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Highly Enantioselective Epoxidation of α,β-Unsaturated Esters by Chiral Dioxirane

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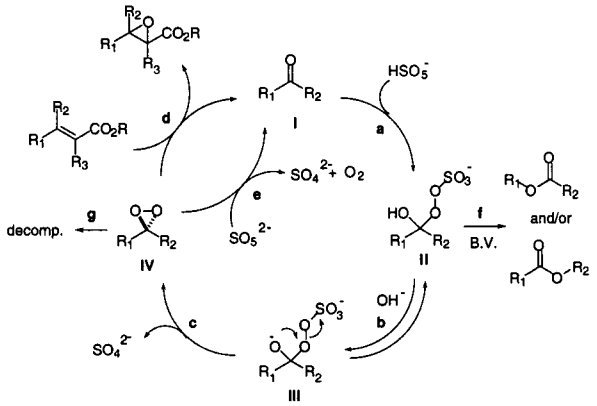
Chiral α,β-epoxy esters are important intermediates for the synthesis of complex molecules. Asymmetric epoxidation of prochiral α,β-unsaturated esters presents an attractive strategy for the synthesis of optically active glycidic esters.[1] However, only a few examples of such epoxidation have been reported.[2] Chiral (salen)Mn(III) catalysts have been found to be effective for the asymmetric epoxidation of (*Z*)-cinnamates.[3] Although great progress has been made for the asymmetric epoxidation of enones under nucleophilic conditions,[4] α,β-unsaturated esters have not been shown to be effective substrates under these conditions. Recently, it has been found that more reactive *trans*-carboxylic acid imidazolides are effective substrates for nucleophilic asymmetric epoxidation and glycidic esters can be obtained with high enantioselectivity upon addition of alcohols to the reaction.[5]

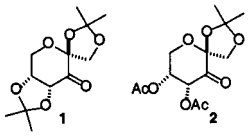
Dioxiranes generated in situ from chiral ketones have been shown to be highly enantioselective for the asymmetric epoxidation of a variety of olefins.[6−10] However, highly enantioselective epoxidation of α,β-unsaturated esters using chiral dioxiranes still remains a challenging problem. The epoxidation of cinnamates by various chiral dioxiranes gave only moderate to good enantioselectivities,[8k,p−t,9] with the highest being 89% ee.[9] In addition to the selectivity, the low reactivity of the ketone catalysts has also been a major obstacle for achieving efficient epoxidation of α,β-unsaturated esters. Being electrophilic reagents, dioxiranes react sluggishly with electron-deficient olefins such as α,β-unsaturated esters.[11] If the epoxidation is slow, the generated dioxirane (**IV**) will unproductively be consumed by reverting to the corresponding ketone (**I**) with Oxone via pathway **e** or by self-decompositions[6] or by both, resulting in a poor conversion of substrates and ultimate consumption of the ketone catalyst via pathways **f** and **g** (Scheme 1). An effective ketone catalyst for this class of olefin, therefore, requires high structural stringency for being both highly active and selective. Herein we report our preliminary progress on this subject.

Recently, we have found that a fructose-derived ketone **1** is an effective epoxidation catalyst and gives high ee's for a variety of *trans*- and trisubstituted olefins (Scheme 2).[10] However, ketone **1** is not effective toward α,β-unsaturated esters due to its decomposition under the reaction conditions presumably via the Baeyer−Villiger oxidation. One of our ongoing approaches to reduce the Baeyer−Villiger decomposition and enhance the ketone stability and reactivity is to replace the fused ketal of **1** with more electron-withdrawing groups.[10c,12] Ketone **2**, a readily available acetate analogue of **1**,[13] was found to be both active and highly enantioselective for the epoxidation of α,β-unsaturated esters. For example, the epoxidation of ethyl *trans*-cinnamate with 30% ketone **2** at 0 °C to room temperature for 24 h gave (2*S*,3*R*)-ethyl

Scheme 1



Scheme 2



3-phenylglycidate in 73% yield with 96% ee as determined by chiral GC (Table 1, entry 1).

The encouraging result obtained with ethyl *trans*-cinnamate prompted us to further study the catalytic properties of ketone **2** toward other α,β-unsaturated esters. Thus, we investigated the epoxidation of a number of substituted cinnamates to test the substituent effect on the epoxidation. As shown in Table 1, the enantiomeric excesses were high for these substrates (90−97% ee) (Table 1, entries 2−8). Trisubstituted cinnamates were also effective substrates, giving high yields and ee's (Table 1, entries 9 and 10). Further studies showed this epoxidation could be extended to a number of other trisubstituted α,β-unsaturated esters (Table 1, entries 11−16). Among these, conjugated enynes were found to be particularly effective substrates in terms of both yields and ee's (Table 1, entries 14−16).[14] In contrast to *trans*-cinnamates, the current catalyst is not effective for *trans*-aliphatic α,β-unsaturated esters. As anticipated, low ee was also obtained for *cis*-cinnamate (Table 1, entry 17).

In summary, we report a highly enantioselective asymmetric epoxidation for α,β-unsaturated esters using chiral ketone **2** as catalyst and Oxone as oxidant. High ee's have been obtained for a number of *trans*- and trisubstituted substrates. The results described show that it is feasible for dioxiranes to effectively epoxidize electron-deficient olefins with high ee's. Ketone **2** revealed a promising structural element required for the ketone to be both active and enantioselective toward this class of olefins, which provides a basis for further optimization of the ketone structure to enhance both enantioselectivity and catalytic activity.

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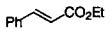
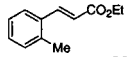
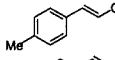
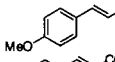
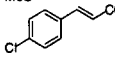
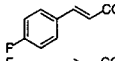
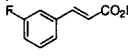
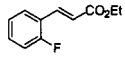
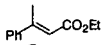
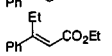
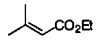
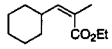
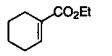
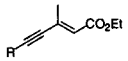
Table 1. Asymmetric Epoxidation of Olefins Catalyzed by Ketone **2**[a]

entry	substrate	yield (%)[b]	ee (%)	config.[m]
1[c]		73	96[f]	(+)-(2S,3R)[9,15a]
2[d]		67	93[g]	(+)[15b]
3[d]		91	97[h]	(+)[11d]
4[e]		57	90[g]	(+)-(2S,3R)[15c]
5[c]		64	97[g]	(+)[11d]
6[c]		77	96[i]	(+)[11d]
7[c]		41	97[h]	(+)
8[c]		40	95[i]	(+)
9[d]		93	96[j]	(+)-(2S,3R)[15d]
10[d]		91	93[i]	(+)[15e]
11[c]		64	82[f]	(+)[15f]
12[c]		77	89[f]	(+)[15g,h]
13[d]		77	93[f]	(+)[15i]
				
14[d]	R = Ph	96	94[g]	(+)
15[c]	R = TMS	94	94[k]	(+)
16[d]	R = n-Bu	74	98[g]	(+)
17[c]		84	44[l]	(-)-(2S,3S)[3c,15a]

[a] All reactions were carried out at 0 °C to room temperature with substrate (1 equiv), ketone (0.20−0.30 equiv), Bu_4NHSO_4 (0.06 equiv), Oxone (5.0 equiv), and $NaHCO_3$ (15.5 equiv) in CH_3CN−aq $Na_2(EDTA)$ (4×10^{-4} M) (1.5:1) and stopped after 24 h. For entry 4, the reaction was run at 0 °C for 12 h. [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] 0.30 equiv of ketone used. [d] 0.25 equiv of ketone used. [e] 0.20 equiv of ketone used. [f] Determined by chiral GC (Chiraldex G-TA). [g] Determined by chiral HPLC (Chiralcel OD). [h] Determined by chiral HPLC (Chiralpak AD). [i] Determined by chiral HPLC (Chiralcel OJ). [j] Determined by chiral HPLC (Chiralcel OB). [k] Determined by ^1H NMR shift analysis with $Eu(hfc)_3$. [l] Determined by chiral GC (Chiraldex B-DM). [m] Determined by comparing the measured optical rotations with the reported ones.

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Supporting Information Available: Experimental procedure for the asymmetric epoxidation reaction, the characterization of the ketone and epoxides, and the data for the determination of the enantiomeric excess of the epoxides (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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