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Highly Enantioselective Epoxidation of Enol Silyl Ethers and Esters

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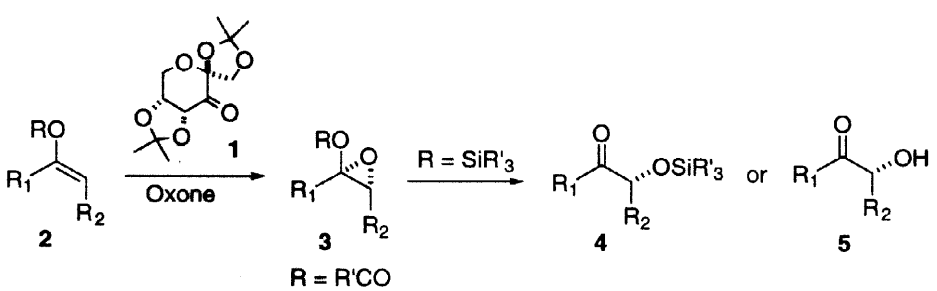
Abstract: High enantioselectivities have been obtained for asymmetric epoxidation of enol silyl ethers and esters using a fructose-derived chiral ketone as catalyst and Oxone as oxidant.

Asymmetric epoxidation of enol derivatives provides an effective approach to prepare chiral oxy-substituted epoxides and hydroxy ketones which are very useful intermediates.[1,2,3,4] Recently we reported a highly enantioselective epoxidation method for *trans*- and trisubstituted olefins using fructose derived ketone **1** as catalyst and Oxone as oxidant.[5] In our efforts to expand the scope of this epoxidation method, we have been investigating the feasibility of enantioselective epoxidation of enol silyl ethers and enol esters (**2**) with this catalyst (Scheme 1). We found these enol derivatives are quite effective substrates, producing oxy-substituted epoxides (**3**) or hydroxy ketones (**5**) with high enantioselectivty.[6]



Scheme 1

Our investigation started with 1-*t*-butyldimethylsiloxy-1-phenylpropene (Table 1, entry 1). Subjecting this enol silyl ether to the epoxidation conditions led to a mixture of α-silyloxy and α-hydroxy propiophenone (**4** & **5**). Treatment of the crude reaction products with 5% HCl/MeOH gave α-hydroxy propiophenone in an 80% isolated yield with 90% ee (HPLC, Chiralcel OD). Good yield and enantioselectivity were also obtained for the epoxidation of the cyclic TMS enol ether of α-tetralone (Table 1, entry 2). However, in the investigation of some other silyl ethers, we found that the α-hydroxy ketones were prone to racemization or dimerization particularly for cyclic systems.[7] Our attention was then turned to the epoxidation of enol esters with the hope to obtain epoxide **3** directly. We first investigated the epoxidation of the enol acetate and enol benzoate of cyclohexanone (Table 1, entries 3 and 4). In both cases the epoxides were indeed found to be relatively stable under the reaction

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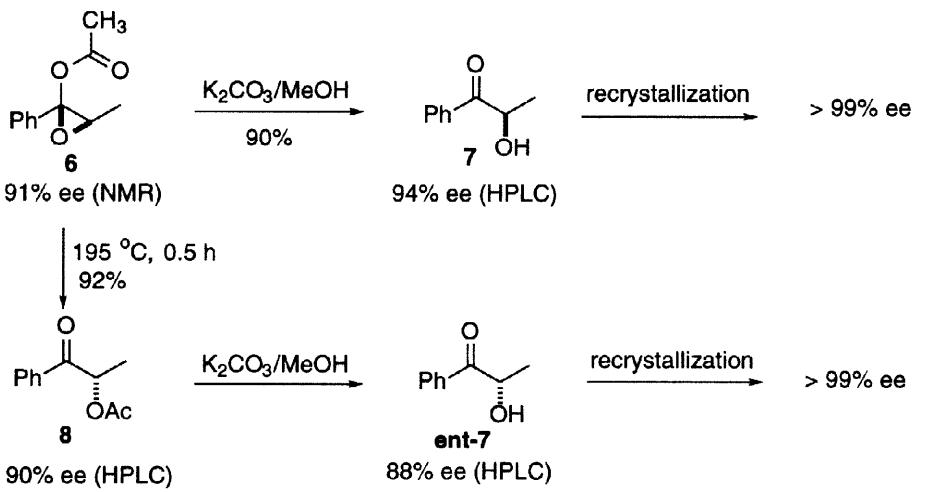
conditions. They could be isolated using a Et_3N-buffered silica gel column and stored in refrigerator for several weeks without significant decomposition. A 93% ee was obtained for the epoxide of the enol benzoate (Table 1, entry 4). Encouraged by this result, a number of cyclic and acyclic enol esters were prepared[8] and epoxidized (Table 1 entries 5-10). In all cases the reactions were relatively clean, the epoxides were isolated in good yields, and the enantioselectivities were high in most cases.

Epoxidations with ketone **1** have been shown to proceed mainly via a spiro mode.[5] This reaction mode is anticipated for the epoxidation of enol silyl ethers and enol esters. The absolute configurations of some of the epoxidation products (Table 1, entries 1, 2, 8, 9, and 10) were determined by comparing the measured rotation with literature values. The results in all these cases were consistent with the spiro model. The absolute configurations of the remaining epoxides (Table 1, entries 3-7) were assigned based on this model.

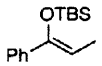
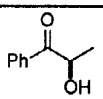
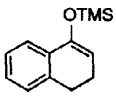
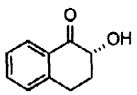
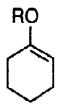
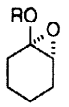
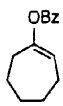
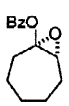
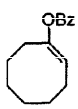
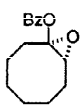
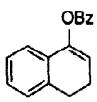
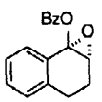
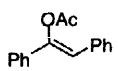
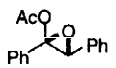
The epoxides derived from the enol esters should be versatile synthetic intermediates. Such an example is illustrated in Scheme 2. One enantiomer of an epoxide could be converted into either enantiomer of a hydroxy ketone. Epoxide **6,** derived from the enol acetate of propiophenone (Table 1, entry 9), was hydrolyzed to (R)-2-hydroxy propiophenone (**7**) with K_2CO_3/MeOH without decreasing the ee. In an alternative pathway, a thermal rearrangement of the same epoxide led to the formation of acetoxy ketone **8** with an inversion of the stereogenic center.[9] Acetate **8** was subsequently hydrolyzed to (S)-2-hydroxy propiophenone (**ent-7**) with K_2CO_3/MeOH. The stereointegrity was maintained during this two-step process. The enantiomeric excesses of both enantiomers could be enhanced to >99% by recrystallization.



Scheme 2

In summary, we have shown that enol silyl ethers and enol esters can be epoxidized with high ee using fructose-derived chiral ketone **1** as catalyst and Oxone as oxidant, which leads to useful synthetic intermediates. The versatility of the enol ester epoxides is highlighted by the formation of both enantiopure isomers of an α-hydroxy ketone from the same epoxide. The availability of the enantiomerically enriched oxy-substituted epoxides opens up potential avenues for various synthetic applications. Such studies are currently under way.

Table 1. Asymmetric Epoxidation of Enol Silyl Ethers and Esters by Ketone **1**[a]

Entry	Substrate	Product	t (h)	Yield (%)[b]	ee (%)
1			2.0	80	90[c,f]
2			1.0	70	83[c,f]
					
3	R = Ac		2.0	59	74[d,g]
4	R = Bz		1.5	82	93[e,g]
5			1.5	79	80[e,g]
6			1.5	87	91[e,g]
7			1.5	82	95[e,g]
8			1.5	92	88[e,h]
9			2.0	66	91[d,h]
10			3.0	46	91[d,h]

[a] All reactions were carried out at 0 °C (bath temperature) with substrate (1 eq.), ketone (0.3 eq.), Oxone (1.38 eq.) and K_2CO_3 (5.8 eq.) in organic solvent (15 mL) and aqueous buffer solution (10 mL) except that for entry 2 where the reaction was carried out at - 5 °C. The organic solvent used was either CH_3CN (entries 1, 2, 5, 7 and 9) or CH_3CN-DMM (1/2, v/v) (entries 3, 4, 6, 8 and 10). For entries 1, 2, 4, 5, 7, 8 and 9, 0.05 M $Na_2B_4O_7 \bullet 10\ H_2O$ of EDTA (4 x 10^{-4} M) was used as buffer; for others, AcOH-0.1M K_2CO_3 (4/1000, v/v) was used as buffer (for a representative procedure see: ref. 10). [b] The α-hydroxy ketones and epoxides were purified on silica gel column (for epoxides, silica gel was pretreated with Et_3N) by flash chromatography and gave satisfactory spectroscopic characterization. [c] Enantioselectivity was determined by chiral HPLC (chiracel OB) (for details see ref. 11). [d] Enantioselectivity was determined by ^1H NMR shift analysis of epoxide products directly with $Eu(hfc)_3$. [e] Enantioselectivity was determined by chiral HPLC (chiracel OD) (for details see ref. 11). [f] The absolute configuration was determined by comparing the measured optical rotations with the reported ones (see: refs. 12, 4, and 13). [g] The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode. [h] The epoxides were hydrolyzed to α-hydroxy ketones and the absolute configurations were determined by comparing the measured optical rotations of the α-hydroxy ketones with the reported ones (see: refs. 13, 12, and 4).

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(10) **A representative epoxidation procedure** (entry 4): To an ice cold mixture of 1-benzoyloxy-1-cyclohexene (0.134 g, 0.67 mmol), 10 mL of CH_3CN-DMM (v/v, 1/2), 6.7 mL of buffer (0.05 M $Na_2B_4O_7$ in $4x10^{-4}$ M aqueous Na_2EDTA), Bu_4NHSO_4 (0.009 g, 0.027 mmol), and ketone **1** (0.0516 g, 0.20 mmol) were added a solution of Oxone (0.567 g, 0.92 mmol) in 4.3 mL of aqueous Na_2EDTA (4×10^{-4} M) and a solution of K_2CO_3 (0.567 g, 3.87 mmol) in 4.3 mL of water simultaneously via syringe pump over a period of 1.5 h. The reaction was quenched with hexane and brine. The mixture was extracted with hexane, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (silica gel was buffered with Et_3N, using 5% ether in hexane as eluent) to afford the epoxide product as a colorless oil (0.12 g, 82% yield, 93% ee).

(11) HPLC conditions: For entries 1 and 2, Chiralcel OB, 10% *i*-PrOH in hexane, 0.5 mL/min; For entry 4, Chiralcel OD, 5% *i*-PrOH in hexane, 1.0 mL/min; For entry 5, Chiralcel OD, 3% *i*-PrOH in hexane, 1.0 mL/min; For entries 6 and 7, Chiralcel OD, 3% *i*-PrOH in hexane, 0.5 mL/min; For entry 8, Chiralcel OD, 4% *i*-PrOH in hexane, 0.8 mL/min. All runs were carried out at room temperature.

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