A Practical and Simple Method of Recycling Catalyst in Asymmetric Aminohydroxylation of Olefins

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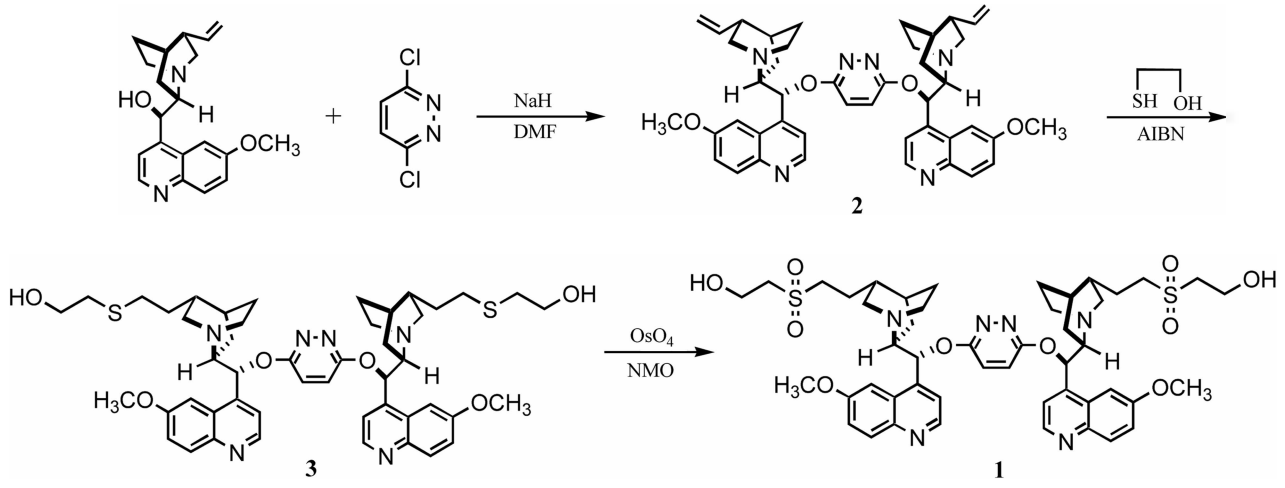
The Os-catalyzed asymmetric aminohydroxylation (AA) of olefins provides a straightforward method for the enantioselective synthesis of a wide variety of protected vicinal aminoalcohols.[1-4] The resulting chiral *β*-aminoalcohols group is the most abundant structural element in many biologically active molecules as well as the starting point in the design of many chiral ligands.[5-7] Although AA reaction servers as a powerful method for the synthesis of a variety of products, its application has still been limited because of the high cost of osmium and chiral ligand. In order to explore the possibility of the repetitive use of ligand and/or osmium, several attempts to immobilize this catalytic system have been made. Nandanan group[8] prepared highly crosslinked copolymers between ethylene glycol dimethacrylate (90 mol%) and a bis(quininyl)pyridazine derivative (10 mol%). This insoluble ligand was then used in AA reaction of various olefins in 52-65% yields and 34-54% *ees*. Up to now, many insoluble polymer-supported ligands have been successfully reused in AA reaction.[8-11] Yang first reported an immobilized soluble PEG-bound bis-cinchona alkaloid ligand which could be recovered and reused in homogeneous AA reactions. Excellent yields and *ees* were obtained in homogeneous system.[12] In most reported recycling methods, osmium component was hardly recovered and sometimes synthesis route of the polymer-supported ligands were complicated. Here we report a recyclable monomeric ligand **1** and its application in homogeneous AA reaction. In addition, poly(ethylene glycol) (PEG, MW 400) linked with the special encapsulating effect on osmium was successfully applied in AD reaction.[13] Enlightened by this, we applied PEG in AA reaction for the recovery of osmium and achieved an amazing result that about 50% amount of osmium component could be efficiently recycled through very simple method.

Results and Discussion

According to the similar synthesis method,[14] ligand **1** was prepared by simple three-step reaction (Scheme 1). 3,6-Dichoropyridazine reacted with quinine in presence of NaH in DMF to give compound **2** (80% yield), which was heated with 2-mercaptoethanol in the presence of 2,2'-azobis-isobutyronitrile (AIBN) in $CHCl_3$ to give the sulfide **3** (66% yield). Compound **3** was then oxidized to the desired sulfone **1** using a mixture of OsO_4/*N*-methylmorpholine *N*-oxide (NMO) in THF/*t*-BuOH (3:1) at room temperature (79% yield).

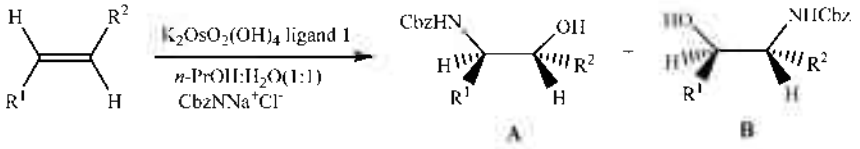
Ligand **1** was applied in the homogeneous AA reactions under conventional Sharpless conditions using benzyloxy-carbonyl carbamate as the oxidant-nitrogen source. The results were summarized in Table 1.

As can be seen from Table 1, all of the six selected olefins



Scheme 1. The synthesis route of ligand 1.

Table 1. The homogeneous asymmetric AA reaction using ligand 1[a]



Entry	Olefins	Product (A)	Regioselectivity (A:B)[b]	Yield (A+B) (%)[c]	%*ee* (A)[d]
1	Styrene	2*S*	> 20:1	50	76
2	2-Naphalene	2*S*	> 20:1	58	89
3	*β*-Methyl *trans*-styrene	2*R*,3*S*	> 20:1	55	62
4	Ethyl *trans*-cinnamate	2*R*,3*S*	3:1	61	> 99
5	*iso*-Propyl *trans*-cinnamate	2*R*,3*S*	2:1	70	98
6	Cyclohexene	2*S*	–	46	12

[a]All reactions were performed on a 1 mmol scale using 4 mol% $K_2OsO_2(OH)_4$ and 5 mol% of ligand **1**. The reactions were carried out at 20 °C except entry **2** (0 °C). [b]Determined by ^{1}H NMR spectroscopy. [c]Isolated yields by column chromatograph. [d]The ees were determined by chiral HPLC analysis. Entry 1: Daicel Chiralcel AD, hexane/*i*-PrOH = 17:3, flow rate 0.7 mL/min. t_R (min) = 16.7 (major), 26.3 (minor); Entry 2: Daicel Chiralcel OD, hexane/*i*-PrOH = 97:3, flow rate 0.8 mL/min. t_R (min) = 29.8 (minor), 31.3 (major); Entry 3: Daicel Chiralcel AD, hexane/*i*-PrOH = 7:3, flow rate 0.7 mL/min. t_R (min) 10.5 (major), 16.1 (minor); Entry 4: Daicel Chiralcel OD-H, hexane/*i*-PrOH 82:18, flow rate 0.4 mL/min. t_R (min) 27.7 (major); Entry 5: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 82:18, flow rate 0.4 mL/min. t_R (min) = 20.4 (minor), 22.7 (major), Entry 6: Daicel Chiralcel AD, hexane/*i*-PrOH = 95:5, flow rate 0.4 mL/min. t_R (min) = 21.7 (major), 27.5 (minor)

were transformed to *β*-aminoalcohols in moderate yields. ligand **1** delivered excellent enantioselectivity for the reaction of *trans*-cinnamate (Table 1, entries 4 and 5).

Just like the soluble polymer-supported ligands, the monomeric ligand **1** was completely insoluble in diethyl ether and could be recovered in 80% according to the reported recycling method.[12] But the osmium was lost. Therefore, we developed a new approach to immobilize osmium by utilizing the encapsulation ability of PEG. Then we investigated the effect of PEG and different amount of PEG on the reactivity and the osmium immobilization. Five AA reactions were performed on a 1 mmol scale with addition of PEG 0 mL, 1.0 mL, 1.5 mL, 2.0 mL and 2.5 mL respectively. When the reaction was finished, the product was extracted with diethyl ether. The ligand **1** still remained in the aqueous phase due to its insolubility in ether while part of osmium leached. We determined the osmium content in the aqueous phase by using inductively coupled plasma atomic emission spectrometry (ICP-AES). The results were shown in Table 2.

The results showed that PEG was essential for the recovery of osmium and 1.5 mL to 2.0 mL PEG was the proper amount to encapsulate osmium effectively. Moreover, addition of 1.0-2.0 mL PEG in reaction medium had no obvious effect on the reactivity and enatioselectivity. Accordingly, for recycle experiment, half initial amount of $K_2OsO_2(OH)_4$, the initial amount of benzyloxycarbonyl carbamate and *t*-BuOCl and proper amount of NaOH (pH = 11) were added to regenerate the reaction condition. *iso*-Propyl *trans*-cinnamate was chosen as the substrate to examine the efficiency, with which the ligand and osmium could be recycled. The reaction time of each run was similar (about 7-8 h). The results were shown in Table 3.

The results in Table 3 showed that no significant decrease in activity and enatioselectivity was observed within the first four recycles using the forementioned recycle method.

In summary, we have prepared recoverable ligand **1** by simple synthesis with cheap starting materials and applied this monomeric ligand in the homogeneous asymmetric aminohydroxylation. With addition of PEG in reaction medium, the monomeric ligand and half amount of osmium can be easily recycled for at least four times without significant decrease of its activity and enantioselectivity. In addition, the Cbz-protected group is easily cleaved by one-step catalytic hydrogenation reaction in presence of 10%Pd/C and H_2 to give the free aminoalcohols.[15] It may improve the possibility of utilizing AA reaction to prepare aminoalcohols in scale.

Table 2. The effects of the amounts of PEG on the reactivity and immobilization ability[a]

Amount of PEG (mL)	Yield (A+B)[b] (%)	%ee (A)[c]	Immobilized Os (%)[d]
0	70	96	9.5
1.0	67	95	43.2
1.5	68	95	49.7
2.0	65	94	50.3
2.5	61	93	50.1

[a]The reactions were carried out on a 1 mmol scale with addition of different amount of PEG. [b]Isolated yields by column chromatograph. [c]Determined by chiral HPLC analysis. [d]Determined by ICP-AES

Table 3. AA reaction of *iso*-Propyl *trans*-cinnamate reusing ligand **1** and OsO_4 in PEG[a]

Entry	1	2	3	4	5	6
Yield (A+B) (%)[b]	70	67	71	69	63	57
%ee (A)[c]	96	93	96	97	98	94

[a]Recycle experiments were carried out on a 1 mmol reaction scale of olefin using 10 mmol% of ligand 1 and 2 mmol% of $K_2OsO_2(OH)_4$ (4%mmol in the first run). [b]Isolated yields by column chromatograph. [c]Determined by chiral HPLC analysis.

Experimental Section

NMR spectra were recorded on a Bruker AV-400 spectrometer. High performance liquid chromatography (HPLC) was performed by Agilent 1100 interfaced to a HP 71 series computer workstation with Daicel Chiralcel OD-H, AD chiral column.

Preparation of compound 2. Under nitrogen, a 100 mL three-necked flask was charged with quinine (5.2 g, 16.0 mmol), 3,6-dichoropyridazine (1.20 g, 8.0 mmol), NaH (1.9 g, 80 mmol) and distilled DMF (30 mL). The mixture was stirred at 60 °C until TLC indicated that quinine had disappeared. The mixture was cooled to room temperature, filtered and concentrated. The residue was recrystallized with ethyl acetate to give white powder **2** 4.64 g (80% yield). m.p. 123-125 °C; IR (cm^{-1}): 3418.83, 3073.40, 2934.51, 2865.66, 1621.41, 1509.83, 1434.68, 1261.53, 1027.94, 991.66. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.81 (m, 10H), 2.21-2.26 (m, 2H, CH), 2.57-2.64 (m, 4H, NCH_2), 3.02-3.09 (m, 4H, NCH_2), 3.38-3.40 (m, 2H, NCH), 3.92 (s, 6H, CH_3O), 4.96-5.00 (m, 4H H_2C=C), 5.75-5.84 (m, 2H, HC=C), 6.79 (s, 2H), 7.00 (s, 2H, HCO),7.27 (d, J = 2.0 Hz, 2H, ArH), 7.37-7.39 (m, 4H, ArH), 7.45 (s, 2H, ArH), 8.00 (d, J = 9.2 Hz, 2H, ArH), 8.68 (d, J = 4.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.74, 157.80, 147.27, 144.56, 144.18, 141.56, 131.47, 127.14, 121.99, 121.43, 114.54, 101.75, 77.26, 59.74, 56.42, 55.77, 42.56, 39.60, 27.57, 23.59, 16.96.

Preparation of compound 3. A solution of compound **2** (3.63 g, 5.0 mmol), 2-mercaptoethanol (3.63 g, 5.0 mmol), 2,2'-azobisisobutyronitrile (3.5 mL, 50 mmol) in $CHCl_3$ (25 mL) was prepared and consequently refluxed for 12 h. Then the reaction liquid was washed with brine (20 mL × 2), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which was purified by column chromatography on silica with $CHCl_3$:CH_3OH:$(C_2H_5)_3N$ 5:1:1 to afford the pure sulfide **3** 2.9 g (66% yield). ^1H NMR (400 MHz, $CDCl_3$), δ: 8.67 (d, J = 4.8 Hz, 2H, ArH), 7.99 (d, J = 9.2 Hz, 2H, ArH), 7.49 (s, 2H, ArH), 7.37-7.38 (m, 4H, ArH), 7.00 (s, 2H, ArH), 6.77 (br, 2H, PhC*H), 3.89 (s, 6H, OCH_3), 3.68 (s, 4H), 3.36 (br, 2H), 2.69-2.46 (m, 10H), 2.45 (br, 2H), 2.30 (br, 2H), 1.75-1.43 (m, 22H); HRMS (ESI), m/z: 881.4077 ($M+H^+$).

Preparation of ligand 1. A 50 mL flask was charged with compound **3** (1.02 g, 1.14 mmol), 50 mg·mL^{-1} OsO_4 (0.56 mL, 0.11 mmol), NMO (0.86 g, 7.6 mmol) and THF/*t*-BuOH (3:1) 30 mL. The mixture was stirred at room temperature until TLC indicated that compound **2** disappeared. Na_2SO_3 (5.00 g) was then added and stirred for 1 h. The mixture was filtered, dried over anhydrous $MgSO_4$ and evaporated to give crude product which was further purified by column chromatography on silica ($CHCl_3$:CH_3OH:$(C_2H_5)_3N$ 5:1:1) to afford the pure ligand **1** 0.85 g (79% yield). ^1H NMR (400 MHz, $CDCl_3$), δ: 8.66 (d, J = 4.8 Hz, 2H, Ar-H), 8.00 (d, J = 9.2 Hz, 2H, ArH), 7.49 (t, 2H, ArH), 7.37-7.38 (m, 4H, ArH), 6.99 (s, 2H, ArH), 6.75 (br, 2H, PhC*H), 4.06 (br, 4H), 3.89 (s, 6H,OCH_3), 3.39 (br, 2H), 3.14-2.99 (m, 10H), 2.54 (br, 2H), 2.33 (br, 2H), 1.86-1.21 (m, 22H); ^{13}C NMR (100 MHz, CD_3OD): δ 171.49, 167.69, 163.92, 152.75, 148.57, 147.48, 144.58, 143.63, 138.82, 130.52, 129.23, 128.45, 126.24, 109.84, 77.33, 74.62, 56.36, 55.80, 55.10, 52.95, 34.49, 26.16, 25.48, 14.09; HRMS (ESI), m/z: 945.3897 ($M+H^+$).

Typical recycling procedure for the asymmetric aminohydroxylation with *iso*-Propyl *trans*-cinnamate as substrate. A solution of benzyloxycarbonyl carbamate (469 mg, 3.1 mmol) in *n*-PrOH (4 mL) was sequentially treated with NaOH (122 mg, 3.05 mmol in 7.5 mL water) and freshly prepared *t*-BuOCl (0.35 mL, 3.05 mmol). After stirring for 5 min at room temperature, a solution of ligand **1** (80 mg, 0.1 mmol in 3.5 mL of *n*-PrOH) and *iso*-Propyl *trans*-cinnamate (190 mg, 1.0 mmol) was added followed by $K_2OsO_2(OH)_4$ (14.7 mg, 0.04 mmol) and PEG-400 (1.5mL). The reaction mixture was stirred until starting material disappeared by TLC analysis. *n*-PrOH was then removed under reduced pressure and the water layer was extracted with Et_2O (20 mL × 2). Ether layer was dried over anhydrous $MgSO_4$ and evaporated to give the crude product, which was purified by silica gel chromatography (hexen/EtOAc, 4:1) to provide protected β-aminoalcohol. Then benzyloxycarbonyl carbamate (469 mg, 3.1 mmol) in *n*-PrOH (7 mL), the proper amount of NaOH (approximately 60 mg, pH = 11), *t*-butylhypochlorite (0.35 mL, 3.05 mmol) and $K_2OsO_2(OH)_4$ (7 mg, 0.02 mmol) were added to regenerate the reaction conditions. *iso*-Propyl *trans*-cinnamate (190 mg, 1.0 mmol) was then added. Similar work-up and purification was repeated for 5 times.

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