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Polyethylene Glycol as an Environmentally Friendly and Recyclable Reaction Medium for Enantioselective Hydrogenation

Hai-Feng Zhou,[a,b] Qing-Hua Fan,[b,*] Wei-Jun Tang,[c] Li-Jin Xu,[c] Yan-Mei He,[b] Guo-Jun Deng,[b] Li-Wen Zhao,[a,b] Lian-Quan Gu,[a,*] and Albert S. C. Chan[c,*]

[a] School of Chemistry and Chemical Engineering, and School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510275, People's Republic of China
Fax: +(86)-20-8411-0272; e-mail: cedc42@zsulink.zsu.edu.cn

[b] National Laboratory of Molecular Sciences, Center for Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, People's Republic of China
Fax: +(86)-10-6255-4449; e-mail: fanqh@iccas.ac.cn

[c] Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, People's Republic of China
Fax: +(852)-2364-9932; e-mail: bcachan@polyu.edu.hk

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Abstract: Polyethylene glycol (PEG) was found to be an inexpensive, non-toxic and recyclable reaction medium for ruthenium- and rhodium-catalyzed asymmetric hydrogenation of 2-arylacrylic acids (Ru-catalyzed C=C bond reduction), enamides (Rh-catalyzed C=C bond reduction), β-keto esters and simple aromatic ketones (Ru-catalyzed C=O bond reduction). In all cases, high catalytic activities and enantioselectivities have been achieved, which are comparable to those obtained in conventional organic solvent systems. The Ru and Rh catalysts prepared with commercially available chiral diphosphine ligands could be readily recycled by simple extraction, as in the case of ionic liquids, and reused up to nine times without obvious loss of catalytic activity and enantioselectivity. The reduced products were obtained from the extracts in high isolated yields. These results indicate that PEGs as new reaction media are attractive alternatives to room temperature ionic liquids.

Keywords: asymmetric hydrogenation; diphosphine ligands; immobilized catalyst; polyethylene glycol; reaction medium; recycling

Introduction

Transition metal-catalyzed 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. High activity and enantioselectivity have been observed using Rh, Ru, and Ir complexes with chiral phosphine, phosphite, or phosphoramidite ligands.[1,2] However, the high cost of both these chiral ligands and the noble metals as well as the toxicity of trace metal contaminants in the organic products have restricted their use in industry. Immobilization of these catalysts offers an attractive solution to these problems.[3–5] Homogeneous chiral catalysts can be anchored onto insoluble[5a–c] or soluble[5d–g] polymers, dendrimers,[5h–l] and inorganic materials[4b,5m–p] *via* covalent or non-covalent attachment. However, all of these approaches often require additional ligand or catalyst modifications, which are tedious and time-consuming. Furthermore, most of these immobilized catalysts have suffered from reduced catalytic activity and/or enantioselectivity due to mass transfer limitations and/or degradation of the support. Alternatively, room temperature ionic liquids can be used to immobilize the transition metal catalysts and to facilitate catalyst recycling, and have consequently attracted a great deal of interest.[6] A series of prochiral olefins, ketones, and imines has been successfully hydrogenated in ionic liquids, and the results were comparable to or even better than those obtained in common organic solvents.[7] In most cases, ionic liquids are miscible with the organic co-solvent, and the catalytic reactions were thus carried out under homogeneous conditions. Upon the completion of the reaction, the organic products could be easily separated *via* extraction with less polar solvents, and the ionic liquid phase containing the active catalyst could be readily reused several times without significant loss of catalytic activity and/or enantioselectivity. However, ionic liquids as solvents still suffer from the disadvantages of tedious preparation, high price, as well as limited

knowledge of their toxicity. We have demonstrated and report here that poly(ethylene glycol) (PEG) is an attractive alternative to room temperature ionic liquids as a reaction medium for catalytic asymmetric hydrogenation reactions.

Recently, liquid PEGs have been attracting increasing interest as novel solvents for organic reactions due to their benign characteristics.[8] Like ionic liquids, PEGs are non-volatile, recyclable, and stable to acid, base and high temperature. On the other hand, PEGs have the following advantages over ionic liquids: (1) much lower cost; (2) completely non-halogenated, and (3) well known low toxicity. Several reviews have covered the chemistry of PEGs and their applications in biotechnology and medicine.[9] PEGs have previously been used as phase-transfer catalysts for catalytic reactions,[10] and as soluble supports for the immobilization of homogeneous catalysts.[5f,g,11] Recently, liquid PEGs have been adopted as a new approach for catalyst recycling, in a broad range of catalytic organic reactions including polymerization and biotransformation.[12–14] However, reports on the utilization of PEG as solvent or co-solvent for asymmetric catalytic reactions and recycling of the homogeneous chiral catalysts are rather limited.[14–16] Very recently, we reported an air-stable Ir-(P-Phos) complex for highly enantioselective hydrogenation of quinolines in a biphasic poly(ethylene glycol) dimethyl ether (DMPEG) and hexane system.[16] The Ir catalyst immobilized in DMPEG could be reused for eight times without significant loss of reactivity and enantioselectivity. In contrast, ionic liquids have proven to be ineffective in this reaction, giving both poor conversions and low enantioselectivities. Similarly, alcoholic PEG (molecular weight = 400) also gave unsatisfactory enantioselectivity due to the detrimental effect of the OH groups on PEG. Based on these observations and as a part of our continuing efforts in the immobilization and recycling of chiral catalysts in asymmetric hydrogenation,[4a,5d,i,7n,11b,c,16,17] we report here a practical protocol for Ru- and Rh-catalyzed asymmetric hydrogenations of prochiral olefins and ketones in PEG using commercially available chiral diphosphine ligands (Figure 1). The catalysts immobilized in PEG could be recycled (up to 9 times) without obvious loss of enantioselectivity, and the results are comparable to or better than those obtained in ionic liquid.

Results and Discussion

Asymmetric Hydrogenation of 2-Arylacrylic Acids in PEG

The asymmetric catalytic hydrogenation of 2-arylacrylic acids provides a convenient way to prepare chiral 2-arylpropionic acid products, which constitute

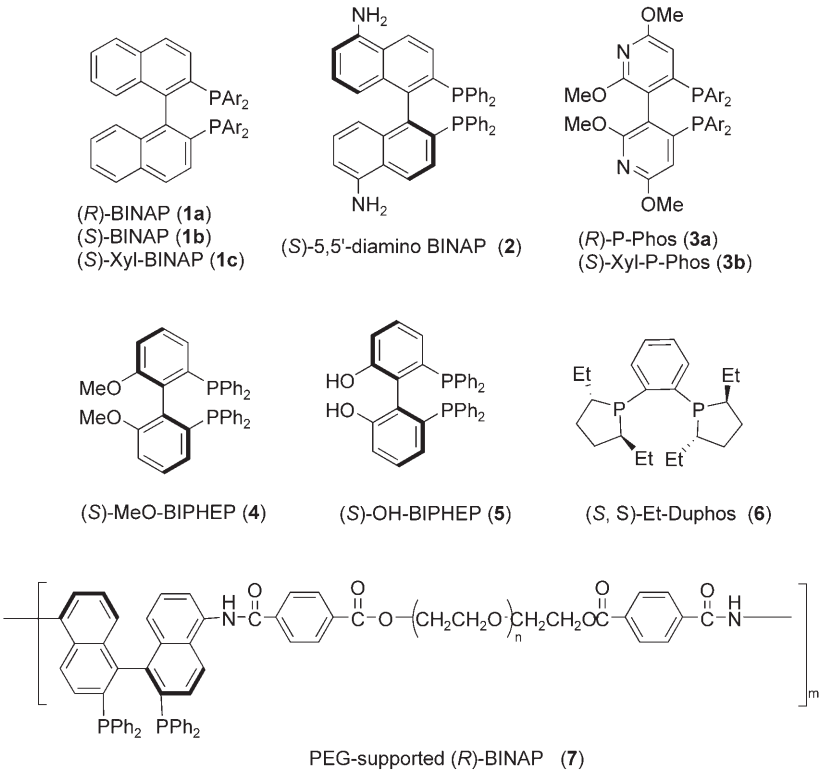
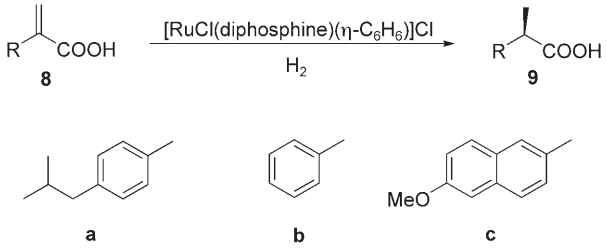


Figure 1. Structures of the ligands used in this study.

an important class of anti-inflammatory drugs and analgesics.[18] High enantioselectivities and conversions have been achieved in alcoholic organic solvents.[11c,19] Such asymmetric hydrogenations performed in ionic liquids also have been reported, but significantly lower enantioselectivities than the best results obtained in alcoholic solvents were observed.[7b–d] To determine whether the catalytic reactions could proceed smoothly in PEG as solvent, the Ru(BINAP)-catalyzed asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid (**8a**) was chosen as a model reaction.[20] As shown in Table 1, much lower catalytic activity and enantioselectivity were observed in pure PEG or dimethyl PEG (DM-PEG) as solvents as compared with those obtained in methanol (entry 1 *vs.* entries 2–4). This might be partially due to the higher viscosity of PEG than that of methanol. In view of the significant co-solvent effect of alcohol in asymmetric hydrogenations in ionic liquids, and in order to lower the viscosity of PEG, we used methanol as a co-solvent for this reaction. To our delight, high enantioselectivities and conversions could be obtained with Ru(BINAP) catalyst in both PEG/MeOH and DM-PEG/MeOH (entries 5–7), and the results were comparable to those obtained in methanol. Lower reaction temperature and higher hydrogen pressure afforded better enantioselectivity (entries 8–11). The hydrogenation was extended to 2-phenylacrylic acid (**8b**) and 2-(6′-methoxy-2′-naphthyl)acrylic acid (**8c**). Similarly, high enantioselectivities were observed, which were comparable to those obtained in MeOH (entries 12, 13). It was notable that the enantioselectivities achieved in this study were higher than those reported for the same reactions in ionic liquids using Ru(tolBINAP) as catalyst (for **8a**: 85% *ee* in [bimim]PF_6/MeOH under 100 bar of H_2; for **8b**: 54% *ee* in [bimim]PF_6/MeOH under 50 bar of H_2).[7c,d]

The recyclability of the Ru catalysts in PEG was investigated using **8a** as a model substrate. Upon completion of the reaction, the methanol was removed under reduced pressure, and the reduced products were extracted with a less polar solvent. After being cooled to 0 °C, the solidified PEG phase could be easily separated *via* decantation of the extract, and was recharged with **8a**, NEt_3 and MeOH and then subjected to hydrogenation again under the same conditions. Firstly, Ru(**1a**) was chosen as the catalyst and degassed anhydrous ethyl ether as the extracting sol-

Table 1. Asymmetric hydrogenation of 2-arylacrylic acids catalyzed by Ru(BINAP) in different solvent systems.[a]



Entry	Substrate	Solvent system (v/v)	H_2 [atm]	Temp. [°C]	*ee* [%][b]	Conv. [%][b]
1	**8a**	MeOH	50	20	87.6	>99
2	**8a**	PEG-300	50	20	58.3	86
3	**8a**	PEG-600	50	20	39.2	61
4	**8a**	DM-PEG-500	50	20	31.0	60
5	**8a**	PEG-600/MeOH = 1/1	50	20	83.0	>99
6	**8a**	PEG-600/MeOH = 1/2	50	20	87.7	>99
7	**8a**	DM-PEG-500/MeOH = 1/2	50	20	88.0	>99
8	**8a**	PEG-600/MeOH = 1/2	20	20	78.2	>99
9	**8a**	PEG-600/MeOH = 1/2	80	20	90.2	>99
10	**8a**	PEG-600/MeOH = 1/2	80	0	92.0	>99
11	**8a**	PEG-600/MeOH = 1/2	50	50	79.2	>99
12	**8b**	PEG-600/MeOH = 1/2	50	20	92.4 (90.6)[c]	>99 (>99)[c]
13[d]	**8c**	PEG-600/MeOH = 1/2	50	20	90.2 (89.7)[c]	99 (99)[c]

[a] The hydrogenations were carried out using 0.04 M of substrate (25 mg) under the following conditions: substrate/catalyst = 100 (M/M), Et_3N/catalyst = 3/2 (M/M), reaction time = 6 h except for entry 10 (12 h).

[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm) after the reduced acids had been transformed to their corresponding methyl esters. All products were in the *R*-configuration.

[c] Data in brackets were obtained by using MeOH as solvent under otherwise identical conditions.

[d] The *ee* values were determined by HPLC with a Sumichiral OA-2500 column after the reduced acids had been transformed to their corresponding methyl esters. The product was in the *R*-configuration.

vent. It was found that 4.2 wt% of PEG leached into the extracted products. In contrast, when hexane was used to extract the products from PEG, a very low degree of leaching (<0.1 wt%) was observed. However, owing to the high polarity of the hydrogenated acid, a very low extracting yield (<27%) was observed by using hexane alone for extraction. For the balance of keeping the PEG and sustaining high product-extraction efficiency, a mixture of ethyl ether and hexane (1:1, v/v) was finally chosen as the solvent for extraction. The mass recovery of the products (after column chromatography) was found to be 65% in the first cycle, and the degree of leaching of PEG was no more than 0.3 wt%. As shown in Table 2, high mass recovery of the product was obtained in the second run, and quantitative recovery of the product has been achieved from the third catalytic run (data shown in brakets in the second column). The Ru(**1a**) catalyst could be recycled at least four times. Interestingly, the level of enantioselectivity increased slightly and the highest *ee* (89.6%) was achieved in the third run. Similar phenomena have been observed in a study of recycling of Ru catalysts in ionic liquids.[7m] In contrast, a significant drop in activity was observed in the fifth run. To further demonstrate the recyclability of this system, we chose some other ligands (Figure 1) for this study. Unexpectedly, when diphosphines **2**,[21] **4**[22] and **7**[11b] were used, much lower enantioselectivities were observed in PEG/MeOH in the first run than those in pure MeOH (Table 2). All catalysts could be recycled and reused in the PEG system, and a similar trend of increase in enantioselectivity was observed except in the case of using Ru(**3a**)[23] catalyst. Good activities for most catalysts were retained in the first four runs. Inductively coupled plasma (ICP) spectroscopy was used to determine the leaching of Ru, and the results are summarized in Table 2. The level of Ru leached into the product depended on the polarity of the ligand. Incorporation of polar groups such as amino groups in **2**, hydroxy groups in **5**,[24] and polar polymer chains in **7** significantly reduced the leaching of catalyst.

Asymmetric Hydrogenation of Enamides in PEG

Chiral amino acids are attractive targets for enantioselective synthesis on account of their vital role in the pharmaceutical industry both as nutritional supplements and as synthetic intermediates. Asymmetric catalytic hydrogenation of prochiral amidoacrylic acids and their esters represents a convenient method for the synthesis of such compounds.[25] Among the variety of chiral rhodium phosphane catalysts reported to date, Rh-DuPHOS has been found to be particularly efficient as a homogeneous catalyst in the asymmetric hydrogenation of enamides.[26] However, as good as its performance is, the rather expensive Rh-DuPHOS is very sensitive to oxidation. The successful separation and recycling of this rhodium catalyst is still a challenge.[7e] We thus chose the commercially available Rh-DuPHOS catalyst for further study. A mixture of PEG and methanol was chosen as the solvent and the results are summarized in Table 3. In the asymmetric hydrogenation of methyl α-acetamidocinnamate (**10a**), it was found that the amount of methanol as co-solvent could significantly influence the enantioselectivity (entries 1–4). High enantioselectivity (up to 98.1% *ee*) was achieved in a mixture of 1:4 PEG/MeOH, which was comparable to that ob-

Table 2. Reuse of catalysts using different chiral diphosphine ligands for asymmetric hydrogenation of **8a** in PEG/MeOH as reaction medium.[a]

Run	**1a** [%][b,c]		**2** [%][b]		**3a** [%][b]		**4** [%][b]		**5** [%][b]		**7** [%][b]	
	Conv.	*ee*	Conv.	*ee*	Conv.	*ee*	Conv.	*ee*	Conv.	*ee*	Conv.	*ee*
1[d]	>99	87.6	>99	88.0	>99	86.2	>99	85.6	>99	83.2	>99	85.8
1	>99 (65)	85.8	>99	79.8	>99	85.5	>99	79.2	>99	82.6	>99	81.8
2	>99 (89)	86.8	>99	87.6	>99	79.0	>99	80.0	>99	83.6	>99	88.2
3	>99 (99)	89.6	>99	88.6	98	78.4	>99	85.4	92	83.5	>99	87.8
4	>99 (99)	88.8	>99	90.0	64	78.4	>99	88.0	75	84.0	>99	88.4
5	76.0 (72)	88.2	58	89.6	40	75.6	67	88.6	30	80.0	63	88.0
Ru (%)[e]	1.99 (0.4)		0.28 (0.06)		3.09 (0.67)		3.86 (0.83)		0.83 (0.18)		0.24 (0.05)	

[a] The hydrogenations were carried out using 0.02 M of **8a** in 6 mL of PEG-600/MeOH (1:2, v/v) under the following conditions: substrate/catalyst = 100 (M/M), Et_3N/catalyst = 3/2 (M/M), $P(H_2) = 50$ atm, reaction time = 6–14 h, room temperature.

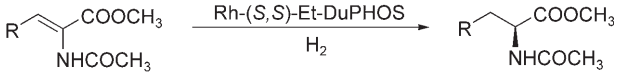
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm) after the reduced acids had been transformed to their corresponding methyl esters.

[c] Data in brackets were isolated yields after column chromatography.

[d] Hydrogenations were carried out using MeOH as solvent under otherwise identical conditions.

[e] Percentage of Ru leached to the product in the second run determined by ICP. Data in brackets are Ru concentration (ppm) in the extract.

Table 3. Asymmetric hydrogenation of enamides catalyzed by [Rh-(*S*,*S*)-Et-DuPHOS]$^+BF_4^-$ in different solvent systems.[a]



10 **11**

Entry	Substrate (R)	Solvent system (v/v)	*ee* [%][b,c]
1	**10a** (C_6H_5)	PEG600/MeOH (1/1)	93.0
2	**10a** (C_6H_5)	PEG600/MeOH (1/2)	93.0
3	**10a** (C_6H_5)	PEG600/MeOH (1/3)	97.6
4	**10a** (C_6H_5)	PEG600/MeOH (1/4)	98.1 (98.6)
5	**10b** (2-Cl-C_6H_4)	PEG600/MeOH (1/3)	94.2 (97.2)
6	**10c** (3-Cl-C_6H_4)	PEG600/MeOH (1/3)	97.0 (98.6)
7	**10d** (4-Cl-C_6H_4)	PEG600/MeOH (1/3)	97.1 (98.8)
8	**10e** (4-NO_2-C_6H_4)	PEG600/MeOH (1/3)	93.4 (95.0)
9	**10f** (4-CH_3O-C_6H_4)	PEG600/MeOH (1/3)	98.6 (99.0)
10	**10g** (H)	PEG600/MeOH (1/3)	98.2 (99.6)

[a] The hydrogenations were carried out using 20–50 mg substrate under the following conditions: substrate/catalyst = 200 (M/M), $P(H_2) = 10$ atm, temperature = 15–20 °C, reaction time = 3 h. Complete conversion was observed in all cases.
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-L-Val column (25 m × 0.25 mm). All products were in the *S*-configuration.
[c] Data in brackets were obtained by using MeOH as solvent under otherwise identical conditions.

tained in pure methanol (entry 4). The hydrogenation was then extended to other substrates and high enantioselectivities (93.4–98.6 %) were observed in all cases, which were slightly lower than those in methanol.

To examine the recyclability of the Rh-DuPHOS catalyst in the PEG/MeOH system, we chose the asymmetric hydrogenation of methyl α-acetamidocinnamate (**10a**) and methyl acetamidoacrylate (**10g**) as the standard reactions. As shown in Table 4, in the first three runs (entries 1–3), the high enantioselectivities obtained for the two substrates in PEG were retained, the values being slightly lower than those in pure methanol. In the case of the asymmetric hydrogenation of **10a**, the catalyst could be reused at least four times with high conversions and isolated yields. Notably, when methyl acetamidoacrylate was used as the substrate, the rhodium catalyst showed extremely high efficiency upon 10 successive cycles, without significant loss of enantioselectivity and catalytic activity. In contrast, the enantioselectivity of the catalyst decreased significantly after the first cycle in ionic liquid (from 93 % to 80 % *ee*).[7e] Furthermore, the Rh catalyst leaching was determined by ICP analysis. As expected, no appreciable leaching (< 0.13 %, 0.02 ppm) of Rh occurred during the extraction of organic products because of the ionic behavior of the catalyst.

Asymmetric Hydrogenation of β-Keto Esters in PEG

Optically active β-hydroxy carboxylic acids and their esters have various applications in the synthesis of enantiomerically pure pharmaceuticals, pesticides, flavors, and as monomers for biodegradable polymers. The enantioselective reduction of β-keto esters to β-

Table 4. Reuse of catalyst for the asymmetric hydrogenation of enamides **10a** and **10g** using [Rh-(*S*,*S*)-Et-DuPHOS]$^+BF_4^-$ as catalyst in PEG-600/MeOH as solvent.[a]

Substrate		Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10
10a	conv. [%][b,c]	> 99 (92)	> 99 (95)	> 99 (99)	99 (98)	99 (98)					
	ee [%][b]	97.0	95.2	93.6	91.1	87.6					
10g	conv. [%][b]	> 99	> 99	> 99	98	99	98	99	99	99	70
	ee [%][b]	98.2	98.4[d]	98.0	95.5	93.5	94.2	94.2	93.1	93.4	92.0

[a] The hydrogenations were carried out using 20–50 mg substrate in 6 mL PEG-600/MeOH (1:3, v/v) under the following conditions: substrate/catalyst = 200 (M/M), $P(H_2) = 10$ atm, temperature = 15–20 °C, reaction time = 3–10 h.
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-L-Val column (25 m × 0.25 mm). All products were in the *S*-configuration.
[c] Data in brackets are isolated yields after column chromatography.
[d] Percentage of Rh leached to the product in the second run was no more than 0.13 % (0.02 ppm) by ICP analysis.

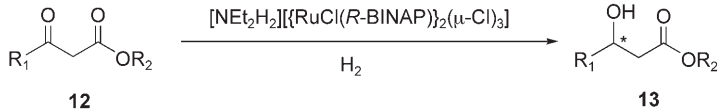
hydroxy esters was successfully achieved with several types of Ru-BINAP complexes in pure alcoholic organic solvents under mild reaction conditions.[27] Such asymmetric hydrogenations performed in a mixture of ionic liquid and MeOH also have been reported.[7l,m] In most cases, however, modification of the catalyst was required. Furthermore, the modified Ru(BINAP) catalysts sometimes suffered from lower enantioselectivities in ionic liquids than those obtained with the parent homogeneous catalyst.[7m] To determine whether the catalytic reduction of prochiral ketones could proceed smoothly in PEG as solvent, we chose the dinuclear complex $[NEt_2H_2][\{RuCl(R\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$ as the catalyst for our study.[28] The effect of solvents on the enantioselectivity was firstly studied and the results are summarized in Table 5. We attempted to hydrogenate methyl acetoacetate (**12a**) with 0.2 mol% Ru(BINAP) in pure PEG. After 20 h of reaction at 10 atm of H_2 pressure, complicated products were obtained. When methanol was used as co-solvent, the hydrogenation reaction proceeded smoothly and cleanly with high enantioselectivity, which was comparable to that obtained in pure methanol (98.8% *vs.* 99.0% *ee*). The use of increased amounts of MeOH did not influence the enantioselectivity but improved the catalytic activity. For the best catalyst activity and enantioselectivity, an equal volume mixture of PEG and MeOH was chosen as the solvent for all the subsequent hydrogenations. As shown in Table 5, a variety of β-alkyl keto esters and β-aryl keto esters were hydrogenated in the homogeneous PEG/MeOH system to afford high enantioselectivities, which were similar to those obtained in pure MeOH.

The recovery and reuse of the catalyst and PEG have also been demonstrated in the asymmetric hydrogenation of methyl acetoacetate (**12a**) and 3-oxo-3-(4′-chlorophenyl)propanoate (**12c**) (Table 6). At the end of each hydrogenation run, the reduced products were extracted with degassed hexane, and the PEG phase was reused directly in the next cycle. We have successfully reused the catalyst in both cases. Notably, the enantioselectivity was retained for all five runs although the activity of the catalyst slightly decreased after the third cycle. These results were better than those obtained in ionic liquid.[7l,m] The inductively coupled plasma (ICP) spectroscopy further showed that no appreciable leaching of Ru occurred during the extraction of organic products because of the ionic behavior of the catalyst. We estimated from ICP experiments that less than 0.34% (0.14 ppm) of the Ru catalyst has leached into the hexane extracts from the PEG phase.

Asymmetric Hydrogenation of Simple Aromatic Ketones in PEG

Enantiomerically pure alcohols are important intermediates in the pharmaceutical industry and are usually available from the reduction of ketones either by chemical means or biotransformation. Among the many protocols available for the transformation of prochiral ketones to chiral alcohols, the catalytic asymmetric hydrogenation of ketones is one of the most efficient and cost-effective methods.[1a] A number of efficient catalysts has been developed for the asymmetric hydrogenation of functionalized ketones.[2b,20] In contrast, only a few catalysts have been re-

Table 5. Asymmetric hydrogenation of β-keto esters catalyzed by $[NEt_2H_2][\{RuCl(R\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$ in different solvent systems.[a]



12 **13**

Entry	Substrate (R^1/R^2)	Solvent system	Conv. [%][b,c]	*ee* [%][b,c]
1	**12a** (CH_3/CH_3)	PEG600/MeOH = 3/1	95	98.8 (99.0)
2	**12a** (CH_3/CH_3)	PEG600/MeOH = 1/1	99	98.8
3	**12a** (CH_3/CH_3)	PEG600/MeOH = 1/3	> 99	99.2
4	**12b** (CH_3/*t*-Bu)	PEG600/MeOH = 1/1	> 99 (> 99)	93.4 (94.3)
5	**12c** (C_6H_5/CH_3)	PEG600/MeOH = 1/1	> 99 (> 99)	90.0 (92.0)
6	**12d** (C_6H_5/C_2H_5)	PEG600/MeOH = 1/1	96 (> 99)	85.8 (83.0)
7	**12e** (4-Cl-C_6H_5/CH_3)	PEG600/MeOH = 1/1	> 99 (> 99)	85.0 (86.0)
8	**12f** (4-F-C_6H_5/CH_3)	PEG600/MeOH = 1/1	96 (99)	85.3 (87.4)

[a] The hydrogenations were carried out using 60–80 mg substrate under the following conditions: substate/catalyst/HCl = 500/1/0.5 (M/M/M), $P(H_2) = 10$ atm, temperature = 60 °C, reaction time = 20 h.
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm). All products were in the *R*-configuration.
[c] Data in brackets were obtained by using MeOH as solvent under otherwise identical conditions.

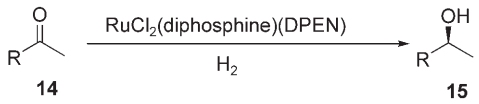
Table 6. Reuse of catalyst for the asymmetric hydrogenation of β-keto esters **12a** and **12c** using $[NEt_2H_2][\{RuCl(R\text{-BINAP})\}_2(\mu\text{-Cl})_3]$ as catalyst in PEG-600/MeOH as solvent.[a]

Run	**12a** Conv. [%][b]	*ee* [%][b]	**12e** Conv. [%][b,c]	*ee* [%][b]
1	>99	98.6	>99 (94)	85.0
2	>99	99.0	>99 (98)	84.6[d]
3	99	98.2	>99 (99)	84.4
4	80	97.8	86 (83)	85.2
5[e]	93	97.6	77 (75)	85.6

[a] The hydrogenations were carried out using 60–80 mg substrate in 6 mL PEG-600/MeOH (1:1, v/v) under the following conditions: substrate/catalyst/HCl = 500/1/0.5 (M/M/M), $P(H_2) = 10$ atm, temperature = 60 °C, reaction time = 20 h.
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm). All products were in the *R*-configuration.
[c] Data in brackets are isolated yields after column chromatography.
[d] Percentage of Ru leached to the product in the second run was no more than 0.34 % (0.14 ppm) by ICP analysis.
[e] Reaction time = 30 h.

ported in the asymmetric hydrogenation of simple ketones.[29] Recently, a significant breakthrough was achieved by Noyori and co-workers by using chiral $RuCl_2$(diphosphine)(diamine) complexes as catalysts in the hydrogenation of a variety of simple ketones.[30] For the best economic effect, it is still highly desirable to make this catalyst system recyclable. Although immobilization of the homogeneous catalyst offers an attractive solution to this problem, so far, only a few successes have been achieved.[5b,r,17d] Most recently, Lin and co-workers reported the successful asymmetric hydrogenation of aromatic ketones in a mixture of ionic liquid and isopropyl alcohol by using a modified BINAP ligand.[7p] Both Ru catalysts and ionic liquid could be recycled by simple extraction and reused for four times. For our study, the commercially available diphosphine ligands xyl-P-Phos, xyl-BINAP and BINAP were chosen for the asymmetric hydrogenation of aromatic ketones. Firstly, we investigated the effect of isopropyl alcohol as a co-solvent on the catalytic activity and enantioselectivity, and the results are summarized in Table 7. To our delight, in the presence of 0.2 mol % of $RuCl_2$[(*S*)-xyl-P-Phos][(*S*,*S*)-DPEN] as catalyst, the hydrogenation of acetophenone (**14a**) proceeded smoothly in a mixture of PEG/isopropyl alcohol with almost the same enantioselectivity as

Table 7. Asymmetric hydrogenation of simple ketones **14** catalyzed by Ru(**1b, 1c** or **3b**)(DPEN) in different solvent systems.[a]



14 **15**

Entry	Substrate (R)	Solvent system (v/v)	Conv. [%][b,c]	*ee* [%][b,c]
1	**14a** (C_6H_5)	PEG600/*i*-PrOH (3/1)	73 (>99)	97.0 (97.0)
2	**14a** (C_6H_5)	PEG600/*i*-PrOH (1/1)	99	98.2
3	**14a** (C_6H_5)	PEG600/*i*-PrOH (1/3)	>99	98.0
4	**14b** (2-CH_3-C_6H_4)	PEG600/*i*-PrOH (1/1)	>99 (>99)	98.2 (98.2)
5	**14c** (4-CH_3O-C_6H_4)	PEG600/*i*-PrOH (1/1)	>99 (>99)	97.8 (96.4)
6	**14d** (1-naphthyl)	PEG600/*i*-PrOH (1/1)	98 (>99)	97.4 (97.0)
7[d]	**14d** (1-naphthyl)	PEG600/*i*-PrOH (1/1)	99 (>99)	94.8 (95.0)
8[e]	**14a** (C_6H_5)	PEG600/*i*-PrOH (1/1)	98 (>99)	97.4 (98.0)

[a] The hydrogenations were carried out using 50–70 mg substrate under the following conditions: (*S*)-xyl-P-Phos as ligand otherwise specified, substate:ligand:Ru:diamine:*t*-C_4H_9OK = 500:1.1:1 :1:6 (mol ratio), $P(H_2) = 20$ atm, reaction time = 20 h, room temperature.
[b] The *ee* values and conversions were determined by GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm). All products were in the *R*-configuration.
[c] Data in brackets were obtained by using *i*-PrOH as solvent under otherwise identical conditions.
[d] (*S*)-BINAP was used as ligand, temperature = 80 °C, $P(H_2) = 40$ atm, reaction time = 4 h.
[e] (*R*)-xyl-BINAP was used as ligand, room temperature, $P(H_2) = 20$ atm, reactiom time = 20 h. The product was in the *S*-configuration.

that in isopropyl alcohol alone (entry 1). The use of an increased amount of isopropyl alcohol improved both the catalytic activities and enantioselectivities (entries 2 and 3). The asymmetric hydrogenation was extended to other simple ketones **14b**, **14c** and **14d**. Similarly, high enantioselectivities were observed, which were comparable to those obtained in pure isopropyl alcohol (entries 4–6). To further demonstrate the efficacy of the PEG/isopropyl alcohol system, other two chiral ruthenium catalysts $RuCl_2$[(*R*)-xyl-BINAP][(*R*,*R*)-DPEN] and $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN] were also employed to the asymmetric hydrogenation of simple ketones. Comparable enantioselectivities and conversions to those obtained in isopropyl alcohol were observed (entries 7 and 8).

Having established the efficacy of this catalytic system, we then investigated the recovery and reuse of the catalysts. All three catalysts were studied and the results are presented in Table 8. At the end of each hydrogenation experiment, the reduced chiral alcohol was extracted with degassed hexane. The PEG phase was washed once more with degassed hexane and was reused in the next run. All three catalysts could be recycled and afforded high enantioselectivities. In particular, the catalyst $RuCl_2$[(*S*)-xyl-P-Phos]-[(*S*,*S*)-DPEN] gave almost the same enantioselectivities in all the five catalytic runs. The conversions were also retained in the first four cycles and decreased significantly only in the fifth run. Furthermore, the leaching of Ru to the hexane extracts was measured by ICP and was found to be no more than 3.54% (0.85 ppm).

Table 8. Reuse of catalysts using different chiral diphosphine ligands for asymmetric hydrogenation of simple ketones in PEG/*i*-PrOH as reaction medium.[a]

Run	**14a**[b]		**14b**[c]		**14d**[d]	
	Conv. [%][e,f]	*ee* [%][e]	Conv. [%][e]	*ee* [%][e]	Conv. [%][e]	*ee* [%][e]
1	>99 (91)	97.4	>99	98.2	99	94.8
2	>99 (95)	97.3	>99	98.0	99	93.6[g]
3	>99 (98)	96.8	>99	97.7	99	94.3
4	>99 (97)	96.0	>99	98.0	76	90.2
5	88 (82)	95.2	56	97.6		

[a] The hydrogenations were carried out using 50–70 mg substrate in 6 mL PEG-600/*i*-PrOH (1:1, v/v) under the following conditions: substrate:ligand:Ru:diamine:*t*-C_4H_9OK = 500:1.1:1:1:6 (mol ratio), $P(H_2)$ = 20 atm, reaction time = 20 h, room temperature.
[b] (*R*)-xyl-BINAP was used as ligand.
[c] (*S*)-xyl-P-Phos was used as ligand.
[d] (*S*)-BINAP was used as ligand, temperature = 80 °C, $P(H_2)$ = 40 atm, reaction time = 4 h.
[e] The *ee* values and conversions were determined by chiral GC with a Chrompack Chirasil-DEX CB column (25 m × 0.25 mm).
[f] Data in brackets are isolated yields after column chromatography.
[g] Percentage of Ru leached to the product in the second run of **14d** was no more than 3.54% (0.85 ppm) by ICP analysis.

Conclusions

A practical protocol for the effective asymmetric hydrogenation of prochiral olefins and ketones and the recycling of catalsyt in PEG has been developed. Ru and Rh catalysts obtained with commercially available chiral diphosphine ligands were employed for the asymmetric hydrogenation of 2-arylacrylic acids, enamides, β-keto esters and simple aromatic ketones in PEG and an organic co-solvent, affording comparable enantioselectivities and catalytic activities to those obtained in conventional organic solvent systems. Both the catalysts and PEG could be readily recycled by simple extraction with immiscible organic solvents such as diethyl ether and hexane, as in the case of ionic liquids, and reused up to nine times without substantial loss of catalytic activity and enantioselectivity. No severe leaching of metal catalysts (<3% in most cases) was observed during the extraction of the organic products. All these results indicated that PEGs as green and recyclable reaction media are attractive alternatives to room temperature ionic liquids.

Experimental Section

General Remarks

All experiments were carried out under a nitrogen atmosphere by using standard Schlenk-type techniques, or were performed in a glove-box. All solvents were dried by using standard, published methods and were distilled under a nitrogen atmosphere before use. PEG was dried under reduced pressure using the toluene azeotrope before use. The β-keto esters and simple ketones were distilled under reduced pressure before use. All other chemicals were used as received from Aldrich, Acros, or Strem without further purification. (*S*)-5,5′-Diamino-BINAP (**2**) and (*S*)-6,6′-dihydroxy-BIPHEP (**5**) were synthesized according to the published methods.[21,24] PEG-supported (*R*)-BINAP (**7**) was synthesized as previously reported.[11b] The set-up of the high-pressure reactor was carried out in a glove-box. GC chromatography was performed on a Varian-6000 with FID detector.

General Procedure for the [RuCl(diphosphine)(η-C_6H_6)]Cl-Catalyzed Asymmetric Hydrogenation of 2-Arylacrylic Acids with Catalyst Recycling

The catalyst [RuCl(diphosphine)(η-C_6H_6)]Cl was prepared *in situ* according to the method reported in the literature.[3l,17i] A mixture of $[RuCl_2(C_6H_6)]_2$ (12 mg) and chiral diphosphine ligand (2.2 equivs.) in dry and degassed DMF (2 mL) was

stirred under N_2 at 100 °C for 30 min. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the catalyst (0.0012 mmol) was transferred to a 20-mL glass-lined stainless steel reactor containing PEG/MeOH (6 mL), NEt_3 and substate (0.12 mmol). The autoclave was closed and pressurized with H_2 to 50 atm. The mixture was stirred with a magnetic stirrer under H_2 pressure at room temperature for a predetermined period of time. After releasing the hydrogen, the methanol was removed under reduced pressure. Anhydrous ether (5 mL) and hexane (5 mL) were added to extract the organic product. The resultant two layers were mixed thoroughly by vigorous stirring for 5 min and then cooled to solidify the catalyst-containing PEG layer. The upper solution layer was separated by decantation. This manipulation was repeated one more time. The combined extracts containing the product was purified by flash chromatography on silica gel. The conversion and the *ee* value of the product were determined by GC with a Chrompack Chirasil-DEX CB column after the reduced acid had been transformed to its corresponding methyl ester. The recovered PEG and catalyst were reused in the next batch of the catalytic reaction under identical conditions.

General Procedure for the [Rh-(*S,S*)-Et-DuPHOS]$^+BF_4^-$-Catalyzed Asymmetric Hydrogenation of Enamides with Catalyst Recycling

In a glove-box under a nitrogen atmosphere, a 20-mL glass-lined stainless steel reactor with a magnetic stirring bar was charged with catalyst (0.0016 mmol), substrate (0.32 mmol), and PEG/MeOH (6 mL). The autoclave was closed and pressurized with H_2 to 10 atm. The mixture was stirred under H_2 pressure at room temperature for a predetermined period of time. After the autoclave was depressurized, the methanol was removed under reduced pressure. Hexane (10 mL × 2) was added to extract the product. The extracts were used for the analysis of the conversion and the *ee* value of the product on GC with a Chrompack Chirasil-L-Val column. The recovered catalyst in PEG was reused in the next batch of the catalytic reaction under identical conditions.

General Procedure for the $[NEt_2H_2][\{RuCl(R\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$-Catalyzed Asymmetric Hydrogenation of β-Keto Esters and the Catalyst Recycling

The catalyst $[NEt_2H_2][\{RuCl(R\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$ were prepared *in situ* according to the method reported in the literature.[28] A mixture of $[RuCl_2(C_6H_6)]_2$ (40 mg, 0.08 mmol), (*R*)-BINAP (100 mg, 0.16 mmol) and $HNEt_2{\cdot}HCl$ (18 mg, 0.16 mmol) in dry and degassed 1,4-dioxane (30 mL) was heated at 50 °C with stirring for 2 h, then refluxed with stirring for further 12 h. The resulting clear red-brown solution was cooled to room temperature, and the solvent was removed under reduced pressure to give a brown solid. The *in situ* prepared catalyst (0.0012 mmol) was transferred to a 20-mL glass-lined stainless steel reactor containing PEG/MeOH (6 mL), hydrochloric acid and substrate (0.6 mmol). The hydrogenation reaction was performed under 10 atm H_2 pressure at 60 °C for 20 h. The reduced product was extracted using a 1:4 mixture of anhydrous ether and hexane (10 mL × 2). The recovered catalyst in PEG media was reused in the next batch of the catalytic reaction under identical conditions. The conversion and the *ee* value of the product were determined by GC analysis with a Chrompack Chirasil-DEX CB column.

General Procedure for the $RuCl_2$(diphosphine)-DPEN-Catalyzed Asymmetric Hydrogenation of Simple Aromatic Ketones and the Catalyst Recycling

The catalysts $RuCl_2$(diphosphine)-DPEN were prepared *in situ* according to the same procedures reported in the literature.[17d,30c] A mixture of $[RuCl_2(C_6H_6)]_2$ (26 mg) and chiral diphosphine ligand (2.2 equivs.) in dry and degassed DMF (2 mL) was stirred under N_2 at 100 °C for 30 min to form a reddish brown solution. After the solution was cooled to room temperature, the *R*- or *S*-form of DPEN (2.2 equivs.) was added and the mixture was stirred for further 10 h. After the solvent had been removed under reduced pressure, the catalyst (0.001 mmol) was transferred to the autoclave in which PEG/*i*-PrOH (6 mL), *t*-C_4H_9OK and substrate (0.5 mmol) were charged. The hydrogenation reaction was performed under 20 atm H_2 pressure at room temperture for 20 h. The reduced product was extracted using a 1:4 mixture of anhydrous ether and hexane (10 mL × 2). The recovered catalyst in PEG media was reused in the next batch of catalytic reaction under identical conditions. The conversion and the *ee* value of the product were determined by GC analysis with a Chrompack Chirasil-DEX CB column.

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