3b**	THF	92	>99	(*R*)
3	**4a**	MeOH	5	65	(*S*)
4	**4a**	EtOH	14	51	(*S*)
5	**4a**	Toluene	92	68	(*R*)
6	**4a**	DCM	79	20	(*R*)
7	**4a**	THF	91	99	(*R*)
8	**5**	MeOH	26	14	(*S*)
9	**5**	EtOH	7	17	(*R*)
10	**5**	Toluene	77	72	(*R*)
11	**5**	DCM	81	15	(*R*)
12	**5**	Ether	66	39	(*R*)
13	**5**	THF	45	53	(*R*)
14	**5**	DCM/THF (1:1)	89	99	(*R*)
15	**6**	MeOH	33	50	(*S*)
16	**6**	EtOH	45	64	(*S*)
17	**6**	Toluene	81	73	(*R*)
18	**6**	DCM	91	54	(*R*)
19	**6**	Ether	77	99	(*R*)
20	**6**	THF	84	63	(*R*)
21	**6**	DCM/THF (1:1)	89	99	(*R*)

[a] Reaction conditions: 0.15 mmol **1a**, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 1.5 ml solvent, 700 psi H_2 pressure at rt for 20 h.
[b] The ee values were determined by HPLC using Chiralpak OJ-H column with mobile phase of IPA/hexane (5:95) at 0.5 ml/min.
[c] The conversions were determined by ^1H NMR spectroscopy of the crude product.

5 and DifluorPhos **6**. For Cl–MeO–BIPHEP **4a** the best solvent was THF with 91% enantioselectivity and 99% conversion. For the purpose of comparison, we carried out the asymmetric hydrogenation of **1a** with the optimal solvent systems of the respective ligands: that is, THF for ligands **3a**, **3b**, and **4a**, DCM (dichloromethane)/THF mixture for ligands SYNPHOS **5** and DifluorPhos **6**.

With the best reaction medium, the effect of pressure and temperature on the hydrogenation was then investigated. Table 3 shows that the conversion was relatively insensitive to changes in hydrogen pressure, but the enantioselectivity slightly decreased at higher pressure for Ir/**4a** and Ir/**6** (entries 3–6). The reaction with Ir/**4a** and Ir/**5** is favored at low temperature (entry 1). The effect of the substrate-to-catalyst (S/C) ratio on the hydrogenation reaction of quinoline was also examined and the results are listed in Table 4. From the table, it can be seen that a change in S/C ratio had a slight effect on enantioselectivities (entries 1–6). Remarkably, this reaction could even be performed at a substrate-to-catalyst (S/C) ratio of 5000:1 without any loss in enantioselectivities for ligands **5** and **6**.

To verify the effectiveness of these catalyst systems in the asymmetric hydrogenation of quinoline substrates, the asymmetric hydrogenation of a series of 2-alkylated quinolines **1b**–**1k** were also carried out under the optimized conditions (Scheme 1), and the results are listed in Table 5.

Table 3. Effect of temperature/pressure on the asymmetric hydrogenation of **1a**[a]

Entry	Temperature (°C)/pressure (psi)	Ligand					
		(*R*)-**4a**		(*R*)-**5**		(*R*)-**6**	
		ee[b] (%)	Conv.[c] (%)	ee[b] (%)	Conv.[c] (%)	ee[b] (%)	Conv.[c] (%)
1	0/700	95	99	93	>99	87	99
2	−30/700	94	99	93	42	80	50
3	rt/100	92	99	87	99	93	99
4	rt/200	—	—	92	>99	90	99
5	rt/500	92	99	91	>99	87	99
6	rt/700	91	99	89	>99	85	99

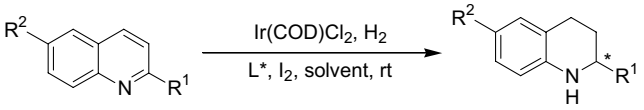
[a] Reaction conditions: 0.15 mmol quinoline, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 1.5 ml solvent at rt for 20 h.
[b] The ee values were determined by HPLC analysis with Chiralpak OJ-H column with mobile phase of IPA/hexane (5:95) at 0.5 ml/min.
[c] The conversion was determined by ^1H NMR spectroscopy of the crude product.

Table 4. Effect of substrate-to-catalyst (S/C) ratio on the asymmetric hydrogenation of **1a**[a]

Entry	S/C ratio	Ligand					
		(*R*)-**4a**		(*R*)-**5**		(*R*)-**6**	
		ee[b] (%)	Conv.[c] (%)	ee[b] (%)	Conv.[c] (%)	ee[b] (%)	Conv.[c] (%)
1	100:1	92	99	87	99	93	99
2	200:1	92	99	90	99	93	99
3	500:1	91	99	91	96	95	98
4	1000:1	92	96	92	83	94	77
5	2000:1	93	93	92	73	95	69
6	5000:1	—	—	90	47	95	37

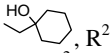
[a] Reaction conditions: 0.15 mmol quinoline, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 1.5 ml solvent at rt for 20 h.
[b] The ee values were determined by HPLC analysis with Chiralpak OJ-H column with mobile phase of IPA/hexane (5:95) at 0.5 ml/min.
[c] The conversion was determined by ^1H NMR spectroscopy of the crude product.

Table 5. Ir complex-catalyzed asymmetric hydrogenation of quinolines **1a**–**1k**[a]



1 **2**

Scheme 1

1a R^1 = Me, R^2 = H; **1e** R^1 = *n*-Pentyl, R^2 = H; **1i** R^1 =  , R^2 = H;
1b R^1 = Et, R^2 = H; **1f** R^1 = Me, R^2 = Me; **1j** R^1 = Me, R^2 = F;
1c R^1 = *n*-Pr, R^2 = H; **1g** R^1 = Me, R^2 = OMe;
1d R^1 = *n*-Bu, R^2 = H; **1h** R^1 = Phenylethyl, R^2 = H; **1k** R^1 =  , R^2 = H.

Entry	Substrate	Ligand				
		(*R*)-**3a**[e] ee[b] (conv.)[c] (%)	(*R*)-**3b**[e] ee[b] (conv.)[c] (%)	(*R*)-**4a**[e] ee[b] (conv.)[c] (%)	(*R*)-**5** ee[b] (conv.)[c] (%)	(*R*)-**6** ee[b] (conv.)[c] (%)
1	**1a**	91 (97)[d]	92 (99)	92 (99)	92 (99)	93 (99)
2	**1b**	92 (99)[d]	92 (99)	90 (99)	92 (99)	94 (99)
3	**1c**	88 (98)	92 (99)	88 (99)	90 (99)	92 (99)
4	**1d**	88 (99)	89 (99)	87 (99)	89 (99)	90 (99)
5	**1e**	91 (97)[d]	89 (99)	88 (99)	88 (99)	92 (99)
6	**1f**	87 (97)	90 (99)	83 (87)	86 (99)	88 (99)
7	**1g**	87 (97)	95 (99)	89 (94)	87 (99)	86 (67)
8	**1h**	90 (99)[d]	84 (99)	88 (73)	92 (99)	93 (99)
9	**1i**	85 (99)	92 (99)	89 (89)	92 (86)	92 (99)
10	**1j**	90 (99)[d]	86 (99)	88 (89)	89 (99)	92 (94)
11	**1k**	91 (99)[d]	94 (99)	85 (93)	91 (91)	90 (99)

[a] Reaction conditions: 0.15 mmol **1a**, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 1.5 ml THF or THF/DCM (1:1, v/v) as solvent at rt for 20 h.
[b] The ee values were determined by HPLC with a Chiralpak OJ-H **2a**–**g**, OJ (**2h**,**i**), or OD-H **2j**,**k** column. The chiral products **2a**–**h** and **2j** are (*R*)-configuration, while **2i** and **2k** are (*S*)-configuration.
[c] The conversion was determined by ^{1}H NMR spectroscopy of the crude product.
[d] Data were taken from Ref. 5a for comparison.
[e] Operation under air without the use of glovebox and degassed solvent.

The Ir-catalyzed hydrogenation of the quinolines bearing a C_1–C_5 side chain at the 2-position of quinoline ring gave products in 87–95% ee (Table 5, entries 1–5). A substituent at the 6-position did not show significant effect on the conversion and enantioselectivity of the reaction (entries 6–7 and 10). Good results were also obtained with 2-phenethyl substituted quinoline (entry 8). The tolerance of the hydroxyl group was well demonstrated by the successful hydrogenation of substrates **1i** and **1k** with 99% conversion and 94% ee (entries 9 and 11).

After establishing a general method for the asymmetric hydrogenation of quinolines, and having a better understanding of the catalyst stability, we examined the effectiveness of these iridium complexes in other solvent systems, namely room temperature ionic liquids or poly(ethyl glycol) dimethyl ether (DMPEG).[9,10] To facilitate the separation of a product from the reaction system, it is generally recognized that there should be distinct solubility differences of the catalysts and products in the solvent systems. In this regard, two common imidazole ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) were first chosen as solvents for the catalysts. The hydrogenation of 2-methylquinoline **1a** in these two imidazole ionic liquid resulted in poor ee's (ca 3%) and conversions (ca 5%), irrespective of the Ir catalyst systems used (Table 6).

Table 6. Asymmetric hydrogenation of **1a** in ionic liquids[a]

Entry	Ligand	[bmim][BF_4]		[bmim][PF_6]	
		ee[b] (%)	Conv.[c] (%)	ee[b] (%)	Conv.[c] (%)
1	(*R*)-**3a**	17	5	4	11
2	(*R*)-**3b**	55	54	3	16
3	(*R*)-**4a**	33	27	8	13
4	(*R*)-**5**	59	99	67	10
5	(*R*)-**6**	24	42	23	34

[a] Reaction conditions: 0.15 mmol quinoline, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), 0.5 ml [bmim][BF_4] or [bmim][PF_6] as solvent; 1000 psi H_2 pressure at rt for 20 h.
[b] The ee values were determined by HPLC analysis with Chiralpak OJ-H column.
[c] The conversion was determined by ^{1}H NMR spectroscopy of the crude product.

Given that using DMPEG as a reaction medium for Ir-P-Phos and Ir-H_8-BINAPO-catalyzed asymmetric hydrogenation of quinoline proceeded readily with good stereoselectivity,[5] we examined the activity of the Ir-catalyst systems for the asymmetric hydrogenation of quinoline in a DMPEG/hexane biphasic system. After balancing the catalyst/product solubility and the medium viscosity, DMPEG ($M_n = 500$) was chosen to be the reaction medium. As shown in Table 7, the catalysts tested provided good conversions (up to 99%) and moderate to high enantioselectivities for the asymmetric hydrogenation of

Table 7. Iridium complex-catalyzed asymmetric hydrogenation of substituted quinolines in DMPEG/hexane biphasic system[a]

Entry	Substrate	Ligand				
		3a[e] ee[b] (conv.)[c] (%)	**3b**[e] ee[b] (conv.)[c] (%)	**4a**[e] ee[b] (conv.)[c] (%)	**4b** ee[b] (conv.)[c] (%)	**5** ee[b] (conv.)[c] (%)
1	**1a**	89 (98)[d]	86 (99)	86 (99)	84 (99)	83 (99)
2	**1b**	90 (99)[d]	82 (97)	92 (99)	79 (99)	85 (98)
3	**1c**	80 (99)	78 (98)	90 (99)	76 (99)	82 (99)
4	**1d**	80 (99)	71 (99)	85 (99)	75 (99)	77 (99)
5	**1e**	80 (99)	72 (97)	87 (99)	78 (99)	80 (98)
6	**1f**	73 (97)	79 (99)	82 (99)	77 (99)	78 (99)
7	**1g**	51 (73)	88 (99)	67 (72)	73 (99)	80 (98)
8	**1h**	86 (99)	64 (99)	91 (99)	71 (99)	78 (98)
9	**1i**	79 (91)	53 (97)	79 (96)	65 (99)	92 (97)
10	**1j**	88 (90)[d]	68 (97)	79 (99)	75 (99)	77 (99)
11	**1k**	88 (99)[d]	80 (95)	82 (89)	79 (99)	75 (98)

[a] Reaction conditions: 0.15 mmol **1a**, $[Ir(COD)Cl]_2$ (0.0015 mmol), ligand (0.0032 mmol), I_2 (0.015 mmol), DMPEG–hexane (1:1, v/v) as solvent, 1000 psi H_2 pressure at rt for 20 h.

[b] The ee values were determined by HPLC with a Chiralpak OJ-H (**2a**–**g**), OJ (**2h**,**i**), or OD-H (**2j**,**k**) column. Chiral products **2a**–**h** and **2j** are (*R*)-configuration while **2i** and **2k** are (*S*)-configuration.

[c] The conversion was determined by ^1H NMR spectroscopy of the crude product.

[d] Data were taken from Ref. 5a for comparison.

[e] Operation under air without the use of glovebox and degassed solvent.

substituted quinolines (up to 92%). Ir-**4a** was found to give the best results in a DMPEG/hexane biphasic system (up to 92% ee). Ir-**3a**, **3b**, and **4a** were found to be air-stable and all the reactions were performed in air without using a glovebox. In contrast, Ir-**4b** and Ir-**5** were rather unstable in air.

The air-stability of these iridium catalyst systems was then tested by comparing the results under dried and anaerobic conditions (with the use of degassed solvents and glovebox) with those under conditions of using unpurified reagent-grade solvents unaffected by air.

The reactions performed in untreated solvents and under open atmosphere catalyzed with Ir-**3a**, Ir-**3b**, and Ir-**4a** gave good conversions and high enantioselectivities. For ligands **3a**, **3b**, and **4a**, the results (91% ee and 97% conversion for ligand **3a**; 92% ee and 99% conversion for ligand **3b** and 92% ee and 99% conversion for ligand **4a**) were comparable to those obtained using glovebox and degassed solvents. Ir-**5** and Ir-**6** were less effective under those reactions and lower ee's were observed: Ir-**5**, 92% ee (glovebox) versus 84% ee (open atmosphere); Ir-**6**, 93% ee (glovebox) versus 90% ee (open atmosphere). These results indicated that the Ir-**3a**, Ir-**3b**, and Ir-**4a** systems were more air-stable than Ir-**5** and Ir-**6**, and therefore were used for further study.

By employing **1a** as a model substrate, we tested the catalyst recyclability in a DMPEG/hexane biphasic system. Results in Table 8 indicate that Ir-**4a**, Ir-**4b**, and Ir-**5** might be suitable for catalyst recovery and reuse. Experiments were carried out to monitor the course of the reaction in DMPEG/hexane biphasic system, and the conversions of **1a** after 1 h of reaction was measured via ^1H NMR analyses of the reaction mixture (Table 8, data in parentheses). The results indicated that the activity decreased slightly after each cycle. The loss of activity might be due to either (i) catalyst loss during the extraction process or (ii) loss of catalyst activity after the recycling process.

Table 8. Recycling and reuse of Ir-**4a**, Ir-**4b** and Ir-**5** for the asymmetric hydrogenation of 2-methylquinoline[a]

Run		1	2	3	4
(*R*)-**4a**[e]	ee[b] (%)	86	84	82	81
	Conv.[c] (%)	99 (70)	99 (61)	99 (56)	93
(*R*)-**4b**	ee[b] (%)	84	84	84	84
	Conv.[c] (%)	99 (53[d])	99 (43[d])	99 (37[d])	99
(*R*)-**5**	ee[b] (%)	83	84	84	83
	Conv.[c] (%)	99 (36)	99 (34)	99 (32)	99

[a] Reaction conditions: 0.5 mmol **1a**, $[Ir(COD)Cl]_2$ (0.0026 mmol), ligand (0.005 mmol), I_2 (0.055 mmol), 2 ml DMPEG and 2 ml hexane as solvent, 1000 psi H_2 pressure at rt for 20 h.

[b] The ee values were determined by HPLC analysis with Chiralpak OJ-H column.

[c] The conversion was determined by ^1H NMR spectroscopy of the crude product.

[d] Reaction time 3 h.

[e] Operation under air without the use of glovebox and degassed solvent.

3. Conclusion

In conclusion, iridium complexes with C_2-symmetric ligands such as Xyl-P-Phos, Cl–MeO–BIPHEP, SYNPHOS, and DifluorPhos are effective catalysts for the asymmetric hydrogenation of quinolines. These catalysts can be retained in low molecular weight poly(ethylene glycol) dimethyl ether (DMPEG, $M_n = 500$), and the asymmetric hydrogenation of 2-methyl quinoline can be carried out in a DMPEG/hexane biphasic system with up to 92% ee. The catalysts and products can be separated via simple phase separation, and the reactivity/stereoselectivity of the catalysts can be retained for at least three reaction cycles.

4. Experimental

4.1. General methods

Reagents were purchased from either Acros or Aldrich and used without further purification. NMR spectra were

recorded on a Varian 500 spectrometer. Chiralpak OJ-H, OD-H and OJ columns were purchased from Daicel. HPLC analyses were performed using HP1100 equipped with UV–visible detector and chiral column using IPA/hexane as eluent.

4.2. General procedure for the asymmetric hydrogenation of quinoline in organic solvents and DMPEG/hexane

For the asymmetric hydrogenation in organic solvent, a mixture of $[Ir(COD)Cl]_2$ (0.0015 mmol) and ligands (0.0032 mmol) in 1.0 ml dried solvent was stirred at room temperature for 30 min in a glovebox. The mixture was transferred with a gas-tight syringe to a stainless steel autoclave, which contains a mixture of I_2 (4 mg, 0.015 mmol) and quinoline (0.15 mmol) in 0.5 ml solvent. The hydrogenation reaction was performed at room temperature under H_2 (700 psi/200 psi/100 psi) for 20 h unless otherwise specified. After careful release of the hydrogen gas, an aqueous sodium carbonate solution (2 ml) was added, and the mixture was stirred for 15 min. The aqueous layer was then extracted with ethyl acetate (3×2 ml). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure in a rotary evaporator to afford the crude product. The substrate conversion was determined by ^1H NMR spectroscopy. The enantiomeric excesses were determined by HPLC after purification on silica gel (*n*-hexane/EA = 5:1) with a chiral column (OJ-H, OD-H or OJ).

For asymmetric hydrogenation in DMPEG ($M_n = 500$)/hexane solvent system, the procedures were the same as above except that the catalyst was generated in situ in 1.0 ml DMPEG; the same amount of substrate (0.15 mmol) with I_2 in 1 ml hexane was added before charging H_2 (1000 psi) at room temperature. After 20 h of reaction, the hexane layer was decanted and the products in DMPEG layer were extracted further with hexane (3×2 ml). The combined hexane layer was concentrated in vacuo to give the crude product, which was analyzed with the same method as described above. All the tetrahydroquinoline products, **2a**–**2k**, are known compounds.[4a]

Acknowledgments

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1. While many consider that the reaction in aqueous phase is more environmentally friendly, some scientists argue that a fundamental mechanistic understanding of the role of water in a reaction is necessary before water can be used in organocatalytic reactions. See for example: Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798.
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