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An improved catalytic system for recycling OsO_4 and chiral ligands in the asymmetric dihydroxylation of olefins

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Abstract—A recyclable catalytic system for the asymmetric dihydroxylation of olefins was developed by using a mono-quaternized bis-cinchona alkaloid ligand **3** and OsO_4 combined with PEG or an ionic liquid. Both the catalytic components could be recovered and reused in five consecutive reactions without any additional OsO_4 or ligand. The catalytic system is effective in the AD reactions of seven olefins.

1. Introduction

The osmium-catalyzed asymmetric dihydroxylation (AD) of olefins using cinchona alkaloid derived ligands is recognized as a very efficient method for the preparation of a wide range of enantiomerically pure vicinal diols.[1] Although the AD reaction can be widely applied to the synthesis of chiral drugs, natural products, fine chemicals, etc., the high cost of osmium and chiral ligands as well as the high toxicity and volatility of the osmium component has restricted its use in industry. There has been a growing interest for exploring the repetitive use of both the catalytic components (OsO_4 and chiral ligand) over the past few years. Attachment of the ligand to a soluble or insoluble support covalently[2] or the immobilization of osmium tetroxide based on microencapsulation,[3] ion-exchange techniques,[4] and osmylation of resins[5] has made it possible to recover and reuse the ligand or osmium, but has failed to recycle the two catalytic components at the same time. Very recently, an ionic liquid[6] and poly(ethylene glycol) (PEG, MW 400)[7] have been employed as reaction media as well as immobilizing agents for the catalyst in AD reactions. When the reaction was finished, the product diol could be extracted with ether, while most of the alkaloid ligand and osmium tetroxide remained in the reaction media due to the low solubility of the ligand in ether and the special encapsulating effect of the ionic liquid and PEG on osmium tetroxide. Unfortunately, leaching of both catalytic components was inevitable during extraction of the product with ether, because the ligand can dissolve in ether to some extent and bring out some osmium by complexation. Sharpless et al. once reported that only one of the two quinuclidine nitrogen atoms of the bis-cinchona alkaloid ligand complexed with osmium tetroxide. Quaterization of another quinuclidine nitrogen atom did not affect the catalytic activity and enantioselectivity.[8] We assumed that mono-quaternization of the bis-*cinchona* alkaloid ligand might minimize the solubility of the ligand in ether due to its ionic character. Song et al. adopted 1,4-bis(9-*O*-quininyl) phthalazine[$(QN)_2$PHAL] **1** as chiral ligand instead of the well-known 1,4-bis(9-*O*-dihydroquininyl)phthalazine [$(DHQ)_2$PHAL] ligand in the AD reaction with an ionic liquid as the reaction medium.[6] They proved that **1** was converted to the bis-cinchona alkaloid **2** bearing four hydroxyl groups during the catalytic reaction. With highly polar residues, ligand **2** improved the recyclability of both catalytic components while affording the same yields and ees as $(DHQ)_2$PHAL. Moreover, **1** is more economically preparable. Taking this into consideration, we designed a mono-quaterized bis-cinchona alkaloid ligand **3**, which combines the ionic character and high polarity (Scheme 1). Here we report the synthesis of **3** and its successful use in the AD reaction with PEG or ionic liquid as the medium. This catalytic system provides a simple and efficient approach to the recycling of both OsO_4 and chiral ligand.

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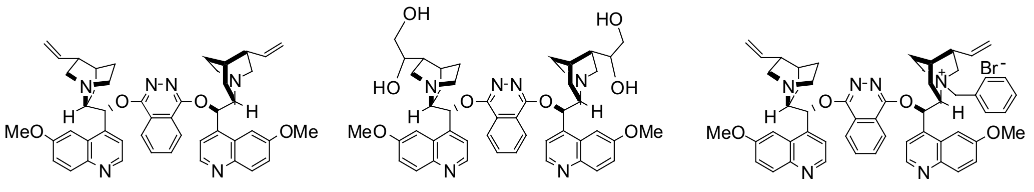

1 **2** **3**

Scheme 1.

2. Results and discussion

The synthesis of **1** was reported by Song et al. in 1996.[9] We prepared **1** in 85% yield with an improved procedure by using NaH as base instead of KOH. **1** was quaternized by refluxing with benzyl bromide in THF to give ligand **3** (Scheme 2).

Scheme 2. Synthesis of ligand **3**.

In our initial studies, we performed the AD reaction of *trans*-stilbene according to the literature by using OsO_4 (0.5 mol%) and chiral ligand **3** (2.0 mol%) in 1 mL PEG (MW 400), with NMO as co-oxidant, and *trans*-stilbene being added in one portion.[7] 94% ee and 91% isolated yield were obtained (entry 2, Table 1). When the system was applied to other olefins, the enantioselectivity decreased dramatically (entries 4, 7 and 9, Table 1). We found that *trans*-stilbene crystals dissolved slowly during the reaction, similar to the way when the substrate was added slowly. Results were different for liquid olefins, which dissolved completely as soon as being added into PEG. A high concentration of the substrate resulted in a decrease of the enantioselectivity. As a result we chose acetone–H_2O (v/v, 10:1) combined with PEG as the medium of the AD reaction, and added the olefins slowly by a syringe pump during a period of 10 h. Satisfactory results were obtained for most of the selected olefins (Table 1). We also found that low temperature (0 °C) increased enantioselectivity (Table 2).

Table 1. AD reaction of olefins using ligand **3** and OsO_4 in PEG[a]

Entry	Olefin	Yield (%)	Ee (%)[b]
1	*trans*-Stilbene	88	95
2[c]	*trans*-Stilbene	91	94
3	Ethyl *trans*-cinnamate	82	95
4[c]	Ethyl *trans*-cinnamate	70	77
5	Methyl *trans*-cinnamate	78	96
6	β-Methyl-*trans*-styrene	89	96
7[c]	β-Methyl-*trans*-styrene	87	73
8	α-Methystyrene	89	78
9[c]	α-Methystyrene	78	62
10	Styrene	88	80
11	Ally naphthyl ether	90	37

[a] Unless otherwise indicated, all reactions were carried out on a 1 mmol reaction scale of olefin using 0.5 mol% of OsO_4, 2.0 mol% of **3**, 1.3 mmol of NMO and 1 mL PEG in 10 mL acetone–H_2O (v/v, 10:1) at 0 °C (the AD reactions of *trans*-cinnamates were carried out at 25 °C). Olefins were added for 10 h.

[b] The diols ee was determined by chiral HPLC.

[c] Olefins were added in one portion at 25 °C.

Table 2. Influence of temperature on asymmetric dihydroxylation of olefins using ligand **3** and OsO_4 in PEG

Entry	Olefin	Temperature (°C)	Yield (%)	Ee (%)
1	β-Methyl-*trans*-styrene	0	79	96
2	β-Methyl-*trans*-styrene	25	80	85
3	Ally naphthyl ether	0	85	37
4	Ally naphthyl ether	25	88	28

The recyclability of osmium and chiral ligand **3** in the PEG system was next examined. We chose *trans*-stilbene as the substrate. After completion of the reaction, all the volatiles were removed under reduced pressure and the chiral diol extracted with *tert*-butyl methyl ether. No OsO_4 detected in the ether layer by iodometry[10] and the remaining PEG layer could be recycled five times without any further addition of OsO_4 and ligand (Table 3).

Table 3. AD reactions of *trans*-stilbene in PEG using OsO_4 and ligand **3** as a recoverable and reusable catalyst[a]

	Run				
	1	2	3	4	5
Yield (%)	88	85	84	80	78
Ee (%)	95	91	95	88	87

[a] Recycle experiments were carried out on a 2 mmol reaction scale of olefin using 0.5 mol% of OsO_4, 2.0 mol% of ligand **3**, 2.6 mmol of NMO and 2 mL of PEG (400 MW) in acetone–H_2O (v/v, 10:1, 20 mL) at 0 °C. Olefins were added by a syringe pump for 10 h.

Encouraged by these promising results, we examined further the catalytic efficiency of **3** and the recyclability in the ionic liquid 1-butyl-3-methylimidazolium hexafluoro-phosphate [bmim][PF_6]. Again *trans*-stilbene was chosen as the standard substrate. The AD reaction was carried out under the same conditions as in the PEG system (OsO_4, 0.5 mol%, ligand **3**, 2.0 mol%). The recovered ionic liquid phase containing osmium and **3** could only be recycled three times. When 1.5 mol% of OsO_4 was used, both the OsO_4 and **3** could be easily recovered and reused in five consecutive reactions without any additional OsO_4 or ligand (Table 4). However, quantitative analysis of OsO_4 by iodometry showed that a small amount of OsO_4 (<2% of the total amount) was transferred into the ether layer during the extraction of diol with *tert*-butyl methyl ether.

Table 4. Reusability of OsO_4 and ligand **3** in ionic liquid[a]

	Run				
	1	2	3	4	5
Yield (%)	86	88	91	82	80
Ee (%)	95	94	90	86	81

[a] Recycle experiments were carried out on a 2 mmol reaction scale of olefin using 1.5 mol% of OsO_4, 2.0 mol% of ligand **3**, 2.6 mmol of NMO and 2 mL of [bmim][PF_6] in acetone–H_2O (v/v, 10:1, 20 mL) at 0 °C. Olefins were added by a syringe pump for 10 h.

In order to widen the scope and application of the catalytic system, various substrates were subjected for AD reactions under these conditions (OsO_4, 1.5 mol%, ligand **3**, 2.0 mol%). The results are summarized in Table 5. In most cases, the desired diols were formed in high yields and ees. We also found that the enantioselectivity improved considerably when tetraethylammonium acetate (TEAA) was added in the AD reaction of 1,2-disubstituted olefins (entries 2, 4, and 7, Table 5). This proves that the hydrolysis of the osmate ester is accelerated with the use of TEAA to afford high ee. These are in agreement with the earlier observations.[4]

Table 5. AD reaction of olefins using ligand **3** and OsO_4 in ionic liquid[a]

Entry	Olefin	Yield (%)	Ee (%)
1	*trans*-Stilbene	86	95
2[b]	*trans*-Stilbene	88	>99
3	Ethyl *trans*-cinnamate	73	94
4[b]	Ethyl *trans*-cinnamate	74	91
5	Methyl *trans*-cinnamate	67	94
6	β-Methyl-*trans*-styrene	82	92
7[b]	β-Methyl-*trans*-styrene	80	95
8	α-Methystyrene	89	66
9	Styrene	85	81
10	Ally naphthyl ether	91	35

[a] Unless indicated otherwise, all reactions were carried out on 1 mmol reaction scale of olefin using 1.5 mol% of OsO_4, 2.0 mol% of **3**, 1.3 mmol of NMO and 1 mL [bmim][PF_6] in 10 mL acetone–H_2O (v/v, 10:1) at 0 °C (the AD reactions of *trans*-cinnamates were carried out at 25 °C). Olefins were added for 10 h.

[b] 1 mmol TEAA was added.

3. Conclusion

We have synthesized a mono-quaternized bis-*cinchona* alkaloid ligand **3** and applied it in the AD reaction of olefins with PEG or ionic liquid as medium. This catalytic system provides a simple and efficient approach to the recovery and reuse of both catalytic components (osmium and ligand). No additional osmium or ligand was necessary when recycling the catalyst even for the fifth run. The system is effective in the AD reactions of a range of olefins. Further study is currently in progress.

4. Experimental

4.1. General

^1H NMR spectra were recorded on a Bruker AV-400 spectrometer, with $CDCl_3$ as solvents. High performance liquid chromatography (HPLC) was performed by Agilent 1100 interfaced to a HP 71 series computer workstation with Daicel Chiralcel OJ-H, OD-H, OB-H chiral column. Optical rotations were obtained on a Perkin-Elmer 343 polarimeter.

4.2. Preparation of 1

A 50 mL three-necked round-bottom flask was charged with quinine (2.5 g, 7.7 mmol), 1,4-dichlorophthalazine (0.76 g, 3.85 mmol), NaH (0.9 g, 38.5 mmol) and dry DMF (20 mL) under nitrogen. The mixture was stirred at 70 °C until TLC indicated that quinine had disappeared. The resulting mixture was cooled to room temperature, filtered and concentrated in vacuo. The residue was recrystallized with ethyl acetate giving 2.5 g of white powder **1** (85% yield). ^1H NMR: $\delta = 8.65$ (d, $J = 5.2$ Hz, 2H), 8.31–8.33 (m, 2H), 7.94–8.00 (m, 4H), 7.58 (s, 2H), 7.43 (d, $J = 4$ Hz, 2H), 7.36–7.38 (m, 2H), 7.03 (s, 2H), 5.78–5.87 (m, 2H), 4.99 (m, 4H), 3.93 (s, 6H), 3.50 (d, $J = 6.4$ Hz, 2H), 3.02–3.14 (m, 4H), 2.60 (m, 4H), 2.27 (s, 2H), 1.50–1.89 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 157.7$, 156.4, 147.4, 144.8, 144.6, 141.9, 132.4, 131.6, 127.2, 122.8, 122.5, 121.9, 116.6, 114.4, 102.2, 60.2, 56.8, 55.7, 42.7, 39.9, 29.3, 27.9, 27.8. MS (FAB): 775.1 ($M+H^+$). $[\alpha]_D = +244.6$ (*c* 1, $CHCl_3$).

4.3. Preparation of 3

Benzyl bromide (0.34 g, 2 mmol) in dry THF (10 mL) was added dropwise into a solution of **1** (1.55 g, 2 mmol) in dry THF (10 mL) under reflux. The mixture was further refluxed for 3 h, and the solvent was removed in vacuo, with the resulting residue purified by flash column chromatography ($CHCl_3$/MeOH 10:1) to give 0.89 g of **3** as a light yellow solid (47% yield). ^1H NMR: $\delta = 7.24$–8.69 (m, 21H), 5.84 (m, 2H), 4.99–5.31 (m, 6H), 4.18 (s, 3H), 3.89 (s, 3H), 3.58 (m, 3H), 3.17 (m, 3H), 2.61 (s, 4H), 1.81–2.28 (m, 9H), 1.28 (s, 1H), 1.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 158.8$, 157.8, 157.5, 155.6, 147.3, 146.7, 144.6, 144.1, 141.6, 138.9, 135.9, 133.8, 133.7, 131.7, 131.6, 130.6, 129.2, 127.1, 126.5, 126.1, 123.4, 123.0, 122.7, 122.3, 122.0, 119.5, 118.5, 114.6, 102.0, 101.4, 69.3, 66.7, 63.4, 60.1, 59.7, 56.7, 56.5, 55.7, 51.7, 42.7, 39.6, 37.8, 21.9, 29.7, 27.8, 27.6, 27.25, 25.5, 23.9, 22.7, 22.4. HRMS (ESI): calcd for $[M-Br^{-1}]$: 865.4440, found 865.4435. $[\alpha]_D = +249.6$ (*c* 1, EtOH).

4.4. Typical procedure for asymmetric dihydroxylation reaction in PEG

A 25 mL flask was charged with acetone–H_2O (10:1, v/v, 8 mL), PEG (400 MW 1 mL), ligand **3** (19 mg, 0.020 mmol), OsO_4 (1.25 mg, 0.005 mmol). After stirring for 10 min, NMO (176 mg, 1.3 mmol) was added. The mixture was cooled to 0 °C and the olefin (1 mmol) dissolved in acetone–H_2O (10:1, v/v, 2 mL) was added by a syringe pump for 10 h. After completion of the reaction, all the volatiles were removed under reduced pressure and *tert*-butyl methyl ether added into the flask and the mixture was stirred for 5 min. The ether layer was separated and the procedure repeated (3 × 5 mL). The combined ether layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removing the solvent, the crude product was purified by flash column chromatography on silica to give the diol. The PEG layer containing OsO_4 and ligand **3** was reused for the next reaction.

4.5. Typical procedure for asymmetric dihydroxylation reaction in ionic liquid

A 25 mL flask was charged with acetone–H_2O (10:1, v/v, 8 mL), [bmim][PF_6] (1 mL), ligand **3** (19 mg, 0.020 mmol), OsO_4 (3.75 mg, 0.015 mmol). After stirring for 10 min, NMO (176 mg, 1.3 mmol) was added. The mixture was cooled to 0 °C and the olefin (1 mmol) dissolved in acetone–H_2O (10:1, v/v, 2 mL) was added by a syringe pump for 10 h. The procedure for the work-up is the same as that for PEG system.

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