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Chiral ketone- or chiral amine-catalyzed asymmetric epoxidation of *cis*-1-propenylphosphonic acid using hydrogen peroxide as oxidant

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Abstract

By using a D-fructose-derived chiral ketone or a D-mannitol-derived chiral amine as catalyst, the organocatalytic asymmetric epoxidation of *cis*-1-propenylphosphoric acid with 30% aqueous hydrogen peroxide in H_2O–CH_3CN mixture (~80:20) afforded (1*R*, 2*S*)-(−)-(1,2)-epoxypropyl phosphoric acid (fosfomycin). Asymmetric epoxidation was carried out at 0 °C for 72 h to achieve 100% conversion with a maximum enantiomeric excess (e.e.) of 74%.

Keywords: Chiral amine; *cis*-1-Propenylphosphoric acid; Hydrogen peroxide; Organocatalysis; Asymmetric epoxidation

1. Introduction

Fosfomycin is an antibiotic used to treat infections of the urinary tract. It is commonly prepared by the epoxidation [1–3] of *cis*-1-propenylphosphonic acid (Scheme 1, **1**) followed by chemical resolution of the obtained racemic epoxide [4–6] (Scheme 1). **1** is an α, β-unsaturated acid and an electron-deficient olefin. Formerly, completing epoxidation required the use of transition metal compounds such as sodium tungstate(VI) and sodium molybdate(VI) as catalysts.

Curci et al. [7,8] first reported organocatalytic asymmetric epoxidation of olefins catalyzed by chiral ketones in 1984. In the last decade, Yang at al. [9] and Shi and co-workers [10–19] conducted research on the asymmetric epoxidation. In their epoxidation, CH_3CN–H_2O was commonly used as solvent; oxone was used as the primary oxidant and the reaction required weak basic conditions. In their research, Shu and Shi [12] also found that hydrogen peroxide (H_2O_2) could be used as an oxidant for chiral ketone catalyzed asymmetric epoxidation of olefins. Their reaction system used a fructose-derived chiral ketone **5** (Scheme 2) as catalyst, 30% of H_2O_2 as oxidant and CH_3CN–buffer (AcOH–K_2CO_3, pH 10.3) as solvent. In asymmetric epoxidation of many olefins, high e.e. values were obtained.

In 2000, Aggarwal and co-workers [20] made the important discovery that chiral amine also can catalyze the asymmetric epoxidation of olefins and that secondary amines have the best efficiency. Using CH_3CN–H_2O (95:5) as solvent and oxone as oxidant at r.t. for 4 h, the asymmetric epoxidation of some non-functional olefins catalyzed by chiral amine **4** (Scheme 2) achieved the highest e.e. of 57%.

In the present study, we found that the reaction system proposed by Shi and co-workers [12,19] using H_2O_2 as oxidant was also suitable for amine-catalyzed epoxidation of α, β-unsaturated acids. The organocatalytic asymmetric epoxidation of **1** opens a new pathway for fosfomycin synthesis.

2. Experimental

The NMR spectra were recorded on a Bruker AC 300 MHz spectrometer in $CDCl_3$ or D_2O with TMS as the internal reference. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. The elemental analyses were performed on a Perkin-Elmer 240C instrument. MS spectra were recorded on a Bruker Esquire-LC-00136 spectrometer. Unless otherwise specified, all reagents were purchased from commercial suppliers and were used without purification.

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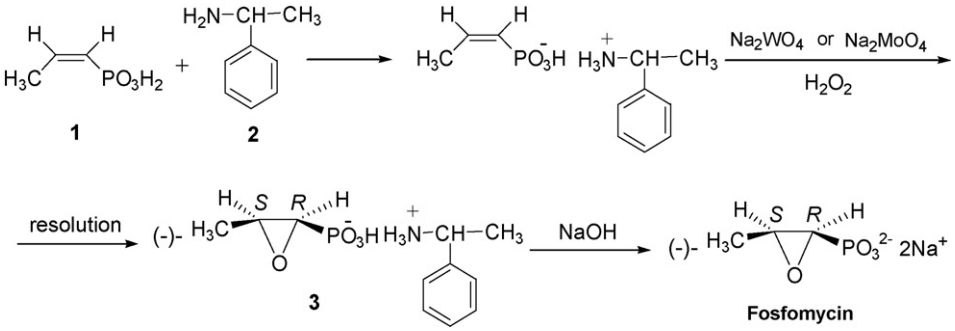


Scheme 1. Traditional fosfomycin preparation method.

2.1. Asymmetric epoxidation of cis-1-propenylphosphoric acid *1*

The epoxidation was carried out with *cis*-1-propenylphosphoric acid **1** (1 mmol), 30% H_2O_2 (5 mmol, 0.6 mL), CH_3CN (1.0 mL) and chiral ketone (0.2 mmol) or chiral amine (0.05 mmol) in aqueous Na_2 (EDTA) (4×10^{-4} M) solution (3.5 mL). Aqueous solution of K_2CO_3 (3 M) was added to adjust the pH to 9–10. After 6 h at 50 °C, 24 h at 25 °C, or 72 h at 0 °C, the solvent was removed by vacuum evaporation. Water was added to the residue in order to dissolve the epoxide. The mixture was filtered and the filtrate was vacuum dried to give epoxide **7**.

^{1}H NMR (300 MHz, D_2O) [δ (ppm)]: 1.39 (d, J = 5.0 Hz, 3H), 3.17 (dd, J_1 = 5.2 Hz, J_2 = 18.6 Hz, 1H), 3.17 (m, J = 5.4 Hz, 1H).

2.2. Preparation of dimethyl ester *8*

Methylsulfonic acid (19.5 mg, 0.2 mmol) was added to the solution of epoxide **7** (21.4 mg, 0.1 mmol) in CH_3OH (5 mL). The process produced white precipitate in the solution. Then under vigorous stirring, diazomethane in ether was added to the mixture. After the mixture had changed to a light yellow solution, it was filtered, and the filtrate was vacuum concentrated to light yellow oil. The crude dimethyl ester was then purified by flash chromatography ($CHCl_3$:C_2H_5OH = 35:1) to give colorless oil, dimethyl ester **8**.

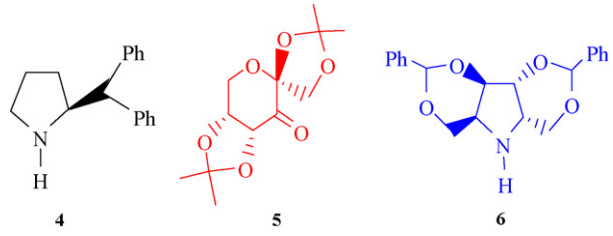
Calcd for $C_5H_{11}O_4P$: C, 36.15; H, 6.67. Found: C, 36.27; H, 6.53%.

IR (KBr, cm^{-1}): ν 3475, 2960, 1413, 1248, 1034, 834, 786, 562.

^{1}H NMR (300 MHz, D_2O) [δ (ppm)] 4.00–3.98 (d, J = 5.5 Hz, 3H), 3.94–3.92 (d, J = 5.4 Hz, 3H), 3.49–3.36 (m, 1H), 3.17–3.15 (d, J = 6.8 Hz, 1H), 3.04–3.01 (d, J = 6.8 Hz, 1H), 1.72–1.70 (d, J = 8.3 Hz, 3H).

^{13}C NMR 53.2, 52.7, 50.6, 47.8, 13.9.

ESI-MS: *m*/*z* 167 (M^++H).



4 5 6

Scheme 2. Chiral ketone and chiral amine catalysts.

3. Results and discussion

3.1. Chiral catalysts

D-Fructose-derived chiral ketone **5** (Scheme 2) synthesized by Shi and co-workers [21] and a D-mannitol-derived chiral amine **6** (Scheme 2) were used as catalysts for asymmetric epoxidation of **1**.

According to Shing's [22] procedure, chiral amine **6** was synthesized (Scheme 3) by using D-mannitol as the initial material and following four sequential steps: benzylidenation, tosylation, pyrrolidine ring formation and hydrogenolysis (the detailed operation and results of preparation of **5** and **6**, see see Appendix A. Supplementary data 1).

Our experimental results indicated that chiral amine **6** is an efficient asymmetric epoxidation catalyst of **1**.

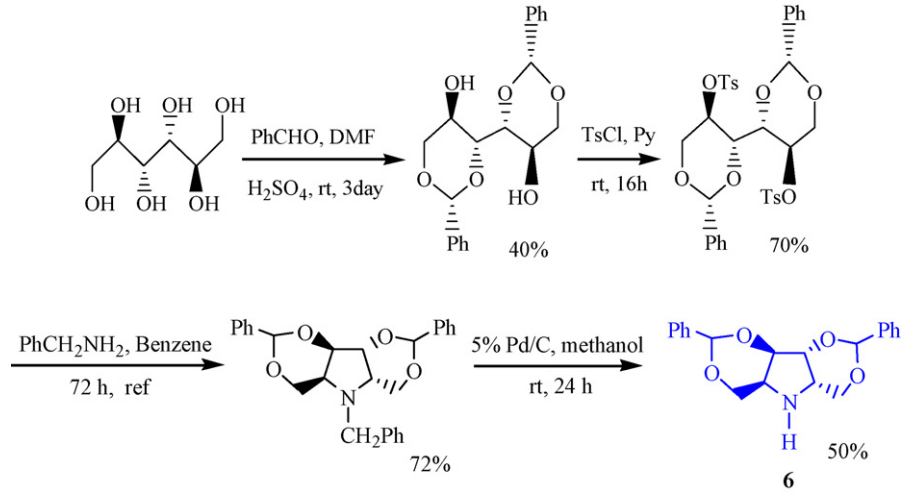
3.2. Catalytic activity and enantioselectivity

The asymmetric epoxidation was completed by using H_2O_2 as oxidant and chiral ketone **5** or chiral amine **6** as catalyst in CH_3CN–H_2O (Scheme 4). The results of the epoxidation are shown in Table 1.

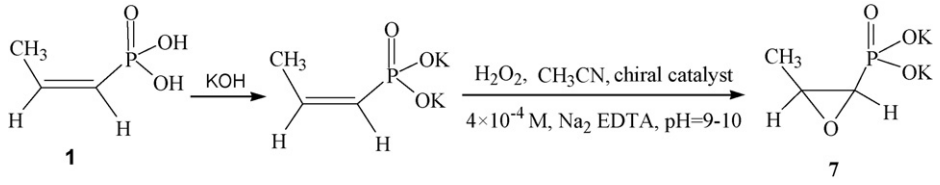
As shown in Table 1, both organic chiral catalysts have high activity (100% conversion) in epoxidation of α, β-unsaturated phosphoric acid **1**. The enantiomeric excess (e.e.) increased along with the drop in the reaction temperature. At 0 °C for 72 h, chiral ketone **5** catalyzed the asymmetric epoxidation at 100% conversion with the highest e.e. of 68% and chiral amine **6** catalyzed the asymmetric epoxidation at 100% conversion with the highest e.e. of 74%.

Chiral amine **6** had higher activity and enantioselectivity than chiral ketone **5**. Under the same reaction conditions, complete epoxidation of **1** required the use of 20 mol% of the chiral ketone, but only 5 mol% of the chiral amine.

Chiral amine **6** was more stable than chiral ketone **5** in the epoxidation. After the catalytic reaction, chiral amine **6** had not decomposed. Therefore, the catalyst was able to be recovered



Scheme 3. Synthesis of chiral amine **6**.



Scheme 4. Asymmetric epoxidation of **1** carried out by H_2O_2, chiral ketone or chiral amine in CH_3CN–H_2O.

Table 1
Yield and e.e. value of CPPA asymmetric epoxidation catalyzed by chiral ketone **5** and chiral amine **6** at different temperatures

Catalysts	50 °C 6 h		25 °C 24 h		0 °C 72 h	
	Conv. (%)	e.e. (%)	Conv. (%)	e.e. (%)	Conv. (%)	e.e. (%)
5 (20 mol%)	100	50	100	58	100	68
6 (5 mol%)	100	63	100	70	100	74

and used again for epoxidation. However, with chiral ketone **5** Baeyer–Villiger rearrangement [14–16] occurred, and so chiral ketone **5** could not be used repeatedly.

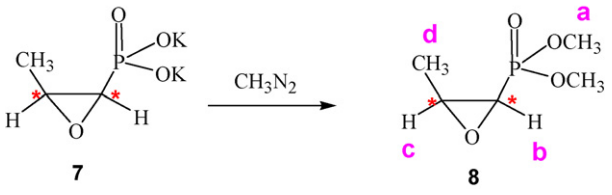
Amine-catalyzed epoxidation with H_2O_2 as oxidant was also suitable for other α, β-unsaturated acids. We conducted the chiral amine **6**-catalyzed epoxidation of crotonic acid, propenoic acid, methyl propenoic acid, and *trans*-butenediacid (their possible enantioselectivities were not taken into account). Under stirring at room temperature for 6 h, the epoxidation of crotonic acid, propenoic acid and methyl propenoic acid reached 100% conversion. The epoxidation of *trans*-butenediacid reached 65% conversion. Whereas *trans*-butenediacid is a deeply electron-deficient olefin, it can be epoxidized at room temperature, showing that the system using H_2O_2 as oxidant and secondary amine as catalyst has high activity in the epoxidation of α, β-unsaturated acids.

3.3. Determination of enantiomeric excess

To measure enantiomeric excess, the epoxide of *cis*-1-propenylphosphoric acid **1** was first esterified by using diazomethane (Scheme 5). Then $Eu(tfc)_3$ as chiral shift reagent was added. It has been proved that the most suitable quantity of $Eu(tfc)_3$ is 10 mol% of the epoxide [23].

The proton chemical shifts of $-OCH_3$ in levo and dextral dimethyl ester of epoxide were separated in a ^1H NMR spectrum and the e.e. value was determined by the integral area of the two peaks (Fig. 1, a_1 and a_2, also see Appendix A. Supplementary data 2).

Fig. 1 and Supplementary data 2 shows that ^1H peaks a_2 and c have a certain overlap and mixing. However, the ^1H peaks of protons c and b have the same integral areas. Therefore, the integral area of a_2 is $a_2 = (a_2 + c) - b$.



Scheme 5. Esterification of epoxide **7** by CH_2N_2.

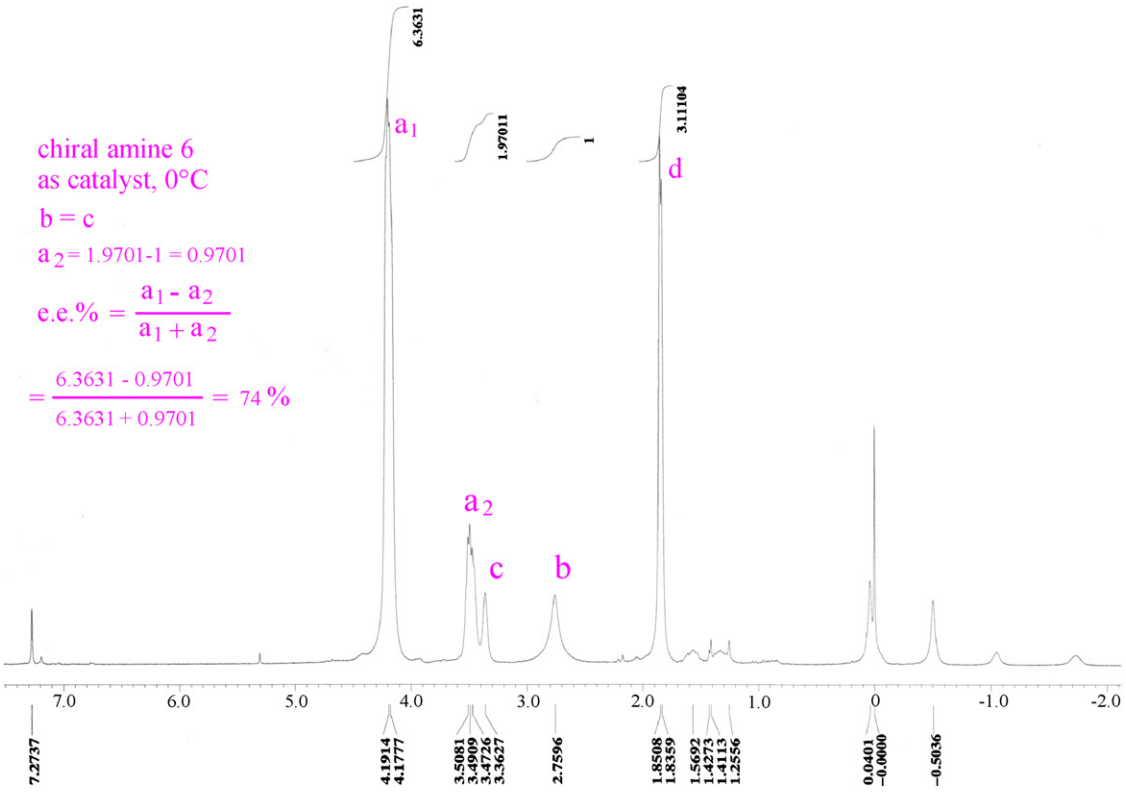


Fig. 1. ^{1}H NMR spectrum of the dimethyl ester (Scheme 5) of the epoxide from chiral amine **6**-catalyzed the asymmetric epoxidation of *cis*-1-propenylphosphoric acid **1** at 0 °C for 72 h. The ^{1}H chemical shifts of CH_3O– in levo and dextral dimethyl ester were separated in the spectrum and the e.e. value was determined. a_1 is the ^{1}H peak of the protons in the two CH_3O– groups of levo dimethyl ester and a_2 is that of dextral dimethyl ester. *b* and *c* are the ^{1}H peaks of protons *b* and *c*, respectively.

4. Conclusion

The results of this study show that chiral amine has higher catalytic activity, enantioselectivity and chemical stability than chiral ketone. In MeCN–H_2O as solvent, under a weakly basic environment, H_2O_2 can complete the asymmetric or ordinary epoxidation of α, β-unsaturated acids catalyzed by amine.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.01.011.

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