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Chinese Chemical Letters 20 (2009) 763–766
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A new free recoverable and reusable mono-alkaloid-type ligand and its use in preparation of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate

Qiao Feng Wang, Hui Chen, Yan Zhao, Xiao Ye Li, Sheng Yong Zhang *

Research Center of Chirotechnology, Fourth Military Medical University, Xi'an, 710032, PR China

Received 13 November 2008

Abstract

A new free recoverable and reusable mono-alkaloid-type ligand has been synthesized by a simple method. With highly polar groups, the ligand can be recycled and reused eight times to prepare ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate with high yield and *ee* via asymmetric dihydroxylation (AD) reaction.

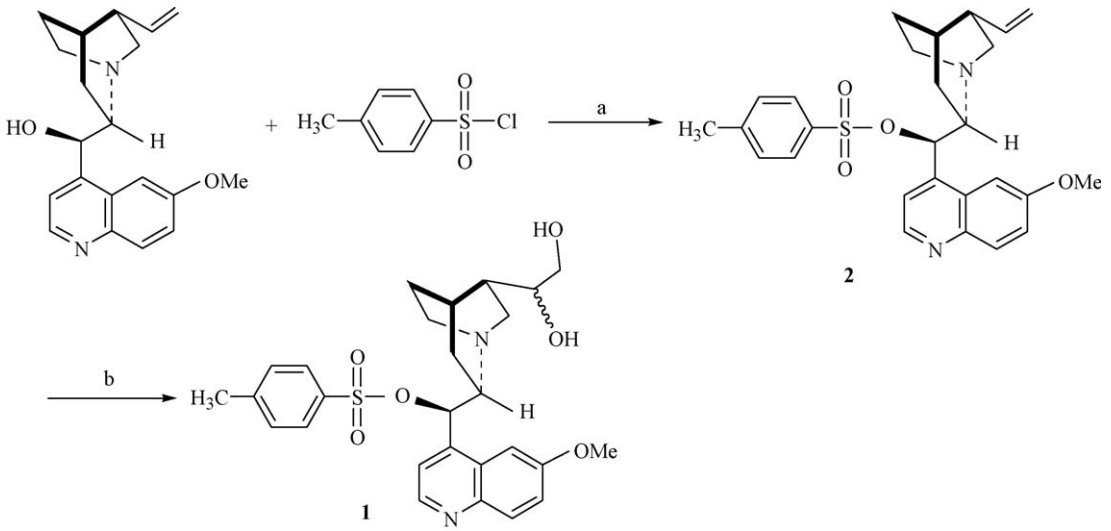
Keywords: Cinchona alkaloid; Recoverable and reusable ligand; Ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate

Ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate is a valuable building block in the production of pharmaceuticals, agrochemicals and other fine chemicals. With this optical material, C_{13} side chain of anticancer drugs, taxol and docetaxel, can be prepared [1]. Meanwhile, the asymmetric dihydroxylation (AD) of ethyl cinnamate works as the most efficient method to achieve it [2]. This catalytic reaction was devised and improved by Sharpless et al. [3]. Since then, many ligands with excellent results obtained have been developed. In most cases, more attention was paid to dimeric cinchona alkaloids and the reaction gave better results than those of mono-alkaloids. But the synthesis of dimeric ligands was more complicated. Both Lin's and our work showed that the second alkaloid moiety of dimeric alkaloid-type ligands was not always indispensable in some catalytic processes [4–6]. It is noteworthy that the AD reaction of some substrates catalyzed by monomer CLB-DHQD ever gave excellent enantioselectivities [7]. Compared with the dimeric ligands, the monomer ones were easily prepared and can be modified for special use. Herein, a new free mono-alkaloid-derivate **1** was synthesized and its reuse in the synthesis of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate was probed.

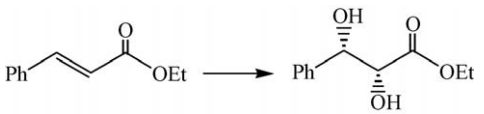
The route for ligand **1** was straightforward (Scheme 1). In the first step, quinine was nucleophilically mono-substituted by *p*-toluenesulfonyl chloride in basic condition to give quinine tosylate **2** as a light yellow solid [8]. Then **2** was directly oxidized to produce goal compound **1** under modified AD condition. The total yield was 66% and the structure of **1** was confirmed by ^{1}H NMR, ^{13}C NMR and MS [9].

* Corresponding author.
E-mail address: syzhang@fmmu.edu.cn (S.Y. Zhang).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.02.018



Scheme 1. Synthetic route of ligand **1**. Reagents and conditions: (a) NaH, THF, reflux, 2 h, then *p*-toluenesulfonyl chloride, 0 °C; r.t., 10 min, reflux, 15 h, 70%; (b) OsO_4, NMO, THF/^{t}BuOH, r.t., 12 h, 95%.



Scheme 2. Reagents and conditions: OsO_4, ligand **1**, NMO, acetone–H_2O, 25 °C.

Table 1
The repeated use of **1** to synthesize ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate via AD reaction.[a]

Run	1	2	3	4	5	6	7	8
Yield (%)	96	95	97	96	94	95	97	95
ee (%)[b]	>99	>99	–	–	–	–	>99	>99

[a] The reactions were run for 6–10 h at 25 °C in acetone–H_2O (1:1) with NMO as the co-oxidant.
[b] Determined by both optical rotation and the chiral HPLC method (Chiral OJ-H column, *n*-hexane/*i*-propanol = 90:10, 1.0 mL/min).

After that, **1** was used to catalyze the AD reaction of ethyl cinnamate (Scheme 2). The reaction proceeded smoothly; high yields and *ee*s were obtained. Due to the polar group (hydroxyl group), **1** was insoluble in Et_2O. It could be recovered in the catalytic system. When the reaction was over, the ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate was extracted by Et_2O. All of the ligand and part of OsO_4 remained in water layer for repeated use. The results indicated that **1** can be reused for eight runs without a significant decrease in yields and *ee*s (Table 1). The ^{1}H NMR and the optical purity of the product are shown in Figs. 1 and 2.

In summary, it is convenient to synthesize a new free recoverable and reusable mono-alkaloid-type ligand **1**. This ligand was also successfully recycled and reused in preparing ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenyl-propionate with high yields and *ee*s.

1. Experimental

*1.1. Preparation of chiral mono-alkaloid-type ligand **1***

Quinine tosylate **2** (2 mmol), NMO (5.2 mmol), THF (20 mL) and ^{t}BuOH (8 mL) were stirred and a solution of OsO_4 in toluene (0.094 mmol) was added dropwise at r.t. After 12 h, Na_2SO_3 (6 g) was added and the mixture was

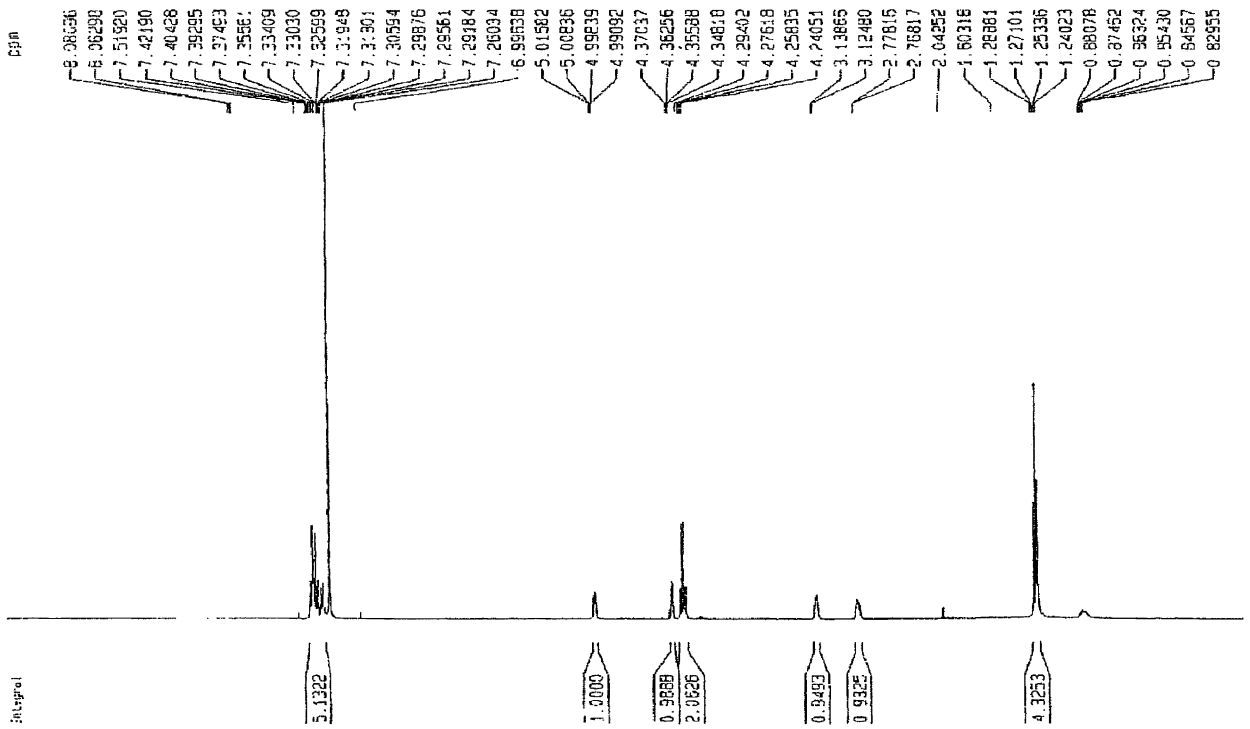


Fig. 1. ^{1}H NMR spectra of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate.

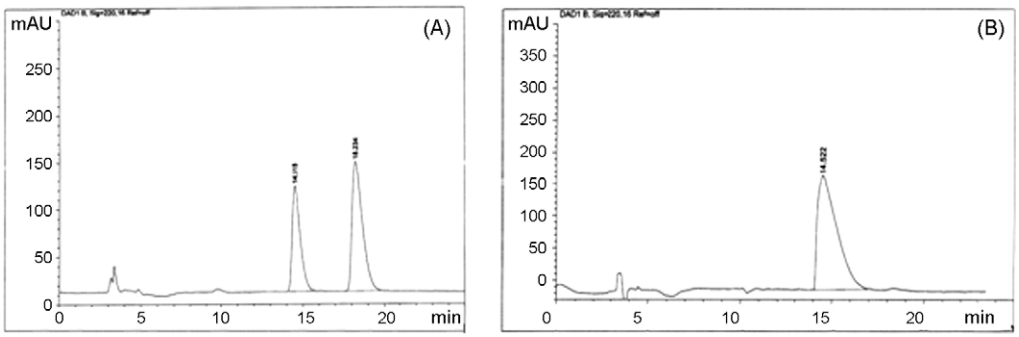


Fig. 2. (A) The HPLC spectra of racemic of ethyl -2,3-dihydroxy-3-phenylpropionate; (B) the HPLC spectra of ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate.

further stirred for 1 h. The mixture was then filtered. The filtrate was dried over anhydrous $MgSO_4$ and concentrated in vacuum. The residue was purified by flash column chromatography, eluting with ethyl acetate–methanol (9:1) to afford **1** (1.9 mmol) as a white solid. Yield: 95%.

1.2. Preparation of ethyl (2R,3S)-2,3-dihydroxy-3-phenylpropionate via asymmetric dihydroxylation

500 mL flask was charged with acetone–H_2O (9:1, v/v) 200 mL, OsO_4 (0.1 mmol) and ligand **1** (1 mmol). After stirring for 10 min, NMO (26 mmol) was added. Ethyl cinnamate (20 mmol) was then added and the reaction mixture was stirred vigorously to the point when no starting material was detected by TLC analysis. Acetone was then removed under reduced pressure and the water layer was extracted with Et_2O (200 mL $\times$ 2). The combined ether extracts were dried over with anhydrous $MgSO_4$ and evaporated to give a white solid product, which was further purified by washing

with hexane (50 mL × 3) to afford the pure diol. All of the ligand and part of OsO_4 still remained in water layer for repeated use.

Repeated use: To the water layer, acetone (180 mL), OsO_4 (0.26 mL, 50% of total amount of the first run), NMO (26 mmol) and ethyl cinnamate (20 mmol) were added to regenerate the reaction. Similar work-up and purification was repeated 8 times to give ethyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate in quantitative yield.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 20572131, 20842007) and Natural Science Basic Research Plan in Shaanxi Province of China (No. SJ08-ZT02) for financial support.

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[8] W. He, S.Y. Zhang, R. Jiang, X.L. Sun, L. Zhang, S.Z. Shen, J. Mol. Catal. 6 (2005) 440 (in Chinese).
[9] Mono-alkaloid-type ligand **1:** mp 58–60 °C $[\alpha]_D^{25}$-3.25 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.01–1.91 (m, 6H), 2.08 (m, 6H), 2.52 (m, 2H), 2.73 (s, 2H), 3.05–3.83 (m, 6H), 6.09 (s, 1H), 6.71 (s, 2H), 7.08–7.10 (m, 4H), 7.79 (br, 2H), 8.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 23.5, 26.9, 27.5, 37.4, 41.9, 53.7, 55.3, 59.7, 64.2, 64.8, 73.3, 73.8, 118.2, 121.3, 125.3, 125.9, 126.9, 127.2, 128.5 128.7, 130.8, 130.9, 132.6, 143.7, 144.2, 146.2, 157.5. HRMS (ESI): Calcd. For $C_{27}H_{32}N_2O_6S$ ($M+H^+$): 513.2. found 513.1.