An Efficient Asymmetric Epoxidation Method for *trans*-Olefins Mediated by a Fructose-Derived Ketone

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Epoxides are very important chiral building blocks for the synthesis of enantiomerically pure complex molecules.[1] Asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides. Great success has been achieved in the epoxidation of allylic alcohols[2] and unfuctionalized *cis*-olefins.[3] However, the epoxidation of *trans*-olefins bearing no allylic alcohol group with high enantiomeric excess still remains a challenging problem.[4] It was desirable to explore alternative systems for a solution. Among many other powerful methods for the epoxidation of olefins,[5] dioxiranes are remarkably versatile oxidation reagents, and their use as epoxidation reagents has risen to particular prominence.[6,7] The reaction is rapid and requires a simple workup. An important feature associated with dioxiranes is that they can be generated *in situ* from Oxone (potassium peroxomonosulfate) and a ketone,[8] which provides opportunities for asymmetric epoxidation when a chiral ketone is used.

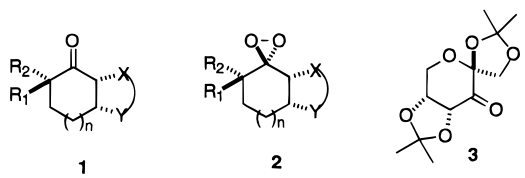
However, progress in the area of dioxirane-mediated asymmetric epoxidation has been limited.[9] The enantiomeric excess (ee) has been low (9−20%). Since dioxiranes have two reacting sites, it is crucial to limit possible competing approaches. Recently, some progress has been made in this regard. Yang reported an intriguing C_2 symmetric cyclic chiral ketone for asymmetric epoxidation.[10] An 87% ee was obtained in one case, although the ee values for most cases were low (5−50%).

Herein we wish to report our efforts in the area of asymmetric epoxidation. We are utilizing ketones containing the following general features: (1) the stereogenic centers are close to the reacting center, resulting in efficient stereochemical communication between substrates and the catalyst; (2) the presence of a fused ring and a quaternary center α to the carbonyl group minimizes the epimerization of the stereogenic centers; (3) one face of the catalyst is sterically blocked to limit the possible competing approaches. Ketone **3** has these desirable structural features, and is readily prepared from very inexpensive D-fructose ($15/kg) by ketalization (acetone, $HClO_4$, 0 °C, 53%) and oxidation (PCC, rt, 93%).[11]

Table 1. Asymmetric Epoxidation of Representative Olefins Catalyzed by Ketone **3**[a]

Entry	Substrate	Yield(%)[b]	ee (%)[c]	Configuration[i]
1[d]		73	>95 (95.2[e], 99.6[e,f])	(+)-(R,R)[13a]
2		81	88	(+)-(R,R)[13b]
3		60	84	(+)-(R,R)[13c]
4		74	93	(+)-(R,R)[13d]
5		61	93	(+)-(2S,3R)[13e]
6		41	93	(+)[j]
7		60	78[g]	(+)-(R,R)[13f]
8		80	93[g]	(+)-(R,R)[13g]
9		70	70[g]	(+)-(R,R)[13h]
10		84	87[g]	(+)-(R,R)[13i]
11		81	90[h]	(+)[j]
12		73	92 (92.1[e])	(+)-(R,R)[4a]
13		65	95 (92.2[e])	(-)-(R)[4a]
14		74	94 (95.2[e])	(-)[j]
15		69	91	(+)-(R,R)[4a]

[a] All reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (3 equiv), Oxone (5 equiv), and $NaHCO_3$ (15.5 equiv) in CH_3CN−aqueous EDTA (4×10^{-4} M) (∼1.5:1) (refs 7b and 10); the reactions were stopped after 2 h (for detail see supporting information). [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] Enantioselectivity was determined by ^{1}H NMR shift analysis of the epoxide products directly with $Eu(hfc)_3$. [d] Enantioselectivity remained unchanged (95% ee) when 0.5 and 0.25 equivs of chiral ketone were used except that the yields were lowered. [e] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [f] After recrystallization. [g] Enantioselectivity was determined by ^{1}H NMR shift analysis of the derived acetate with $Eu(hfc)_3$. [h] The epoxide was opened (NaOMe−MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ^{1}H NMR shift analysis of the resulting acetate with $Eu(hfc)_3$. [i] The absolute configurations were determined by comparing the measured optical rotations with the reported ones. [j] The absolute configuration was not determined.



Initial studies involving ketone **3** in the epoxidation of *trans*-stilbene revealed that while the yield of stilbene epoxide increased with the reaction time, the enantiomeric excess decreased. Upon examination, we determined that ketone **3**

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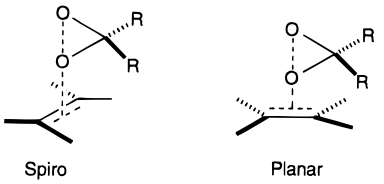

Figure 1. The spiro and planar transition states for the dioxirane epoxidation of olefins.

decomposed over time under the reaction conditions.[12] The decreased ee could be attributed to the epoxidation being catalyzed by an achiral or less enantioselective ketone resulting from the decomposition of ketone **3**. However, >95% ee could be achieved for stilbene oxide if the reaction was terminated in a short reaction time (2 h).

Encouraged by this result, we investigated the asymmetric epoxidation with a variety of olefins in order to explore the generality of this system. To maximize the enantiomeric excess, epoxidations were carried out using an excess of ketone **3** and a short reaction time (Table 1). The enantiomeric excesses are generally high for a wide range of olefins, in which a variety of functional groups are present. For example, the halide (entry 5) can be directly epoxidized and the resulting epoxide can be used for further transformations. Trisubstituted olefins are also good substrates for high selectivity. *It is very encouraging to note that high enantiomeric excess can be obtained with trans-7-tetradecene (entry 11), which suggests that this epoxidation may be general for simple unfunctionalized trans-olefins.*

It is of interest to understand the possible geometry of the transition state in dioxirane epoxidations. Two mechanistic extremes (planar and spiro) are presented in Figure 1.[14,15,6c] A spiro transition state was proposed by Baumstark, based on the observation that *cis*-olefins were more reactive than the corresponding *trans*-olefins for epoxidation using dimethyldioxirane.[14] His proposal came from analyzing steric effects in both transition states. Stereochemical analysis provides another valuable way to address this issue. The results in Table 1 provide valuable information about the reaction mode of the epoxidation by dioxiranes. If the reaction proceeds *via* a spiro mode, (*R*,*R*)-stilbene oxide is expected to be favored (spiro-1 *vs* spiro-2) (Figure 2). In contrast, (*S*,*S*)-stilbene oxide will be favored if the reaction proceeds *via* a planar mode (planar-2 *vs* planar-1). In the present study, it is found that (*R*,*R*)-stilbene oxide is produced predominately, which supports the spiro transition state. All the examples with known epoxide configurations in Table 1 are consistent with the spiro mode. Therefore, the stereochemical outcome of the reactions can be predicted with a reasonable level of confidence based on the spiro model.

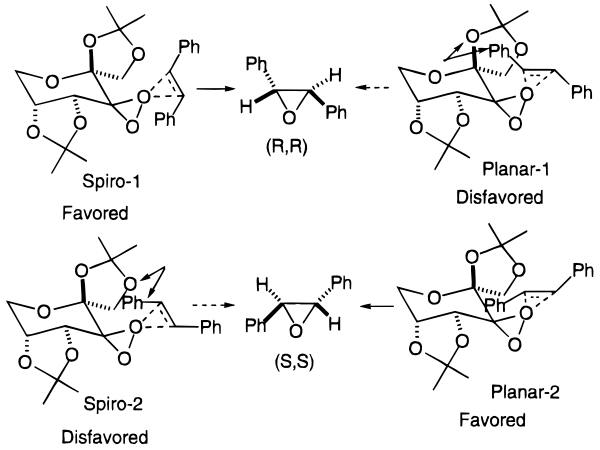

Figure 2. The spiro and planar transition states for *trans*-stilbene epoxidation catalyzed by ketone **3**.

In summary, we report a highly effective and mild asymmetric epoxidation for *trans*- and trisubstituted olefins using a fructose-derived ketone as catalyst and Oxone as oxidant. Both Oxone and the ketone catalyst are inexpensive. The enantioselectivity is very high in most cases studied. A variety of functional groups can be tolerated in the olefin substrates. *Most significantly, high enantioselectivity can be achieved for the epoxidation of unfunctionalized trans-olefins.* As a first step, we have revealed a promising structural element required for the ketone to induce the high enantioselectivity for the epoxidation. Future efforts will be devoted to the optimization of the ketone structure to enhance both enantioselectivity and stability of the ketone to make this process truly catalytic.

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Supporting Information Available: Experimental procedure for the *in situ* asymmetric epoxidation reaction, the NMR spectral and HPLC data for the determination of the enantiomeric excess of the formed epoxides, and the characterization data of the epoxides in Table 1 (22 pages). See any current masthead page for ordering and Internet access instructions.

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(12) We are currently investigating the possible decomposition pathways for ketone **3**.

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