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Catalytic Asymmetric Dihydroxylation of Olefins Using a Recoverable and Reusable Ligand

Qiao Feng Wang, Xiao Li Sun,* Sheng Yong Zhang, Xiang Yang Qin, and Yan Zhao

Department of Chemistry, Fourth Military Medical University, Xi'an, Shanxi, 710032, China
17 Changlexi Street, Xi'an 710032, Shannxi, P.R.C

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A free bis-cinchona alkaloid derivative ligand was prepared by a simple synthetic manipulation. With ligand/olefin mole ratio of 1%, the asymmetric dihydroxylation reactions of six olefins proceeded smoothly to give the chiral vicinal diols in high chemical yields and optical yields. The ligand itself could be recovered quantitatively by a simple operation and reused five times without loss of enantioselectivity.

INTRODUCTION

The osmium-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most elegant methods for the preparation of chiral vicinal diols, the key intermediates in pharmaceutical and chemical synthesis.[1] However, the high cost of osmium and ligands has restricted its use in industry. Many efforts were made to address this issue in the past decade. The ligand immobilized on an insoluble polymer was synthesized in order to recover the expensive ligand and a small amount of OsO_4. But, low catalytic activity and enantioselectivity were reported. This is because the restrictions of the polymer matrix resulted in limited mobility and accessibility to the active sites and thus obstructed the ligand-accelerated catalysis in the AD reaction.[2–4] To take advantage of homogeneous catalysis with respect to the easy separation of a ligand bound to the solid phase, cinchona alkaloid-type ligands were attached to a soluble polymer, polyethylene glycol monomethyl ether.[5–9] However, complicated synthetic manipulations were required for the preparation of PEG-bound ligand. Moreover, for all of the reported PEG-bound cinchona alkaloid-derived ligands, the required mole ratio of ligand with respect to olefin in the AD reactions was as high as 10–25 %, much higher than the corresponding ratio for the extensively used free ligands 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine [$(DHQD)_2$PHAL] and 1,4-bis(9-*O*-dihydroquininyl)phthalazine [$(DHQ)_2$PHAL].[10] In 2002, a recoverable and reusable free ligand was reported originally by our group.[11] This free ligand showed high catalytic activity and enantioselectivity with a low ligand/olefin mole ratio (5 %).

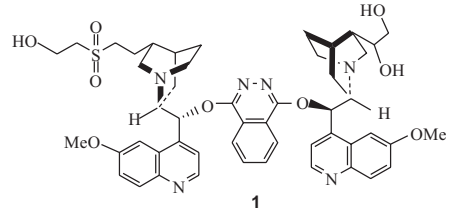

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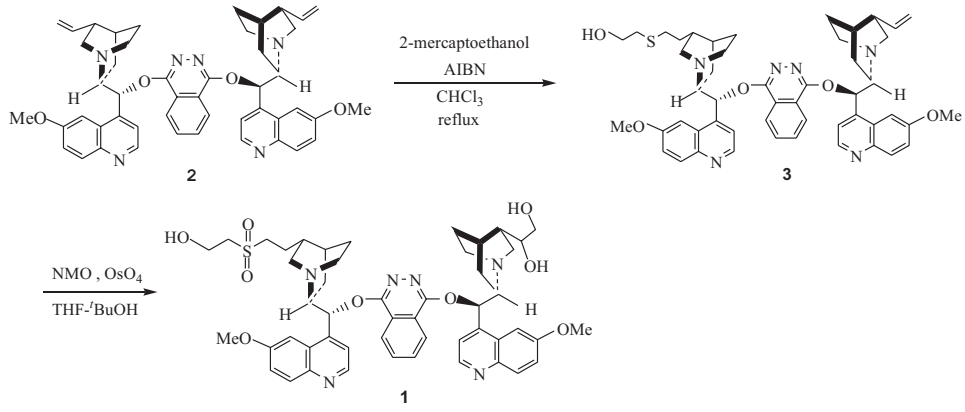
Figure 1. The structure of ligand **1**.

* Author to whom correspondence should be addressed. (E-mail: sxwqf@yahoo.com.cn)



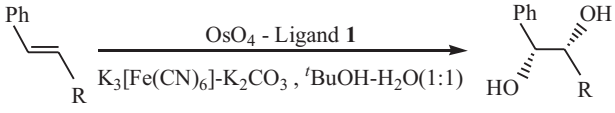
Scheme 1. Synthesis of ligand **1**.

Herein, we introduce another free ligand for the AD reaction (Figure 1). This ligand can be also circularly used but is more efficient. With this ligand, the AD reaction of six olefins gave high chemical yields and optical yields. Furthermore, the ligand was recovered and reused in the AD reaction of ethyl *trans*-cinnamate for 5 runs without any loss of catalytic activity and enantioselectivity.

RESULTS AND DISCUSSION

Ligand **1** was easily prepared from the starting material 1,4-bis(9-*O*-quininyl)phthalazine **2** [$(QN)_2PHAL$] (Scheme 1). Through a radical mechanism, $(QN)_2PHAL$ reacted with 2-mercaptoethanol in the presence of 2,2'-azobisisobutyronitrile (AIBN) to give sulfide **3**. After that, with a mixture of OsO_4–*N*-methylmorpholine (NMO), sulfide and the C=C double bond were oxidized simultaneously to produce ligand **1**.

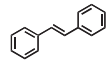
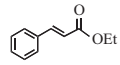
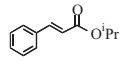
When ligand **1** was used to catalyze the AD reaction of olefins (Scheme 2), it was completely soluble in the



Scheme 2. AD reaction of olefins catalyzed by ligand **1**.

reaction solvent in favor of homogeneous catalysis. Six olefins were converted into the corresponding diols in excellent yields and ees during 24 hours at room temperature. Especially, the AD reactions of ethyl *trans*-cinnamate and isopropyl *trans*-cinnamate were totally completed within 6–10 h by TLC examination. Both reactions consumed less time compared to other olefins. Evidently, ligand **1** has a special catalytic ability for dihydroxylation of *trans*-cinnamate. It may be because the AD reactions can be effected by the asymmetry of ligand **1**. The reaction results for the selected olefins are presented in Table I.

TABLE I. Results of AD reaction of olefins using ligand **1**[a]

Entry	Olefin	Time / h	Yield / %	Ee / % [b]
1		21	95	>99
2		18	85	93
3		21	85	91
4		20	92	98
5		6	95	>99
6		10	95	>99

[a] All reactions were performed at 25 °C in *t*-BuOH–H_2O (volume ratio, ψ = 1:1), $K_3Fe(CN)_6$ as a co-oxidant. The mole ratio, *r* (olefin, ligand, OsO_4) = 1 : 0.01 : 0.002.

[b] The ee values were determined by HPLC analysis of the diols (see Ref. 13).

To evaluate the recyclability of ligand **1** in the AD reaction, ethyl *trans*-cinnamate was employed as the substrate. After the reaction, ligand **1** was extracted with CH_2Cl_2 and precipitated by addition of diethyl ether. 92–96 % of the ligand was recovered by simple filtration. Pure diol can be obtained by washing the crude product with n-hexane. The results are presented in Table II.

TABLE II. Recovery and reuse of ligand **1** in the AD reaction of ethyl *trans*-cinnamate [a]

Run	Yield / %	Ee / %
1	95	99
2	94	99
3	95	98
4	93	98
5	94	98

[a] All reactions were performed at 25 °C in *t*-BuOH–H_2O (volume ratio, ψ = 1:1), $K_3Fe(CN)_6$ as a co oxidant. The mole ratio, *r* (olefin, ligand, OsO_4) = 1 : 0.05 : 0.005.

Despite the high recoverability, leaching of OsO_4 was recorded during the period of washing the recovered ligand with diethyl ether. By replenishment of 30 % of OsO_4, the recovered ligand **1** was recycled five times without significant loss of its catalytic activity and enantioselectivity.

CONCLUSIONS

In conclusion, we have demonstrated that ligand **1** was not only obtained easily but also showed powerful catalytic ability. This recoverable and reusable bis-cinchona alkaloid derivative effectively catalyzed the AD reactions of six olefins to give the corresponding chiral diols in excellent yields and ees. Without significant loss of enantioselectivity, repetitive use of the ligand was also possible by addition of a small amount of OsO_4 after each run.

EXPERIMENTAL

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with $CDCl_3$ as solvents. MS was performed on a Bruker APEX2. High performance liquid chromatography (HPLC) was performed by Agilent 1100 interfaced to a HP 71 series computer workstation with Daicel Chiralcel OD-H, OJ-H and OB-H chiral columns. Optical rotations were obtained on a Perkin-Elmer 343 polarimeter. $(QN)_2PHAL$ (**2**) was prepared according to published methods.[12] All other solvents and chemicals were obtained from commercial sources and were used without further purification unless otherwise stated.

*Procedure for the Preparation of Intermediate **3***

A 100 mL three-necked round-bottom flask was charged with **2** (3.1 g, 4.0 mmol), AIBN (0.26 g, 1.6 mmol), 2-mercaptoethanol (0.3 mL, 4.2 mmol) and $CHCl_3$ (20 mL) under nitrogen. The mixture was refluxed for 36 h, and then cooled to room temperature. H_2O (20 mL) was added and the mixture was extracted with $CHCl_3$ (30 mL × 3). The combined organic layers were subsequently dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (eluent MeOH–$CHCl_3$ 1:6) to give a white solid (**3**) in 50 % yield. m.p. 126.5–8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.64 (2H, s), 8.32(2H, s), 8.00 (4H, s), 7.59 (2H, s), 7.41 (4H, s), 7.04 (4H, s), 5.80 (2H, s), 5.02(2H, d, J = 15.6 Hz), 3.92 (8H, s), 3.69 (4H, s), 3.49 (4H, s), 3.10 (4H, m,), 2.88–1.60 (14H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.76, 156.37, 147.33, 144.66, 141.84, 132.39, 131.53, 127.20, 122.80, 122.46, 121.96, 118.44, 114.42, 101.94, 60.22, 60.12, 59.98, 58.01, 56.72, 55.77, 42.67, 41.19, 39.81, 35.32, 34.77, 29.67, 28.31, 27.85, 27.72, 25.62, 23.73, 23.45. HRMS (ESI): calcd. for $C_{50}H_{56}N_6O_5S_1$+H: 853.4106; found, 853.4116.

*Procedure for the Preparation of Ligand (**1**)*

Intermediate **3** (1.7 g, 20 mmol), NMO (0.7 g, 6 mmol), THF (20 mL), *t*-BuOH (8 mL) and a solution of OsO_4 in toluene (0.24 mL, 0.094 mmol) were added to a flask. The reaction mixture was stirred for 12 h at room temperature. $NaSO_3$ (6 g) was added and stirred for another 2 h. The mixture was subsequently filtered. The filtrate was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was then purified by flash column chromatography (eluent MeOH–CH_2Cl_2 1:5) to afford a white solid (**1**) in 70 % yield. m.p. 164.5–6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.62 (2H, s), 8.32 (2H, s), 7.97 (4H, d), 7.57 (2H, d), 7.41–7.36 (4H, m), 6.99 (2H, d), 4.09 (4H, d, J = 5.6 Hz), 3.90 (6H, s), 3.64 (2H, m), 3.15 (4H, m), 3.03 (4H, m), 2.80 (1H, s), 2.52 (4H, m), 2.32 (2H, d, J = 12.8 Hz), 2.17 (1H, s), 1.84–1.25 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 158.03, 157.79, 156.58, 155.59, 146.89, 146.69, 144.33, 144.08, 132.61, 132.29, 131.25, 131.06, 127.16, 126.06, 124.54, 121.95, 121.26, 117.44, 101.68, 101.42, 62.56, 58.75, 56.36, 55.58, 55.32, 55.12, 52.31, 52.04, 45.44, 42.53, 41.25, 40.19, 39.91, 39.64, 39.36, 39.08, 32.53, 29.21, 25.46, 24.84. HRMS (ESI): calcd. for $C_{50}H_{60}N_6O_9S_1$+H: 919.4059; found, 919.4048.

Typical Procedure for Asymmetric Dihydroxylation

$K_3Fe(CN)_6$ (1.96 g, 6.0 mmol), K_2CO_3 (0.82 g, 6.0 mmol) were dissolved in *t*-BuOH–H_2O (20 mL, ψ = 1:1) at room temperature, followed by addition of OsO_4 in toluene (26 μL, 0.01 mmol) and ligand **1** (0.92 g, 0.10 mmol). Then, olefin (2.0 mmol) was added into the mixture. For *trans*-1,2-disubstituted olefins, $CH_3SO_2NH_2$ (0.19 g, 2.0 mmol) was needed. The mixture was then stirred vigorously at 25 °C for 24 h. When the reaction was over (monitored by TLC), Na_2SO_3 (2.5 g) was added into the solution and stirred for 45 min. CH_2Cl_2 (20 mL) was subsequently added to the reaction mixture, followed by separation of the organic layer. The aqueous phase was further extracted with CH_2Cl_2 (10 mL × 3) (When $CH_3SO_2NH_2$ was used, the combined organic layers had to be washed with NaOH (2 mol /L). The combined organic layers were then dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and dry Et_2O (30 mL) was slowly added to the solution under vigorous stirring. The obtained precipitate was collected by filtration, washed with cool Et_2O and dried under vacuum. The filtrate was evaporated to give the crude product, which was washed by n-hexane to afford pure diol.

With ethyl *trans*-cinnamate as substrate, similar work-up was repeated four times using the recovered ligand. Each time, 30 % of the initial amount of OsO_4 was added to regenerate the reaction.

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SAŽETAK

Katalitička asimetrična dihidroksilacija olefina uz uporabu liganda koji se može rekuperirati i ponovo upotrijebiti

Qiao Feng Wang, Xiao Li Sun, Sheng Yong Zhang, Xiang Yang Qin i Yan Zhao

Slobodni ligand bis-*cinchona* alkaloidnog derivata priređen je jednostavnim sintetskim putem. Reakcije asimetrične dihidroksilacije (AD), šest olefina, uz molni omjer ligand/olefin od 1%, daju kiralne vicinalne diole u visokim kemijskim i optičkim iskorištenjima. Jednostavnim postupkom ligand se može kvantitativno rekuperirati i ponovo upotrijebiti pet puta bez gubitka enantioselektivnosti.