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Asymmetric Hydrogenation

SPECIAL ISSUE

Solvent-Regulated Asymmetric Hydrogenation of Quinoline Derivatives in Oligo(Ethylene Glycol)s through Host–Guest Interactions

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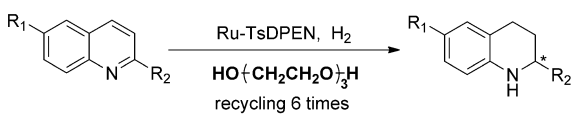
Abstract: The asymmetric hydrogenation of quinolines in oligo(ethylene glycol)s (OEGs) and poly(ethylene glycol)s (PEGs) with chiral cationic ruthenium diamine complexes has been investigated. Interestingly, in liquid PEGs or long-chain OEGs, the Ru catalysts lost their reactivity. Upon the addition of a little MeOH, the hydrogenation of quinoline was switched "ON". Evidence from mass spectrometry and control experiments revealed that encapsulation of the quinolinium salt by PEG or long-chain OEG molecules through supramolecular interactions is possibly the main reason for such a switchable hydrogenation reaction. Moreover, the asymmetric hydrogenation of 2-substituted quinoline derivatives was achieved in triethylene glycol (3-OEG), thereby affording 1,2,3,4-tetrahydroquinolines with excellent reactivities and enantioselectivities (up to 99% *ee*). Furthermore, the Ru catalyst could be readily recycled for both pure 3-OEG and biphasic 3-OEG/*n*-hexane systems without a clear loss of reactivity and enantioselectivity.

Introduction

Seeking new and environmentally benign reaction media is one of the major goals of "green" chemistry research and has attracted increased interest in recent years.[1] The use of alternative solvents in catalytic reactions is not merely a case of simply switching the solvent; it also offers fascinating possibilities, such as enhanced catalytic performance, thereby uncovering new reactions that couldn't occur in common organic media, and facilitating catalyst immobilization and reuse. As a new type of alternative solvent, liquid PEGs are cheap, non-volatile, non-halogenated, and have low toxicity and high chemical stability.[2] More importantly, as linear counterparts of crown ethers, PEGs have been considered as "host" solvents, owing to their ability to associate with cations, as exemplified in phase-transfer catalysis. Recently, crown ethers and their linear counterparts have been used for the construction of chiral ligands and/or catalysts, and they have been employed in studies on supramolecular asymmetric catalysis.[3] Moreover, PEG solvents have also shown an ability to fine-tune reactions through supramolecular adjustments.[4] In fact, liquid PEGs have been intensively studied as solvent in a broad range of organic reactions;[2] however, the utilization of PEGs for asymmetric hydrogenation reactions and for the recycling of chiral metallic catalysts, in particular as host molecules that participate in tuning the reaction outcome remain limited.[5]

Recently, we developed an asymmetric hydrogenation reaction of quinolines, olefins, and ketones in PEGs with transition-metal complexes of chiral diphosphine ligands. High catalytic activities and enantioselectivities, similar to those obtained with conventional organic solvents, and recycling of the catalysts were achieved.[5b–d] As part of our continuing efforts on the development of "green" methods for asymmetric hydrogenation reactions,[6] herein, we report a practical procedure for the asymmetric hydrogenation of quinoline derivatives by using phosphine-free chiral cationic ruthenium diamine complexes (Scheme 1).[7] We observed that the reactivity of the hydrogenation reaction varied quite widely in OEGs and PEGs of different molecular weights. Further studies attributed the dif-



Scheme 1. Asymmetric hydrogenation of quinoline derivatives catalyzed by a chiral cationic Ru catalyst in 3-OEG.

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ferent reactivities to encapsulation of the quinolinium salts by PEG or long-chain OEG molecules. The reactivity of the hydrogenation reaction could be turned "ON" by the addition of a small amount of MeOH or by selecting a short-chain OEG as the solvent. The asymmetric hydrogenation reaction of a range of 2-substituted quinoline derivatives and catalyst recycling were also achieved by using a short-chain 3-OEG as the reaction medium.

Results and Discussion

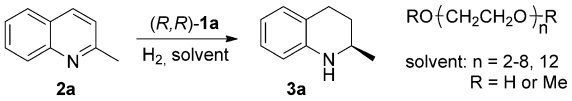
In our previous work, we performed comprehensive and systematic studies on the hydrogenation of quinolines catalyzed by cationic η^6-arene-*N*-tosylethylenediamine–ruthenium(II) complexes and we discovered an ionic and cascade reaction pathway that involved a stepwise H^+/H^--transfer process outside the coordination sphere.[8] Considering that the key intermediates were cationic compounds, as well as the ruthenium catalytic species, which are reasonable guest molecules for PEG and long-chain OEG hosts, we anticipated that effective supramolecular regulation could be observed by using PEGs or OEGs as reaction media for the hydrogenation of quinoline derivatives.

Asymmetric Hydrogenation of Quinoline Derivatives in PEGs and OEGs

To assess the validity of this hypothesis, we tentatively examined the asymmetric hydrogenation reaction of 2-methylquinoline (**2a**) with Ru–TsDPEN (**1a**; Scheme 2) in pure PEGs or DMPEG (poly(ethylene glycol) dimethyl ether; Table 1, entries 1–3). To our surprise, no conversion was observed in these solvents, even after screening different reaction conditions. We suspected that the reaction was impeded by host–guest interactions with the PEG solvent, and that shortening the PEG chain length might help to promote the reaction. Therefore, a series of OEGs of different lengths were synthesized and tested in the model hydrogenation reaction of compound **2a** with (*R,R*)-**1a** as a catalyst. The reaction proceeded smoothly in short-chain OEGs (less than four ethylene glycol (EG) units), thereby affording 1,2,3,4-tetrahydroquinoline (**3a**) with complete conversion and excellent enantioselectivity (Table 1, entries 4 and 5). Similarly, complete conversions and slightly lower enantioselectivities (92% *ee*) were obtained in oligo(ethylene glycol) dimethyl ethers (DMOEGs; Table 1, entries 4–6). The reactivity and enantioselectivity gradually decreased on increasing the OEG chain length (Table 1, entries 6–8) and, when the OEG length reached seven EG units, the hydrogenation reaction did not occur, in a similar manner to the long-chain PEGs (Table 1, entries 9–11). Therefore, in terms of both reactivity and enantioselectivity, triethylene glycol (3-OEG) was selected for further optimization of the catalyst and other reaction conditions.

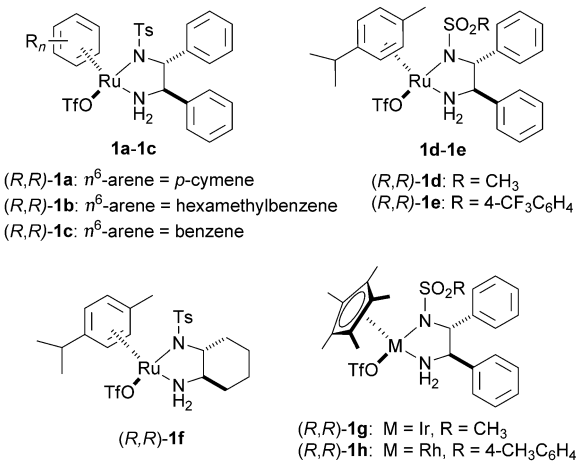
Next, we examined the effect of catalyst structure on the catalytic performance and we found that the substituents on both the η^6-arene and the *N*-sulfonate groups significantly affected the catalytic performance (Table 2, entries 1–5). The replacement of TsDPEN with TsCYDN led to much-lower enantioselectivity and reactivity (Table 2, entry 6 *vs* entry 1), whilst iridium and rhodium complexes both gave lower conversions and enantioselectivities (Table 2, entries 7–8). Thus, catalyst (*R,R*)-**1a** was found to be optimal in terms of both reactivity and enantioselectivity. In addition, the reaction temperature and hydrogen pressure were also screened with catalyst (*R,R*)-**1a**. Complete conversion was observed at high temperature (Table 2, entry 9) and lowering the hydrogen pressure resulted in a remarkable decrease in activity (Table 2, entries 10 and 11). Notably, the enantioselectivity was insensitive to both the reaction temperature and hydrogen pressure. When the reaction was

Table 1. Asymmetric hydrogenation of compound **2a** catalyzed by compound (*R,R*)-**1a** in OEGs or PEGs.[a]



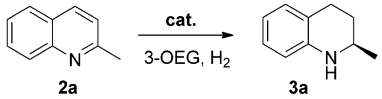
Entry	Solvent (M_w)	T [°C]	Conversion [%][b]	*ee* [%][c]
1	PEG-300	35	n.r.	–
2	PEG-500	35	n.r.	–
3	DMPEG-500	35	n.r.	–
4	2-OEG (106)	25	>99 (>99%)	96 (92)
5	3-OEG (150)	25	>99 (>99%)	96 (92)
6	4-OEG (194)	25	94 (>99%)	97 (92)
7	5-OEG (238)	25	70	92
8	6-OEG (282)	25	41	92
9	7-OEG (326)	25	n.r.	–
10	8-OEG (370)	25	n.r.	–
11	12-OEG (546)	25	n.r.	–

[a] Reaction conditions: 2-methylquinoline (**2a**; 0.2 mmol), solvent (1 mL), catalyst (*R,R*)-**1a** (1.0 mol%), H_2 (50 atm), 20 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. Data in parentheses were obtained in DMOEGs as the reaction solvents. M_w = molecular weight, n.r. = no reaction, PEG-300: PEG Mw = 300, DMPEG-500: DMPEG Mw = 500.



Scheme 2. Chiral cationic Ru catalysts for the asymmetric hydrogenation of quinoline derivatives in 3-OEG. Ts = *para*-toluenesulfonyl, Tf = trifluoromethanesulfonyl

Table 2. Optimization of the reaction conditions.[a]



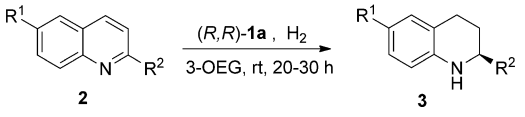
Entry	Catalyst	H_2 [atm]	T [°C]	Conversion [%][b]	*ee* [%][c]
1	(*R*,*R*)-**1a**	50	25	67	96
2	(*R*,*R*)-**1b**	50	25	<5	n.d.
3	(*R*,*R*)-**1c**	50	25	13	84
4	(*R*,*R*)-**1d**	50	25	60	95
5	(*R*,*R*)-**1e**	50	25	26	95
6	(*R*,*R*)-**1f**	50	25	26	75
7	(*R*,*R*)-**1g**	50	25	58	84
8	(*R*,*R*)-**1h**	50	25	<5	n.d.
9	(*R*,*R*)-**1a**	50	60	>99	95
10	(*R*,*R*)-**1a**	20	25	40	97
11	(*R*,*R*)-**1a**	1	25	14	95
12[d]	(*R*,*R*)-**1a**	50	25	10	93

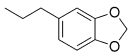
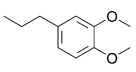
[a] Reaction conditions: compound **2a** (0.2 mmol), 3-OEG (1 mL), catalyst (1.0 mol%), 10 h; [b] determined by ^{1}H NMR spectroscopy; [c] determined by HPLC analysis on a chiral stationary phase; [d] S/C = 500:1, n.d. = not detected.

performed at a substrate/catalyst (S/C) molar ratio of 500:1, much-lower conversion was observed (Table 2, entry 12).

Having established the optimal catalyst and reaction conditions, we explored the substrate scope of the Ru-catalyzed asymmetric hydrogenation of 2-substituted quinolines in 3-OEG (Table 3). In general, all of the tested 2-alkyl-substituted quinoline derivatives were hydrogenated with complete conversions and excellent enantioselectivities (92–99% *ee*). The reaction was found to be relatively insensitive to the length of the side chain on the 2-alkylated quinolines (Table 3, entries 1–4) and excellent results were also achieved with 2-phenethyl quinolines (Table 3, entries 5 and 6). Notably, the quinoline with a hydroxy group on the side chain provided the highest enantioselectivity of 99% *ee* (Table 3, entry 7). The presence of a substituent group at the 6-position had no clear effect on either the reactivity or enantioselectivity of the reaction (Table 3, entries 8–10). The hydrogenation of 2-phenylquinoline also proceeded smoothly, but gave a lower enantioselectivity than those of the 2-alkylated quinolines (Table 3, entry 11).

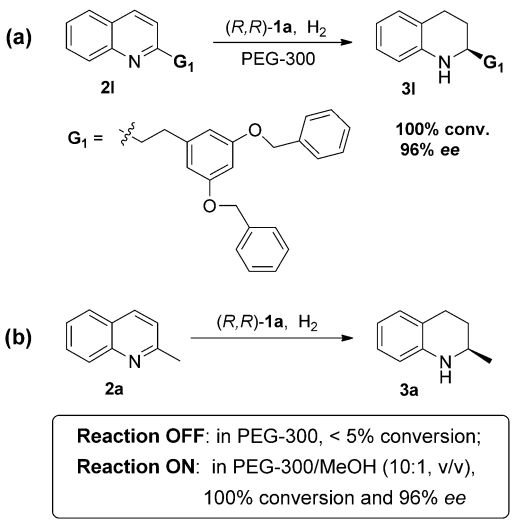
Table 3. Asymmetric hydrogenation of 2-substituted quinoline derivatives catalyzed by compound (*R*,*R*)-**1a** in 3-OEG.[a]



Entry	R^1	R^2		Conversion [%][b]	*ee* [%][c]
1	H	Me	**2a**	>99 (99)	96
2	H	Et	**2b**	>99 (98)	94
3	H	*n*-Pr	**2c**	>99 (98)	94
4	H	*n*-pentyl	**2d**	>99 (97)	95
5	H		**2e**	>99 (98)	92
6	H		**2f**	>99 (98)	95
7	H		**2g**	>99 (95)	99
8	MeO	Me	**2h**	>99 (96)	96
9	Me	Me	**2i**	>99 (93)	93
10	F	Me	**2j**	>99 (94)	95
11	H	Ph	**2k**	>99 (94)	82

[a] Reaction conditions: substrate **2** (0.2 mmol), 3-OEG (1 mL), catalyst (*R*,*R*)-**1a** (1.0 mol%), H_2 (50 atm), 25 °C, 20–30 h. [b] Determined by ^{1}H NMR analysis; data in parentheses denote the yields of the isolated products. [c] Determined by HPLC analysis on a chiral stationary phase.

Based on the coordinating ability of metal or organic cations to PEGs and long-chain OEGs, we anticipated that possible associations between solvent molecules and the activated substrate (quinolinium salt) or the cationic ruthenium complex might be the reason why the hydrogenation reaction didn't occur in these solvents. As expected, electrospray ionization mass spectroscopy revealed the existence of complexes between molecules of 12-OEG and the quinolinium salt or the ruthenium complex (see the Supporting Information, Figures S1–S3). As shown in the Supporting Information, Figure S2, a strong signal for the ion peak at $m/z = 690.40554$ suggested the formation of [12-OEG·**2a**H]$^+$. A similar complex was also observed for the ruthenium catalyst (see the Supporting Information, Figure S3), but the signal was much weaker than that obtained with the quinolinium salt. To pursue further experimental evidence of these associations, we performed two control experiments. Firstly, a new substrate that contained a sterically demanding dendritic substituent (**2l**) was designed, synthesized, and applied to the asymmetric hydrogenation reaction in PEG-300. The reaction was found to proceed smoothly, thereby affording the reduced product in complete conversion and 96% *ee* (Scheme 3), thus indicating that the bulk substrate could not be encapsulated by PEG-300 and that the cat-



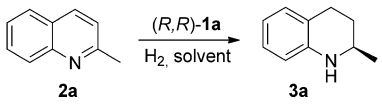
Scheme 3. Control experiments: a) asymmetric hydrogenation of dendritic quinoline **2l**; b) solvent-regulated asymmetric hydrogenation of compound **2a**. Reaction conditions: catalyst (*R*,*R*)-**1a** (1.0 mol%), H_2 (50 atm), 25 °C, 24 h.

alyst could not be deactivated by supramolecular recognition with PEG-300. We also performed the hydrogenation reaction of compound **2a** in a mixture of PEG-300/MeOH (Scheme 3) and found that the hydrogenation reaction was switched "ON" by simply adding a small amount of MeOH, which presumably weakened the host–guest interactions. Based on these observations, encapsulation of the activated quinoline substrate by PEG or long-chain OEG molecules might be the main reason for the shutdown of the reaction.

Catalyst Recycling and Reuse

Another noteworthy feature of this catalytic system is the reusability of the catalyst. Taking the asymmetric hydrogenation of 2-methylquinoline (**2a**) as a model reaction, we first examined the recyclability of Ru catalyst (*R,R*)-**1a** in pure 3-OEG. Upon completion of the hydrogenation reaction, the product was separated by extraction with *n*-hexane. Then, the OEG phase was directly recharged with compound **2a** and subjected to a second hydrogenation reaction under identical conditions. As shown in Table 4, the ruthenium catalyst could be reused at least six times without a clear loss of reactivity or enantioselectivity.

Table 4. Reuse of catalyst (*R,R*)-**1a** in the asymmetric hydrogenation of compound **2a** in different solvent systems.[a]



2a **3a**

Run	Conversion [%][b]	Yield [%][c]	*ee* [%][d]
1	>99 (>99)	93 (94)	97 (97)
2	>99 (>99)	96 (95)	97 (97)
3	>99 (>99)	95 (96)	97 (97)
4	>99 (>99)	96 (94)	97 (97)
5	>99 (>99)	94 (93)	97 (96)
6	90 (94)	84 (89)	96 (96)
7	84 (82)	78 (77)	96 (95)

[a] Reaction conditions: compound **2a** (0.2 mmol), 3-OEG (1 mL), catalyst (*R,R*)-**1a** (1.0 mol%), H_2 (50 atm), 25 °C, 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of the isolated product. [d] Determined by HPLC analysis on a chiral stationary phase; data in parentheses were obtained in a 3-OEG/*n*-hexane (1:1, v/v) biphasic catalytic system.

Next, to further facilitate the catalyst recovery and decrease the use of organic solvent, we studied a two-phase catalytic system. Thus, a mixture of 3-OEG and *n*-hexane was used as the reaction medium and, after the reaction was complete, the product was easily separated by decantation. Similar results were obtained by using this biphasic catalytic system compared to pure 3-OEG (Table 4). Based on inductively coupled plasma (ICP) analysis, we estimated that only 0.26% (in pure 3-OEG) and 0.28% (in 3-OEG/*n*-hexane) of the ruthenium catalyst had leached from the OEG phase during the second runs. These results further demonstrated that OEGs are efficient reaction media that can facilitate the immobilization and recycling of homogeneous metallic catalysts.

Conclusion

In summary, we have investigated the asymmetric hydrogenation reaction of quinoline derivatives in OEGs and PEGs catalyzed by chiral ruthenium diamine complexes. In PEGs or long-chain OEGs, the quinolines did not undergo hydrogenation, owing to encapsulation inside PEG or OEG molecules through host–guest interactions. The reactivity of the hydrogenation reaction could be easily turned "on" by simply adding a small amount of MeOH into the reaction mixture. The asymmetric hydrogenation reactions of a range of 2-substituted quinoline derivatives were achieved in short-chain 3-OEG with excellent reactivities and enantioselectivities. In addition, catalyst recycling and reuse were demonstrated in both pure 3-OEG and in a biphasic 3-OEG/*n*-hexane system. Further efforts to extend this solvent-controlled strategy to other asymmetric catalytic reactions are underway.

Experimental Section

General Information

All of the experiments were performed under a nitrogen atmosphere by using standard Schlenk techniques or in a glove-box. All of the solvents were treated prior to use according to the standard methods. PEGs and short-chain OEGs were commercially available and dried under reduced pressure by using a toluene azeotrope prior to use. Long-chain OEGs (more than four EG units) were synthesized according to a literature procedure.[9] Silica gel was dried at 300 °C for 6 h prior to use. Other commercially available reagents were purchased from Alfa Aeser and Aldrich and used as received without further purification. All of the ruthenium catalysts were synthesized according to a literature procedure.[8,10] ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ on a Bruker Model Advance DMX 300 Spectrometer (^{1}H: 300 MHz; ^{13}C: 75 MHz) with tetramethylsilane (TMS) as an internal standard. Enantiomeric excesses were determined by chiral HPLC analysis on a Varian Prostar 210 liquid chromatograph. Optical rotations were measured on a Rudolph Autopol VI polarimeter.

General Procedure for the Asymmetric Hydrogenation of Quinoline Derivatives in 3-OEG

A 50 mL glass-lined stainless-steel reactor was charged with ruthenium catalyst (*R,R*)-**1a** (0.002 mmol), substrate **2** (0.2 mmol), 3-OEG (1 mL), and a magnetic stirrer bar under a N_2 atmosphere in a glove box. The autoclave was closed and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave several times with hydrogen gas. The reaction mixture was stirred at RT for 20–30 h and, after carefully releasing the hydrogen gas, the OEG phase was extracted with *n*-hexane (5×1 mL). The combined *n*-hexane solution was concentrated under vacuum to afford the crude product and the reaction conversion was determined by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel (petroleum ether/CH_2Cl_2, 1:1 v/v) gave the pure product. Enantiomeric excess was determined by HPLC on a chiral column (OD-H, OJ-H, AS-H, or AD-H). The absolute configuration of the product was assigned by comparison with literature data.[6b,11]

In the catalyst-recycling experiments, the recovered catalyst in 3-OEG was directly reused in the next catalytic hydrogenation reaction of the same substrate (**2a**) under identical reaction conditions.

Acknowledgements

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Keywords: asymmetric catalysis · hydrogenation · oligo(ethylene glycol)s · ruthenium · solvent effects

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FULL PAPER

Asymmetric Hydrogenation

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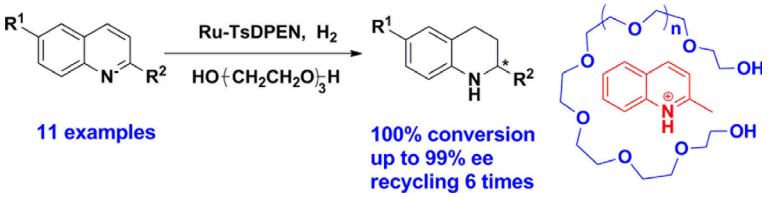
■■ – ■■

Solvent-Regulated Asymmetric Hydrogenation of Quinoline Derivatives in Oligo(Ethylene Glycol)s through Host–Guest Interactions



Taken down a PEG: The asymmetric hydrogenation of quinoline derivatives catalyzed by chiral cationic ruthenium diamine complexes in oligo(ethylene glycol)s is reported. A range of quinoline derivatives was effectively hydrogenated in triethylene glycol.