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Homogeneous catalytic asymmetric dihydroxylation of olefins induced by an efficient and recoverable polymer-bound ligand QN–AQN–OPEG-OMe

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A novel polymer-bound alkaloid ligand QN–AQN–OPEG-OMe, which was characterized by an anthraquinone core at the 9-*O* position of quinine, was synthesized conveniently. It delivered up to 99% ees in the homogeneous catalytic asymmetric dihydroxylation of seven olefins, comparable to that reported for the homogeneous catalyst with free ligand $(DHQ)_2$AQN. This ligand was recovered almost quantitatively by a simple filtration and reused for five cycles without obvious decreased enantioselectivities and catalytic activities. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: homogeneous catalysis; polymer-bound ligand; anthraquinone; asymmetric dihydroxylation

INTRODUCTION

Osmium-catalyzed asymmetric dihydroxylation (AD reaction) of olefins is one of the eminent contributions of Sharpless for the convenient preparation of chiral vicinal diols in a single pot from the available alkenes.[1–4] Up to now, it has been improved and optimized by using cinchona alkaloid derivatives as chiral ligands. Although this reaction has had widespread application in organic synthesis, there have been few large-scale industrial products because of the complicated synthetic manipulations required to produce the chiral ligands. Therefore, attachment of the cinchona alkaloid to insoluble or soluble polymers and catalyst recycling have been of great interest.[5,6]

Organic polymers or functionalized silica insoluble supports have been used in several heterogenized AD reactions.[7–9] These heterogenized catalytic systems are favored for recycling after the catalytic reaction without addition of another solvent, but the catalytic activity and enantioselectivity observed are less effective in the majority of cases. The reason for the decreased yields and ees was that the ligand remains in the insoluble phase, whereas the OsO_4 and olefins are in solution. To realize homogeneous catalysis, soluble polymers such as polyethylene glycol monomethyl ether (PEG-OMe) emerged as ideal supports for AD reactions.[10]

In some dimeric alkaloid-type ligands, dihydroquinidine (DHQD) or dihydroquinine (DHQ) derivatives were anchored on PEG or PEG-OMe to afford soluble polymer-bound ligands for various olefinic substrates for AD reactions, showing that enantioselectivities were achieved at a range from moderate to excellent.[11–13]

To our knowledge, only Bolm and Maischak[14] reported immobilization of dimeric alkaloid-type ligands with an anthraquinone (AQN) core to a soluble polymer and its application in the asymmetric dihydroxylation of two 'difficult' substrates, such as allyl iodide and indene, with only moderate enantioselectivities obtained. Bolm selected a remote position of the AQN core intentionally and the vinyl of the quinuclidine present in the quinidine as the binding polymer's sites. The results highlighted that there was no significant influence of the linking site or attachment type on the enantioselectivity of the AD reaction. This encouraged us to modify the structure of dimeric alkaloid ligands with AQN as a core in a simple way.

We report herein the synthesis of a simple and effective ligand QN–AQN–OPEG-OMe (**1**) and investigate its behavior in homogeneous catalytic AD reactions with various olefins, as well as its recycling.

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EXPERIMENTAL

Materials

Toluene, diethyl ether and tetrahydrofuran (THF) were purchased from Tianjin Chemical Reagent Co. Inc. and freshly distilled from sodium–benzophenone. Dichloromethane was purchased from Tianjin Chemical Reagent Co. Inc. and refluxed over calcium hydride and distilled before use. PEG-OMe (FW = 5000) was purchased from Fluka and dried over P_2O_5 under vacuum before use. The silica gel, which was used for chromatography, was purchased from Qingdao Haiyang Chemical Co., Ltd. All other chemicals were purchased from Tianjin Chemical Reagent Co. Inc. and used as received.

NMR analyses

^{1}H NMR was performed in $CDCl_3$ and recorded on a Varian INOVA 400 MHz spectrometer, and ^{1}H NMR spectra were collected at 400.0 MHz using a 10 000 Hz spectral width, a relaxation delay of 1.0 s, a pulse width of 45°, and tetramethylsilane (0.0 ppm) as the internal reference.

Analytical thin-layer chromatography

All thin-layer chromatography (TLC) analyses were performed with precoated glass-backed plates (silica gel 60-GF_{254}).

Flash column chromatography

Flash column chromatography was performed on silica gel 60 (230–400 mesh).

Chiral chromatography analyses

Chiral high-performance liquid chromatography analyses were performed on a Waters–Breeze system equipped with 1525 HPLC pump, 2487 UV detector, a corresponding Chiral column (25×0.46 cm^2) and hexane/^{i}PrOH (v/v) as solvent.

Melting points

Melting points were taken using an XR-1 melting-point apparatus, and thermometer readings were uncorrected.

Optical rotations analyses

All optical rotations ($[\alpha]_D^{25}$) analyses were performed on a Perkin–Elmer 343 polarimeter. Optical rotations are measured at the wavelength of the sodium D-line (589.3 nm) at a temperature of 25 °C, with reference to a layer 1 dm thick of a solution containing 1 g of the substance per milliliter.

Synthesis of ligand 1

*Intermediate (F-AQN–OPEG-OMe) (**2**)*

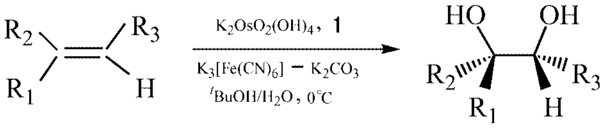
A flame-dried 150 ml one-necked round-bottom flask was charged with 10 g (2.0 mmol) of OPEG-OMe (FW = 5000), 1.35 g (6.0 mmol) of 1,4-difluoroanthraquinone, 400 mg (2.90 mmol) of K_2CO_3, and 80 ml of anhydrous toluene. The flask was flushed with nitrogen and then equipped with a Dean–Stark condenser. Under nitrogen atmosphere, the mixture was refluxed for 5 h. Then 200 mg (2.92 mmol) of KOH pellets (82%) were added and the mixture refluxed (with azeotropic removal of water) for an additional 28 h. The solution was cooled to room temperature, diluted with 80 ml of CH_2Cl_2, and allowed to stand for 2 h. After filtration, the solvent was removed *in vacuo*. The residue was taken up in 60 ml of CH_2Cl_2; after that, 400 ml of dry diethyl ether was slowly added to the solution with vigorous stirring, and a precipitate formed as a yellow solid. This material was washed with absolute ethanol–diethyl ether (v/v = 3/1) and diethyl ether, then dried over P_2O_5 *in vacuo* (9.16 g, 88%). ^{1}H NMR: δ 3.3–3.8 (PEG peaks), 3.98 (s, 2H, –AQN–O–CH_2–), 6.8–8.1 (m, 6H, Ar-H).

*Ligand (QN–AQN–OPEG-OMe) (**1**)*

A flame-dried 150 ml three-necked round-bottom flask was charged with 2.60 g (0.50 mmol) of F-AQN–OPEG-OMe (**2**) and 50 ml of anhydrous toluene, and equipped with a condenser. The system was under an atmosphere of dry nitrogen and warmed to dissolve **2**, and then cooled to room temperature. 0.49 g (1.5 mmol) of quinine in 10 ml of dry THF was cooled to −50 °C and 0.62 ml of 2.89 mol l^{-1} ^{n}BuLi in hexane was added slowly over 10 min. The solution turned slightly red at the end of the addition. It was stirred for 15 min, warmed to room temperature, and then the solution was added slowly to the above solution. The reaction mixture was refluxed for 26 h (oil temperature 135 °C). All the volatiles were removed *in vacuo*, and the resulting residue was taken up in 35 ml of CH_2Cl_2. 150 ml of dry diethyl ether was slowly added to the solution with vigorous stirring, and a precipitate formed as a purplish red solid. The reaction mixture was filtered, and the solid was washed with absolute ethanol–diethyl ether (v/v = 3/1) and diethyl ether, then dried over P_2O_5 *in vacuo* (2.63 g, 95.6%). ^{1}H NMR: δ 3.38 (s, 3H, –OCH_3), 3.4–3.7 (PEG peaks), 3.8 (s, 2H, –AQN–O–CH_2–), 5.33 (m, 2H, HC=C), 4.27 (m, 4H, H_2C=C), 6.9–8.1 (m, 6H, Ar-H).

Asymmetric dihydroxylation of olefins catalyzed by 1–OsO_4 complex

1 (0.55 g, 0.1 mmol), $K_3[Fe(CN)_6]$ (0.99 g, 3.0 mmol), K_2CO_3 (0.42 g, 3.0 mmol) and $K_2OsO_2(OH)_4$ (0.0015 g, 0.004 mmol) were dissolved in ^{t}BuOH–H_2O (1 : 1, v/v, 10 ml) at room temperature. For *trans*-disubstituted olefins, $CH_3SO_2NH_2$ (95 mg, 1 mmol) was added. The solution was cooled to 0 °C (with the exception of *trans*-stilbene; see Table 1) and the olefin (1 mmol) added in two portions. The mixture was stirred for 17–24 h. After TLC analysis confirmed the absence of starting material, Na_2SO_3 (0.8 g) was added and the mixture was stirred at room temperature for 30 min. CH_2Cl_2 was used, and the combined organic layers were washed with 2 mol l^{-1} aqueous KOH. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to about 10 ml; diethyl ether (50 ml) was slowly added to the mixture under vigorous stirring conditions. The precipitate obtained was collected on a glass filter, washed with cold absolute ethanol–diethyl ether and then diethyl ether, and dried *in vacuo* for recycling (more



Olefins	1	2	3	4	5	6	7
R_1	4-Chlorophenyl	Ph	Ph	2-Naphthyl	^{n}Bu	Ph	Ph
R_2	H	H	H	H	H	Me	H
R_3	H	H	Me	H	^{n}Bu	H	Ph

Scheme 1. Asymmetric dihydroxylation of olefins.

than 95% recovery of ligand resulted from this procedure). The filtrate was evaporated to give the crude product, which was purified by flash chromatography on silica gel to afford the corresponding diols (Scheme 1).

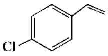
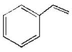
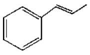
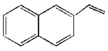
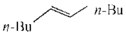
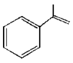
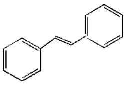
(S)-(+)-1-(4-Chlorophenyl)ethane-1,2-diol

Table 1, entry 1; 99% ee (*S*), $[\alpha]_D^{25} = +68^\circ$ (*c* 1.0, EtOH). ^{1}H NMR: δ 7.36–7.27 (4H, m), 4.83–4.80 (1H, dd, $J_1 = 3.2$ Hz, $J_2 = 3.6$ Hz), 3.78–3.74 (1H, dd, $J_1 = 3.2$ Hz, $J_2 = 3.2$ Hz), 3.65–3.60 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz), 2.66–1.63 (2H, br, s). HPLC Daicel Chiralpak AD, hexane/^{i}PrOH = 9 : 1, flow rate 0.7 ml min^{-1}. t_R(min) = 8.45 (major), 13.4 (minor).

(S)-(+)-1-Phenyl-1,2-ethanediol

Table 1, entry 2; 91% ee (*S*), $[\alpha]_D^{25} = +60.1^\circ$ (*c* 1.0, $CHCl_3$) [Ref. 15 $[\alpha]_D^{25} = +66.0^\circ$ (*c* 1.0, $CHCl_3$)]. ^{1}H NMR: δ 7.32–7.27 (5H, m), 4.85–4.83 (1H, m), 3.80–3.66 (2H, m), 2.24 (2H, s). HPLC Chiralcel OB-H, hexane/^{i}PrOH = 10 : 1, flow rate 0.5 ml min^{-1}. t_R(min) = 14.4 (minor), 15.6 (major).

Table 1. Catalytic activity and enantioselectivity of ligand in the asymmetric dihydroxylation of various olefins

Entry	Olefin	*T* (°C)	*t* (h)	Yield (%)[a]	ee (%)[b]
1		0	24	94	99
2		0	19	89	91 (89)[c]
3		0	24	90	93 (92)[c]
4		0	24	91	98
5		0	24	92	95 (98)[c]
6		0	17	92	80 (82)[c]
7		RT	24	80	92 (98)[d]

[a] Isolated yields.

[b] The ee values were determined by HPLC analysis of the diols.

[c] Results for a free ligand $(QN)_2AQN$ from Ref. 16.

[d] Result for a soluble polymer-bound ligand DHQD–PHAL–OPEG-OMe from Ref. 19.

(1S,2S)-(+)-1-Phenyl-1,2-propanediol

Table 1, entry 3; 93% ee (1*S*,2*S*), $[\alpha]_D^{25} = +1.72^\circ$ (*c* 1.05, EtOH) [Ref. 16 $[\alpha]_D^{25} = +1.72^\circ$ (*c* 1.05, EtOH)]. ^{1}H NMR: δ 7.39–7.32 (5H, m), 4.40–4.39 (1H, d, $J = 7.2$ Hz), 3.90–3.85 (1H, dd, $J_1 = 7.2$ Hz, $J_2 = 6$ Hz), 2.20 (2H, br), 1.09 (3H, d, $J = 4$ Hz). HPLC Daicel Chiralcel AD, hexane/^{i}PrOH = 10 : 1, flow rate 1.0 ml min^{-1}. t_R(min) = 19.0 (major), 25.2 (minor).

(S)-(+)-1-(2-Naphthyl)-1,2-ethanediol

Table 1, entry 4; 98% ee (*S*), $[\alpha]_D^{25} = +33.3^\circ$ (*c* 1.0, EtOH) [Ref. 17 $[\alpha]_D^{25} = +34.0^\circ$ (*c* 1.0, EtOH)]. ^{1}H NMR : d7.86–7.84 (4H, m), 7.51–7.46 (2H, m), 5.03–5.00 (^{1}H, m), 3.88–3.85 (^{1}H, m), 3.79–3.74 (^{1}H, m), 1.97 (2H, br); HPLC Daicel Chiralpak AD, hexane/^{i}PrOH = 7 : 3, flow rate 0.7 ml min^{-1}. t_R(min) = 7.2 (major), 8.9 (minor).

(5S,6S)-(−)-5, 6-Decanediol

Table 1, entry 5; 95% ee (5*S*,6*S*), $[\alpha]_D^{25} = -37.4^\circ$ (*c* 0.96, EtOH) [Ref. 16 $[\alpha]_D^{25} = +38.6^\circ$ (*c* 0.96, EtOH)]. ^{1}H NMR: δ 3.41 (2H, s), 2.03–1.98 (2H, br), 1.47–1.33 (12H, m), 0.94–0.90 (6H, t, $J = 6.8$ Hz). HPLC (bisbenzoate) Daicel Chiralcel OD-H, hexane/^{i}PrOH = 500 : 1, flow rate 1.0 ml min^{-1}. t_R(min) = 6.6 (minor), 8.3 (major).

(S)-(+)-2-Phenyl-1,2-propanediol

Table 1, entry 6; 80% ee (*S*), $[\alpha]_D^{25} = +4.29^\circ$ (*c* 0.96, EtOH) [Ref. 16 $[\alpha]_D^{25} = -4.4^\circ$ (*c* 0.96, EtOH)]. ^{1}H NMR: δ 7.47–7.29 (5H, m), 3.82–3.77 (1H, dd, $J_1 = 9.2$ Hz, $J_2 = 8.4$ Hz), 3.65–3.61 (1H, m), 2.24–2.05 (2H, br), 1.54 (3H, s). HPLC Daicel Chiralcel OD-H, hexane/^{i}PrOH = 100 : 2.5, flow rate 1.0 ml min^{-1}. t_R(min) = 18.4 (minor), 19.8 (major).

(1S,2S)-(−)-1,2-Diphenyl-1,2-ethanediol

Table 1, entry 7; 92% ee (1*S*,2*S*), $[\alpha]_D^{25} = -87.4^\circ$ (*c* 2.5, EtOH) [Ref. 18 $[\alpha]_D^{25} = -95.0^\circ$ (*c* 2.5, EtOH)]. ^{1}H NMR: δ 7.24–7.13 (10H, m), 4.72 (2H, s), 2.81 (2H, s). HPLC Chiralcel OJ, hexane/^{i}PrOH = 4 : 1, flow rate 0.6 ml min^{-1}. t_R(min) = 12.1 (minor), 13.4 (major).

RESULTS AND DISCUSSION

Scheme 2 shows the simple two-step synthesis of **1** in 85% overall yield. In the first step, 1,4-difluoroanthraquinone was nucleophilically mono-substituted by HO-OPEG-OMe (FW = 5000) in the presence of KOH and K_2CO_3 in dry toluene, with concurrent azeotropic removal of water, to give intermediate F-AQN–OPEG-OMe (**2**) in 88% yield. Then, **1** was obtained in 96% yield by reaction of **2** with QN (1/3, mol/mol) utilizing butyllithium as base.

The ligand structure–enantioselectivity relationship (LSER) studies showed that in Sharpless second-generation ligands' molecules, one alkaloid moiety was responsible for the catalytic process and the other provided the binding pocket for the substrate.[1] Recently, we designed a simple and effective soluble polymer-bound ligand for the asymmetric dihydroxylation of olefins.[19] Also recently, Lin and co-workers[20] reported a new PEG-bound cinchona alkaloid ligand for the catalytic asymmetric aminohydroxylation of alkenes. Studying the LSER of the two ligands clearly showed that the second alkaloid moiety of dimeric alkaloid-type ligands was not always indispensable in some catalytic process.

In ligand **1**, the 9-*O* position of QN was linked to a tricyclic planar anthraquinone group to form an ether (Scheme 2), which should be helpful to increase the enantioselectivity in AD reactions of olefins.[21] In addition, naturally occurring QN is much more attractive in cost, and in this paper 1,4-difluoroanthraquinone was used as coupling reagent to connect QN and PEG-OMe (FW = 5000) to afford the mono-alkaloid ligand **1**.

During the AD reaction, the quinuclidine nitrogen atom of QN is expected to complex with OsO_4 *in situ* to form the catalyst. In the ^{t}BuOH/H_2O (1/1, v/v) system, the catalyst is completely soluble, which accelerates homogeneous catalysis. The reaction results are summarized in Table 1, and the catalytic activity and enantioselectivity of **1** is as follows: (*E*)-5-decene, *β*-vinylnaphthalene, styrene, (*E*)-*β*-methyl-styrene and (*E*)-stilbene convert to the corresponding chiral diols in good yields and excellent enantiomeric excesses when catalyzed by **1**–OsO4. In particular, **1** gives excellent yields and ees in the AD reaction of *p*-chlorostyrene. When the reaction is finished, **1** can be extracted with CH_2Cl_2 and precipitated by addition of diethyl ether. More than 95% of the ligand can be recovered by simple filtration. The efficiency of the recovered catalyst was validated by the standard AD experimental procedure in which *p*-chlorostyrene was chosen as model substrate. These results are summarized in Table 2. The recovered catalyst could be recycled five times without any significant loss of its activity.

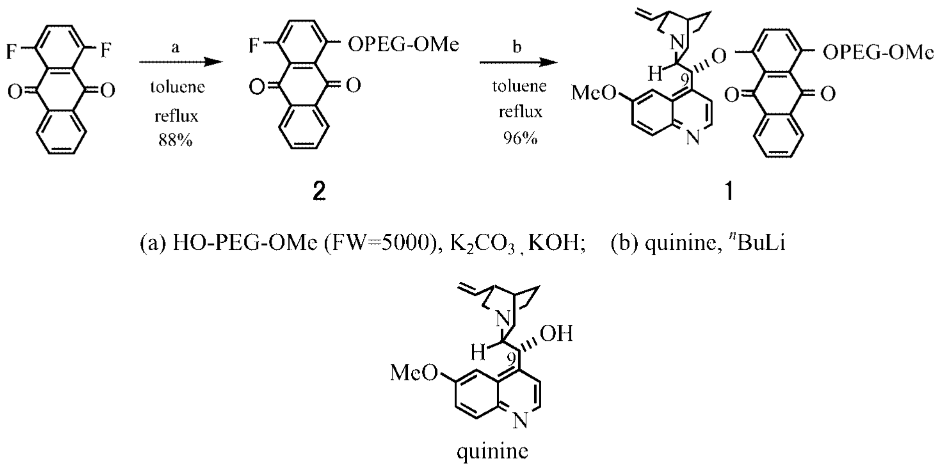
CONCLUSIONS

We have demonstrated a novel soluble polymer-anchored mono-cinchona alkaloids ligand with anthraquinone as coupling moiety. The catalytic activity and enantioselectivity of **1** are comparable to those of the free ligand $(DHQ)_2AQN$[16]

Table 2. Reuse of ligand **1**[a,b]

Run	Yield (%)	Ligand recovery (%)	ee (%)
1	94	97	99
2	93	96	98
3	94	96	96
4	91	96	97
5	93	95	98

[a] *p*-Chlorostyrene as the substrate in AD reaction.
[b] Adding 40% initial amount of $K_2OsO_2(OH)_4$ before restarting the reaction.



Scheme 2. Synthesis of ligand **1**.

in the AD reactions. After recycling five times, there is no obvious decrease in observed on catalytic activity or enantioselectivity.

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