Pergamon

Tetrahedron Letters 43 (2002) 3669–3671

TETRAHEDRON LETTERS

A free ligand for the asymmetric dihydroxylation of olefins utilizing one-phase catalysis and two-phase separation

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Received 5 February 2002; accepted 28 March 2002

Abstract—A free cinchona alkaloid derivative, which can be recovered and reused in the same way as the reported soluble polymer-supported cinchona alkaloid-derived ligands, was applied to the homogeneous asymmetric dihydroxylation of olefins. The molar ratio of ligand/olefin was 5%, being much lower than that required for the corresponding soluble polymer-supported ligands (10–25%). Yields of 82–93% and ees of 89–99% have been obtained. © 2002 Elsevier Science Ltd. All rights reserved.

The osmium-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most efficient methods for the preparation of chiral vicinal diols.[1] Although the reactions can be applied to the synthesis of natural products, pharmaceuticals, fine chemicals, etc. the high cost of osmium and the ligands as well as the high toxicity of osmium compounds has prevented their use in industry. To solve this problem, several methods have been introduced for the recovery and reuse of the ligand and/or osmium.[2] One simple approach is to recover the ligand from the reaction mixture by extraction with dilute sulfuric acid.[1a] However, the osmium is totally lost in this procedure because OsO_4 cannot complex with cinchona alkaloid-derived ligands under acidic conditions. Another possible solution is to anchor the ligand on an insoluble polymer.[2a,3] Despite the advantages of easy separation, the use of insoluble polymer-supported ligands suffered from lowered catalytic activity and enantioselectivity due to the restrictions of the polymer matrix, which resulted in limited mobility and accessibility to the active sites and thus obstructed the ligand-accelerated catalysis (LAC) AD reaction.[4] In some cases, the cinchona alkaloid monomer was not covalently linked to the polymer matrix but physically trapped within the swelled polymer, leading to leaching of the ligand.[5] To combine the advantages of homogeneous catalysis with 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 (OH-PEG-OMe, MW = 5000).[4a,6] Unfortunately, the PEG-bound mono-cinchona alkaloid ligand lacking an aromatic group at its 9-*O*-position showed low enantioselectivity (even the AD reaction of stilbene gave only 88% ee),[4a] and the PEG-bound bis-cinchona alkaloid ligands required complicated synthetic manipulations.[6a,6b] Very recently, we reported a simple PEG-bound mono-cinchona alkaloid-derived ligand possessing a phthalazine group at the 9-*O*-position of DHQD.[6c] Satisfactory results were achieved for *trans*-1,2-disubstituted olefins, but the enantioselectivity for some terminal olefins was not so good. Moreover, for all of the reported PEG-bound cinchona alkaloid-derived ligands, the required molar ratio of ligand/olefin in the AD reactions was as high as 10–25% (calculated from the bound alkaloid),[4a,6,7] and is much higher than that for the extensively used free ligands $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$.[8]

Herein we report a recoverable and reusable free ligand **1** for AD reactions by using the concept of one-phase catalysis and two-phase separation.[4c] The bis(4-vinylbenzoyl) derivative of **1** has been used as a precursor in the synthesis of insoluble polymer-supported ligands,[3,7] but the detailed information about the preparation and characterization of **1** has not been reported. When developing a new polymer-supported ligand with **1** as one of the monomers, we found that **1** itself was completely soluble in $^tBuOH–H_2O$ (1:1), the standard solvent system for AD reactions,[8] and could be recovered by extraction with CH_2Cl_2 followed by precipitation upon addition of diethyl ether. The above properties of **1** allowed us to apply **1** to homogeneous AD reaction of olefins in place of PEG-bound ligands.

Keywords: asymmetric dihydroxylation; cinchona alkaloid derivative; homogeneous catalysis; osmium catalyst.

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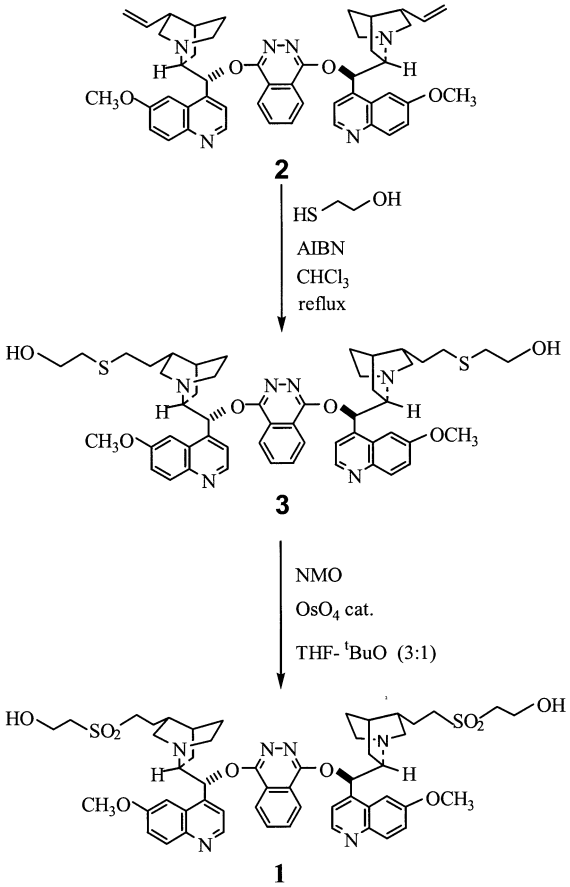
PII: S0040-4039(02)00624-X

Ligand **1** was prepared following the synthetic procedure used for its analogues.[9] The synthetic route to **1** is outlined in Scheme 1. 1,4-Bis(9-*O*-quininyl)phthalazine **2** was prepared according to the reported method,[10] and heated with 2-mercaptoethanol in the presence of 2,2′-azobisisobutyronitrile (AIBN) in $CHCl_3$ to give the sulfide **3** (64% yield),[11] which was 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 (53% yield).[12]

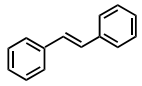
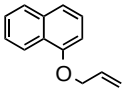
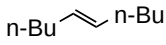
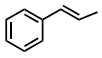
We performed the AD reactions using ligand **1**, the molar ratio of ligand/olefin being 5%. The AD reaction results for the selected olefins are presented in Table 1. All of the olefins were converted into the corresponding diols in very good yields and high ees.

Stilbene was chosen as the substrate to examine the efficiency with which the catalyst could be recycled. When the reaction was finished, the ligand could be recovered in 92–96% yields by extraction with CH_2Cl_2 and precipitation upon addition of diethyl ether followed by filtration. However, some OsO_4 was lost to the mother liquor as well as the solvent used to wash the recovered ligand. Therefore, a small amount of OsO_4 (30% of the total amount of the first run) was added to regenerate the reaction conditions. The results of the repeated use of the catalyst are shown in Fig. 1.



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

Table 1. Asymmetric dihydroxylation of olefins using ligand **1**[a]

Entry	Olefin	Yield(%)[b]	ee(%)[c]
1[d]		91	99(>99[e])
2		87	97(97[e])
3		82	91(93[e])
4		93	89(88[e])
5		85	95(93[e])
6		90	98

[a] The asymmetric dihydroxylation reactions were run for 24 h at 0°C (entries 1–5) or for 15 h at 10°C (entry 6) in ^{t}BuOH–H_2O (1:1), with $K_3Fe(CN)_6$ as the cooxidant; the molar ratio of olefin/ligand/OsO_4 = 1/0.05/0.005.

[b] Isolated yields by column chromatography.

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

[d] The average value for five runs (see Fig. 1).

[e] Results for the free ligand $(DHQ)_2PHAL$ from Ref. 8.

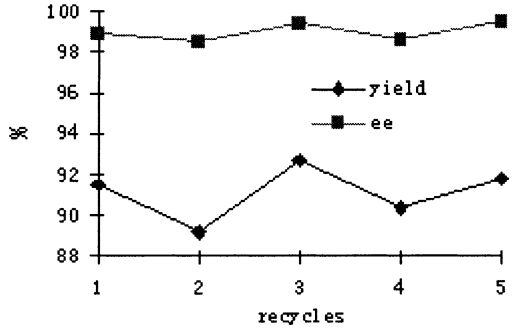


Figure 1. Plot of yields and ees versus recycles of the asymmetric dihydroxylation of stilbene using ligand **1**.

In conclusion, we have successfully applied a free biscinchona alkaloid derivative to the homogeneous AD reaction of olefins utilizing one-phase catalysis and two-phase separation. The ligand can be easily prepared and the molar ratio of ligand/olefin in the AD reaction is much lower than that for the reported polymer-supported cinchona alkaloid ligands.[4a,6,7] Repetitive use of the ligand is possible without significant loss of enantioselectivity when a small amount of OsO_4 is added after each run.

Typical procedure for asymmetric dihydroxylation: $K_3Fe(CN)_6$ (1.96 g, 6.0 mmol), K_2CO_3 (0.82 g, 6.0 mmol), ligand **1** (100 mg, 0.101 mmol) were dissolved in ^{t}BuOH/H_2O (1:1, 20 mL) at room temperature, followed by addition of 100 mg mL^{-1} OsO_4 in toluene (26

μL, 0.01 mmol). For *trans*-1,2-disubstituted olefins, $CH_3SO_2NH_2$ (190 mg, 2.0 mmol) was added. The solution was cooled to 0°C (with the exception of *trans*-β-methylstyrene, entry 6 in Table 1) and the olefin (2.0 mmol) was added. The mixture was stirred vigorously at 0°C for 24 h. While the mixture was stirred at 0°C, Na_2SO_3 (2.5 g) was added and the mixture was allowed to warm to room temperature and stirred for 45 min. CH_2Cl_2 (20 mL) was added to the reaction mixture, and after separation of the layers the aqueous phase was further extracted with CH_2Cl_2 (10 mL×3) (if $CH_3SO_2NH_2$ was used, the combined organic layers were washed with 2 mol L^{-1} NaOH). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and dry Et_2O (50 mL) was slowly added to the solution under vigorous stirring conditions. The precipitate obtained was collected by filtration, washed with cool Et_2O/EtOH (3:1) and Et_2O, and dried in vacuo. The filtrate was evaporated to give the crude product, which was further purified by column chromatography to afford the pure diol.

Acknowledgements

We thank National Natural Science Foundation of China (NSFC) for financial support.

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11. Compound **3**: Mp 139–141.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J=4.4 Hz, 2H), 8.32 (m, 2H), 7.99 (d, J=9.2 Hz, 2H), 7.96 (m, 2H), 7.58 (d, J=2.0 Hz, 2H), 7.42 (d, J=4.8 Hz, 2H), 7.38 (d, J=8.8 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 7.04 (s, 2H), 3.92 (s, 6H), 3.68 (m, 4H), 3.46 (m, 2H), 3.07 (m, 4H), 2.32–2.70 (m, 16H), 1.55–1.82 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.85, 156.44, 147.34, 144.72, 132.42, 131.55, 127.29, 122.84, 122.51, 121.97, 118.41, 102.09, 76.10, 60.43, 60.09, 58.10, 55.80, 42.71, 35.38, 34.86, 34.82, 29.85, 28.40, 25.71, 23.55; HRMS (ESI): calcd for $C_{52}H_{62}N_6O_6S_2$+H: 931.4251, found: 931.4237. Anal. calcd for $C_{52}H_{62}N_6O_6S$: C, 67.07; H, 6.72; N, 9.03; S, 6.87. Found: C, 66.89; H, 6.62; N, 8.85; S, 6.72%.
12. Compound **1**: Mp 173–174.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J=4.4 Hz, 2H), 8.31 (m, 2H), 7.97 (d, J=9.2 Hz, 2H), 7.96 (m, 2H), 7.58 (d, J=2.4 Hz, 2H), 7.43 (d, J=4.4 Hz, 2H), 7.36 (d, J=9.2 Hz, 1H), 7.35 (d, J=9.2 Hz, 1H), 6.99 (d, J=5.6 Hz, 2H), 4.06 (t, J=5.2 Hz, 4H), 3.90 (s, 6H), 3.48 (m, 2H), 3.16 (m, 6H), 3.01 (m, 6H), 2.53 (m, 2H), 2.36 (m, 2H), 1.60–1.92 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.86, 156.46, 147.17, 144.70, 144.45, 132.59, 131.27, 127.29, 122.81, 122.37, 121.96, 118.56, 102.13, 75.88, 60.01, 57.50, 56.16, 55.75, 55.32, 53.02, 42.48, 34.57, 28.10, 26.23, 25.65, 23.46; HRMS (ESI): calcd for $C_{52}H_{62}N_6O_{10}S_2$+H: 995.4047, found 995.4039. Anal. calcd for $C_{52}H_{62}N_6O_{10}S_2$: C, 62.75; H, 6.28; N, 8.45; S, 6.43. Found: C, 62.41; H, 6.52; N, 8.11; S, 6.29%.
13. **Entry 1 (diol)**: Daicel Chiralcel OJ, hexane/^{i}PrOH=4:1, flow rate 0.6 mL/min, t_R (min)=12.2 (minor), 13.8 (major); **entry 2 (diol)**: Daicel Chiralcel OB-H, hexane/^{i}PrOH=9:1, flow rate 0.5 mL/min, t_R (min)=14.7 (minor), 17.8 (major); **entry 3 (diol)**: Daicel Chiralcel OD, hexane/^{i}PrOH=40:1, flow rate 1.0 mL/min, t_R (min)= 27.8 (minor), 29.7 (major); **entry 4 (diol)**: Daicel Chiralcel OD, hexane/^{i}PrOH=19:1, flow rate 1.0 mL/min, t_R (min)=14.1 (major), 20.6 (minor); **entry 5 (bisbenzoate)**: Daicel Chiralcel OD-H, hexane/^{i}PrOH=500:1, flow rate 1.0 mL/min, t_R (min)=6.3 (major), 7.5 (minor); **entry 6 (diol)**: Daicel Chiralcel OD, hexane/^{i}PrOH=20:1, flow rate 1.0 mL/min, t_R (min)=15.0 (minor), 16.4 (major).