Organo-Catalysis: Developing Ketone Catalysts for Asymmetric Epoxidation of Olefins

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Abstract: Dioxiranes are remarkably versatile oxidizing agents that show great potential for asymmetric synthesis, particularly asymmetric epoxidation of olefins. This article outlines some recent progress in this area from the author's laboratories.

Asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides. A variety of efficient methods have been developed.¹⁻⁵ Recently, chiral dioxiranes generated from ketones in situ have emerged as a class of remarkably effective agents for the epoxidation of olefins (Scheme 1), particularly for unfunctionalized *trans*-olefins, a long-standing challenge.^{6,7,8} Since the first chiral ketone reported by Curci in 1984,^{8a} this area has received intensive interest and a variety of chiral ketone catalysts have been investigated in a number of laboratories. A representative survey of chiral ketones is shown in Scheme 2. This account will briefly summarize some of the studies carried out in the author's laboratories.

Our studies on asymmetric epoxidation have focused on ketones possessing the following general features (Scheme 3): (1) the stereogenic centers are close to the reacting center, resulting in efficient stereochemical communication between substrate and catalyst; (2) the presence of a quaternary center or fused ring(s) α to the carbonyl group minimizes the epimerization of the stereogenic centers; (3) approach of an olefin to the reacting dioxirane can be controlled by sterically blocking one face or using a C_2 or pseudo C_2 symmetry element; (4) inductively withdrawing substituents are introduced to activate the carbonyl.

Based on this design, the fructose-derived ketone **1** was developed, and has been shown to be a highly effective epoxidation catalyst. Ketone **1** can be synthesized in two steps from D-fructose by ketalization and oxidation (Scheme 4).^{9,10,12} The enantiomer of ketone catalyst **1** (ketone **ent-1**) can be prepared in the same way from L-fructose, which can be prepared from readily available L-sorbose following a literature procedure.^{12,13} Ketone **ent-1** prepared by this way gives the same enantioselectivity for the epoxidation as ketone **1**.

The epoxidation with in situ generated dioxiranes is highly dependent on the reaction pH.^{14,8d} Ozone autodecomposes rapidly at high pH,^{15,16} thus leading to a low epoxidation efficiency. For this reason, ketone mediated epoxidations are typically carried out around pH 7. Initial epoxidations with ketone **1** were therefore conducted at pH 7-8, and high enantioselectivities (>90% ee) were obtained for a variety of *trans*-disubstituted and trisubstituted olefins.⁹ However, at this pH, a large amount of ketone was required to achieve good

conversion of substrate due to the rapid decomposition of the ketone. The possible decomposition pathway for ketone **1** was envisioned to be Baeyer-Villiger oxidation from interme-

Scheme 1

Scheme 2. Selected examples of chiral ketones reported.

Scheme 3

Scheme 4

Figure 1. X-ray structure of ketone **1** (ORTEP view).

Scheme 5

diate **2** (Scheme 5), although the corresponding lactone had not been isolated. It was hoped that this competing reaction (B.V.) could be suppressed by raising the pH to favor the formation of intermediate **3** and subsequently dioxirane **4**. It was also hoped that the autodecomposition of oxone at high pH could possibly be overridden if ketone **1** was sufficiently reactive.

Based on these considerations, the pH effect on the epoxidation of *trans*- β -methylstyrene was then studied.^{11,12} As shown in Figure 2, the pH displayed a profound effect on the substrate conversion, and the catalyst efficiency was indeed enhanced at higher pH. The conversion of *trans*- β -methylstyrene to its epoxide increased more than 10 fold from a lower pH (7-8) to a higher pH (>10) and the enantioselectivi-

Figure 2. Plot of the conversion of *trans*- β -methylstyrene against pH using ketone **1** (0.2 eq.) as catalyst in two solvent systems, H₂O-CH₃CN (1 : 1.5, V/V) (A), H₂O-CH₃CN-DMM (2 : 1 : 2, V/V) (B) (ref. 12).

Figure 3. Plot of the conversion of *trans*- β -methylstyrene against pH using acetone (3 eq.) as catalyst in H₂O-CH₃CN (1 : 1.5, V/V). Samples were taken at different reaction times for the determination of conversion, 0.5 h (A), 1.0 h (B), 1.5 h (C), 2.0 h (D) (ref. 12).

Figure 4. Plot of the conversion of *trans*- β -methylstyrene against pH using CF₃COCH₃ (0.05 eq) as catalyst and oxone as oxidant (ref. 18).

ty remained high (90-92% ee). This dramatic pH effect leads to a catalytic asymmetric epoxidation process, which significantly enhances the utility of the current epoxidation. The broad optimal pH range simplifies the experimental operation. The epoxidation is typically carried out at pH around 10.5, which can be conveniently achieved by adding either K₂CO₃ or KOH as the reaction proceeds. This catalytic procedure also required significantly less oxone, suggesting that ketone **1** was indeed reactive enough to compete with the

Scheme 6. Epoxidation of *trans*-disubstituted olefins with ketone **1** (ref. 12).

Scheme 7. Epoxidation of trisubstituted olefins with ketone **1** (ref. 12).

Scheme 8. Epoxidation of 2,2-disubstituted vinylsilanes with ketone **1** (ref. 19).

Scheme 9. Epoxidation of hydroxyalkenes with ketone **1** (ref. 20).

autodecomposition of oxone. A comparison study showed that the efficiency of the acetone and trifluoroacetone catalyzed epoxidations were generally enhanced as well at higher pH (Figures 3 and 4).^{12,17,18} A clearer understanding of the mechanistic consequence of the pH effect on ketone-catalyzed epoxidation awaits further studies.

The generality of this epoxidation was subsequently studied using a variety of olefins with a catalytic amount of

ketone **1** (typically 20-30 mol%). These results are summarized in Schemes 6-12. High enantioselectivities are obtained for a variety of unfunctionalized *trans*- and trisubstituted olefins (Schemes 6 & 7).¹² In particular, the high ee obtained with *trans*-7-tetradecene suggests that this epoxidation is quite general for simple *trans*-olefins.

Among other olefins, a variety of 2,2-disubstituted vinyl silanes can also be enantioselectively epoxidized (Scheme 8).¹⁹ Subsequent desilylation of the resulting epoxysilanes using TBAF provides easy access to 1,1-disubstituted terminal epoxides with high enantioselectivity. Hydroxyalkenes can be epoxidized nicely as well (Scheme 9).²⁰ This method is complementary to the Sharpless asymmetric epoxidation since homoallylic alcohols can be epoxidized with high ee's. Conjugated dienes can be regio- and enantioselectively epoxidized to provide vinyl epoxides with high ee's (Scheme 10).²¹ Monoepoxides are predominately produced if the amount of catalyst is properly controlled. The high selectivity of monoepoxidation over bisepoxidation could be due to the fact that the first epoxide introduced deactivated the remaining olefin by the inductive effect. For unsymmetrical dienes, the regioselectivity can be regulated by using both steric or electronic control. Conjugated enynes can be highly chemo- and enantioselectively epoxidized to produce chiral propargyl epoxides (Scheme 11).^{22,23}

Enol silyl ethers and esters can also be enantioselectively epoxidized to produce optically active α -hydroxy ketones and enol ester epoxides respectively (Scheme 12).^{24,25} The resulting chiral enol ester epoxides are versatile synthetic intermediates. Such an example is illustrated in Scheme 13.²⁴ One enantiomer of an epoxide could be converted into either enantiomer of α -hydroxy ketone. The epoxide derived from the enol acetate of propiophenone was hydrolyzed to (*R*)-2-hydroxy propiophenone 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 with an inversion of the stereogenic center. The resulting α -acetoxy ketone could be subsequently hydrolyzed to (*S*)-2-hydroxy propiophenone with $K_2CO_3/MeOH$. The enantiomeric excesses of both enantiomers could be enhanced to >99% by recrystallization.

It is also worthy of mentioning here that enol ester epoxides can readily rearrange to α -acyloxy ketones or aldehydes under acidic conditions. The availability of enantiomerically enriched enol ester epoxides reveals that this rearrangement can operate through two distinct pathways, one with retention of configuration and the other with inversion (Scheme 14).^{25,26} Competition between the two pathways depends on the nature of the acid catalyst. The duality of this rearrangement provides the flexibility to synthesize either enantiomer of an α -acyloxy ketone from one enantiomer of an enol ester epoxide by judicious choice of reaction conditions (Scheme 15).^{25,26}

In further studies, we have shown that racemic enol ester epoxides can be kinetically resolved using chiral Lewis acids through these rearrangement processes.²⁷ Among the Lewis acids studied, a (BINOL)₂-Ti system has been found to be particularly effective (Scheme 16). Good enantiomeric excess can be obtained for both the recovered enol ester epoxides and the rearranged α -acyloxy ketones. With this Ti catalyst, we have found that the rearrangement proceeds with inver-

Scheme 10. Epoxidation of dienes with ketone **1** (ref. 21).

Scheme 11. Epoxidation of enynes with ketone **1** (refs. 22 & 23).

Scheme 12. Epoxidation of enol silyl ethers and esters with ketone **1** (refs. 24 & 25).

Scheme 13

sion of configuration. The resulting mixture can be subsequently treated with *p*-TsOH to convert the remaining epoxide into the rearranged ketone product stereospecifically with retention of configuration. The overall result is that a racemic enol ester epoxide can be completely converted into an enantiomerically enriched α -acyloxy ketone using a catalytic amount of a chiral Lewis acid followed by a catalytic amount of an achiral Brønsted acid. These studies provide

Scheme 14

Scheme 15

Scheme 16

conv. %	93	44	8	16	32	61
ee %	92	61	65	67	86	87

Scheme 17

us efficient methods to prepare enantiomerically enriched α -acyloxy ketones, which are useful chiral building blocks and key structural units of many natural products.

Further studies with a variety of ketone catalysts showed that the catalytic properties of ketone catalysts were highly dependent on the precise nature of the ketone structure. As shown in Scheme 17, the rigid 5-membered ring spiro ketal of **1** was structurally better than the 6-membered cyclic ketal of **6** and the acyclic groups of **7** and **8** for both reactivity and enantioselectivity of the epoxidation.²⁸ Studies showed that the epoxidation was also largely affected by the size of the groups attached to the ketals. Generally speaking, the smaller the groups, the higher reactivity and selectivity (**1** vs **9**).²⁸ The fact that the carbocyclic analogue **10** gave lower conversion and ee than **1** suggests that the oxygen of the pyranose ring is beneficial to catalysis.²⁹ Studies also showed that 5-

membered ring ketones were less effective catalysts, owing to their facile Baeyer-Villiger oxidative decomposition caused by the ring strain associated with the 5-membered ring.²⁸

Regarding the ketone catalyzed asymmetric epoxidation, understanding the transition state is extremely valuable for predicting the stereochemistry of the reaction product and for designing new ketone catalysts. Figure 5 shows the two extreme transition state geometries (spiro and planar).^{30,31,32,6c,9,12,8f,81,33,34} Baumstark and coworkers found that a spiro transition state is likely to be operating based on the observation that *cis*-hexenes were 7-9 fold more reactive than the corresponding *trans*-hexenes for epoxidation using dimethyldioxirane.³⁰ Computational studies also show that the spiro transition state is the optimized transition state for oxygen atom transfer from dimethyldioxirane to ethylene.³²⁻³⁴ The favoring of a spiro transition state over a planar one could be due to the stabilizing interaction of an oxygen lone pair with π^* orbital of the alkene in the spiro transition state (stereoelectronic origin). Such stabilizing orbital interaction can not be achieved geometrically in the planar transition state (Figure 5).^{32,33}

Analyzing the stereochemistry of epoxides produced by chiral dioxiranes provides the opportunity for further exploration of the transition state. Our studies show that the epoxidation of *trans*- and trisubstituted olefins with ketone **1** proceeds through spiro **A** and the main competing mode is planar **B** (Figure 6).^{9,12,18-25} The extent of the involvement of the planar transition state is dependent on the substituents on the olefins.¹² Generally speaking, higher ee can be obtained by decreasing the size of R_1 (favoring spiro **A**) and increasing the size of R_3 (disfavoring planar **B**).

Further analysis of the transition state model led us to believe that certain racemic olefins might be able to be kinetically resolved. To this end, a number of 1,6 and 1,3-disubstituted cyclohexenes could be efficiently resolved with ketone **1** (Scheme 18).³⁵ Transition states **C** and **D** in Figure 7 represents the spiro transition states for the epoxidation of each enantiomer of a racemic 1,6-disubstituted cyclohexene using ketone **1** as catalyst. Transition state **C** is expected to be favored compared to transition state **D**, in which there is a destabilizing steric interaction between R_2 and one of the dioxirane oxygens. This kinetic resolution provides a valuable way to prepare certain chiral intermediates and further validates the transition state analysis.

The fructose-derived ketone **1** is an effective epoxidation catalyst and gives high ee's for a variety of *trans*- and trisubstituted olefins. However, epoxidation of *cis*- and terminal olefins using this ketone led to rather poor enantioselectivity (Scheme 19).^{12,36} For example, epoxidation of *cis*- β -methylstyrene and styrene using ketone **1** gave only 39% and 24% ee, respectively. The low ee obtained indicates that the ketone catalyst does not have the necessary structural environment to differentiate between the phenyl and methyl (or hydrogen) groups of the olefin in the transition states spiro **E** and **F** (Scheme 20).

During our continuing studies of ketone catalysts, ketone **11**, a nitrogen analogue of **1**, was found to be effective catalyst for the epoxidation of *cis*-olefins. High ee's have been obtained for a number of both acyclic and cyclic olefins (Scheme 21).³⁶ The epoxidation was stereospecific with no isomerization observed in the epoxidation of acyclic systems.

Figure 5. The spiro and planar transition states for the dioxirane epoxidation of olefins.

Figure 6. The spiro and planar transition states for the epoxidation with ketone **1**.

Scheme 18

Figure 7. The spiro ts for the epoxidation of 1,6-disubstituted cyclohexenes with **1**.

Scheme 19. Epoxidation of *cis*- and terminal olefins with ketone **1** (refs. 12 & 36).

Scheme 20

Also ketone **11** provides encouragingly high ee's for certain terminal olefins.³⁷ Generally, ketone **11** gives poorer enantioselectivities than **1** for *trans*- and trisubstituted olefins.

Ketones **1** and **11** use a fused ring and a quaternary carbon α to the carbonyl group, placing the stereogenic centers close to the reacting center and minimizing potential epimerization of chiral elements (Scheme 22). We also investigated ketones containing two fused rings at each side of the carbonyl group (Scheme 22). As member of this class of ketones, pseudo C_2 symmetric ketone **12** was prepared from quinic acid (Scheme 23).³⁸ Some selected epoxidation examples with ketone **12** ($R = CMe_2OH$) are shown in Scheme 24. Ketone **12** is a very active catalyst, with only a small amount (5-10 mol%) required to achieve good conversion. Certain electron deficient olefins can also be epoxidized, indicating that the dioxirane is very electrophilic. Generally speaking, ketone **12** gives lower enantioselectivities than **1** for *trans*- and trisubstituted olefins.

The ketals or oxazolidinone in ketones **1**, **11**, and **12** are placed at α positions of the carbonyl. Further studies with ketones **13**, **14**, and **15** (Scheme 25) showed that moving the ketal from the α to β positions led to lower ee for the epoxidation, suggesting that efficient stereochemical communication between the substrate and the catalyst requires the stereogenic centers being close to the reacting center (carbonyl).^{29,39}

Potassium peroxomonosulfate ($KHSO_5$) is typically used as oxidant to generate dioxiranes (Scheme 26).^{40,41,42} The formation of dioxiranes for a synthetic purpose using substantially different oxidants is largely unexplored. It is particularly of interest whether hydrogen peroxide (H_2O_2) can be used as oxidant, since hydrogen peroxide has a high active oxygen content and its reduction product is water.⁴³ Our recent study with the fructose-derived ketone **1** showed that indeed H_2O_2 could be used as primary oxidant in combination with a nitrile (Scheme 27).^{44,45} Under these conditions, peroxyimide acid **20** (an analogous intermediate of Payne oxidation⁴⁶) is likely to be the active oxidant. Among various

Scheme 21. Epoxidation of *cis*- and terminal olefins with ketone **11** (refs. 36 & 37).

Scheme 22

Scheme 23

Scheme 24. Epoxidation of olefins with ketone **12** ($R = CMe_2OH$) (ref. 38).

Scheme 25

Scheme 26

nitriles tested, CH_3CN and CH_3CH_2CN are of choice in terms of both conversion and enantioselectivity (Scheme 28).⁴⁵ High yields and ee's have been obtained for a variety of olefins (Scheme 29).⁴⁵ This epoxidation system proceeds under mild conditions while requiring less solvents to be used in the reaction. In addition to ketone **1**, some other ketones have also been found to be effective catalysts using the $RCN-H_2O_2$ system. For example, high yields of epoxides can be obtained when 10-30% trifluoroacetone is used as catalyst.¹⁸

Scheme 27

RCN	Conv. (%)	ee (%)
CH ₃ CN	94	93
CH ₃ CH ₂ CN	92	94
CH ₃ CH ₂ CH ₂ CN	27	94
<i>t</i> -BuCN	4	93
PhCN	50	92
Cl ₃ CCN	11	13

Scheme 28

Scheme 29. Epoxidation of olefins with ketone **1** using H₂O₂ (ref. 45).

In conclusion, during the past few years, chiral ketone-catalyzed asymmetric epoxidation has received intensive interest. A variety of chiral ketones have been investigated in a number of laboratories, and significant progress has been made in the field. The challenge for developing efficient ketone catalyst lies in delicately balancing the sterics and electronics of the chiral control elements around the carbonyl group. The studies in our laboratories have shown that the fructose-derived ketone (**1**) is highly general and enantioselective catalyst for the epoxidation of *trans*- and trisubstituted olefins.⁴⁷ Recently, we have also found that ketone **11**, a nitrogen analogue of **1**, gives high enantioselectivity for a number of *cis*-olefins and useful levels of enantioselectivity for certain ter-

minal olefins. Further studies of ketone structure and catalytic properties will certainly facilitate the development of more efficient ketone catalysts.

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- 42) The formation of dioxiranes have also been reported when a ketone reacts with an oxidant such as CH_3COOOH , HOF, and ONOO- (a) for CH_3COOOH see: Murray, R.W.; Ramachandran, V. *Photochem. and Photobiol.* **1979**, *30*, 187. (b) for HOF see: Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169. (c) for ONOO- see: Yang, D.; Tang, Y.-C.; Chen, J.; Wang, X.-C.; Bartberger, M.D.; Houk, K.N.; Olson, L. *J. Am. Chem. Soc.* **1999**, *121*, 11976.
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PROFILE

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