

## ARTICLES

## Organocatalytic Asymmetric Epoxidation of Olefins by Chiral Ketones

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## ABSTRACT

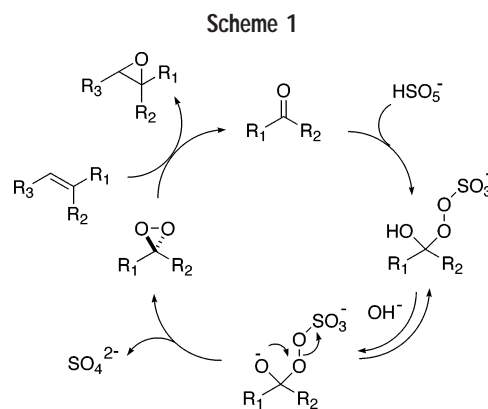
Chiral ketones have been shown to be effective organocatalysts for asymmetric epoxidation of olefins with broad substrate scope. High enantioselectivity has been obtained for a wide variety of trans and trisubstituted olefins, as well as a number of cis olefins, with encouragingly high ee's for some terminal olefins. The stereochemical outcome of the reaction can be rationalized by a spiro transition state model.

## Introduction

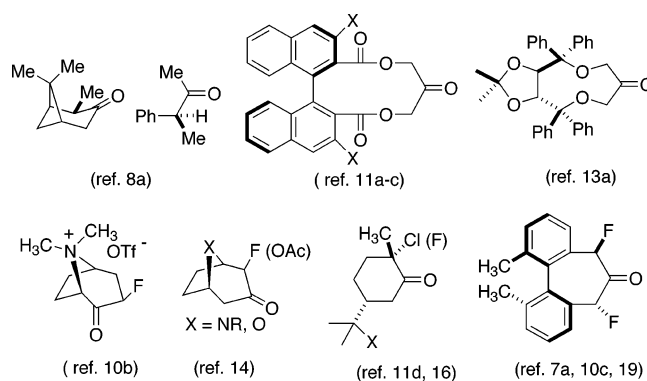
Optically active epoxides are highly versatile intermediates that can be converted into a wide variety of enantiomerically enriched molecules. Various useful methods have been developed for the preparation of chiral epoxides.<sup>1,2</sup> Asymmetric epoxidation of olefins provides a powerful approach to the synthesis of such epoxides. Great progress has been achieved for the epoxidation of allylic alcohols,<sup>3</sup> the metal-catalyzed epoxidation of unfunctionalized olefins (particularly for conjugated cis and trisubstituted olefins),<sup>4</sup> and the nucleophilic epoxidation of electron-deficient olefins.<sup>5</sup> In recent years, chiral dioxiranes have been shown to be powerful agents for asymmetric epoxidation of olefins,<sup>6,7</sup> particularly for unfunctionalized trans and trisubstituted olefins, which has been a long-standing problem.

Dioxiranes are usually generated from Oxone (potassium peroxomonosulfate) and ketones (Scheme 1).<sup>6</sup> The epoxidation can be performed using either isolated dioxiranes or dioxiranes formed in situ. In principle, when the dioxirane is formed in situ, the ketone can be used as catalyst since it can be regenerated upon epoxidation. Furthermore, asymmetric epoxidation could also be realized if a chiral ketone catalyst is used. The first asymmetric epoxidation using a chiral ketone was reported by Curci in 1984.<sup>8</sup> During the past few years, various chiral ketones have been studied and reported by a number of labora-

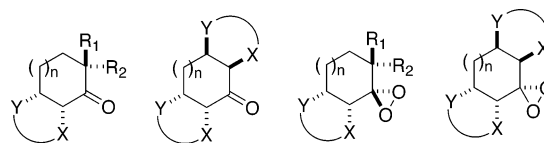
Yian Shi is currently Professor of Chemistry at Colorado State University. He was born in Jiangsu, China, in 1963. Upon receiving his B.Sc. degree in chemistry from Nanjing University in 1983 and M.Sc. degree from University of Toronto in 1987 under the supervision of Professor I. W. J. Still, he pursued his doctoral studies at Stanford University under the direction of Professor Barry M. Trost and obtained his Ph.D. in 1992. After his postdoctoral studies in Professor Christopher Walsh's group at Harvard Medical School from 1992 to 1995, he joined Colorado State University as assistant professor in 1995 and was promoted to associate professor in 2000 and professor in 2003.



## Scheme 2. Some Examples of Chiral Ketones Reported



## Scheme 3

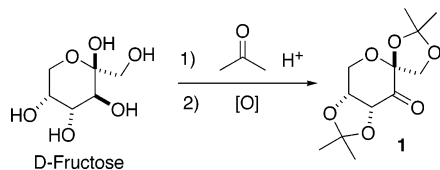


tories (Scheme 2).<sup>8–23</sup> This account describes our studies on this subject.

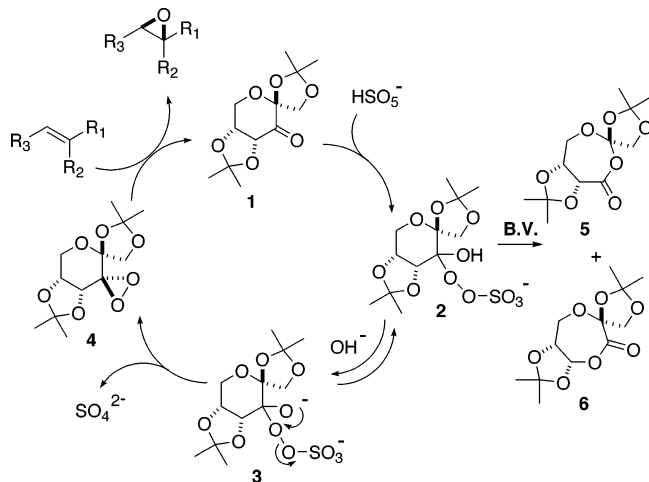
## Initial Design of Ketone Catalysts

Our search for ketone catalysts was initially based on the following general themes (Scheme 3): (1) the chiral control element is placed in close proximity to the reacting carbonyl to maximize the stereochemical interaction between substrate and catalyst; (2) a fused ring is introduced  $\alpha$  to the carbonyl group to minimize the potential epimerization of the stereogenic centers caused by the acidity of the  $\alpha$  proton; (3) the approach of an olefin to the reacting dioxirane is controlled by sterically blocking one face or by a  $C_2$  or pseudo- $C_2$  symmetric element; (4) electron-withdrawing substituents are introduced to activate the carbonyl. On the basis of these considerations, fructose-derived ketone **1**, readily prepared in two steps from D-fructose (Scheme 4), has been developed into a highly enantioselective epoxidation catalyst.<sup>24–27</sup>

Scheme 4



Scheme 5



## The pH Effect on Epoxidation

The epoxidation with in situ generated dioxiranes often requires careful control of the reaction pH.<sup>10a,28</sup> Ketone-mediated epoxidations are usually performed at pH 7–8 since higher pH could lead to the rapid autodecomposition of Oxone,<sup>29–31</sup> thus giving poor conversion for the epoxidation. When epoxidations with ketone 1 were initially conducted at pH 7–8, high enantioselectivities (>90% ee) were obtained for a variety of trans and trisubstituted olefins.<sup>24</sup> However, under these reaction conditions, an excess amount of ketone 1 was needed for good conversion of substrate due to the rapid decomposition of the ketone. The next key issue was to reduce the ketone decomposition, thus lowering the catalyst loading. Analysis of the reaction cycle implied that a Baeyer–Villiger oxidation from intermediate 2 could be one of the possible decomposition pathways for ketone 1, although the corresponding lactones had not been isolated, possibly due to hydrolysis in situ (Scheme 5). At this point, it was felt that raising the reaction pH could be beneficial for the epoxidation since a higher pH could facilitate the formation of anion 3 and subsequent formation of dioxirane 4, thus suppressing the competing Baeyer–Villiger oxidation. At the same time, it was also hoped that ketone 1 would be sufficiently reactive to override the autodecomposition of Oxone at high pH.

On the basis of these assumptions and considerations, the pH effect on the epoxidation of *trans*- $\beta$ -methylstyrene with ketone 1 was then studied.<sup>25,26</sup> As shown in Figure 1, pH had a dramatic effect on the reaction, and raising the reaction pH indeed enhanced the catalyst efficiency. With 20 mol % ketone 1, the conversion of *trans*- $\beta$ -methylstyrene increased from <10% at pH 7–8 to around 80% at pH >10. Importantly, the enantioselectivity remained high

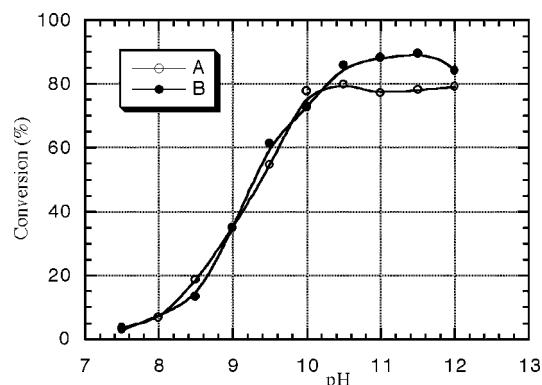
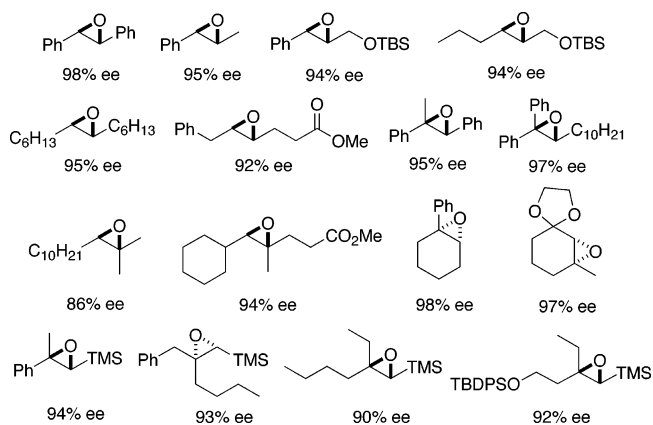
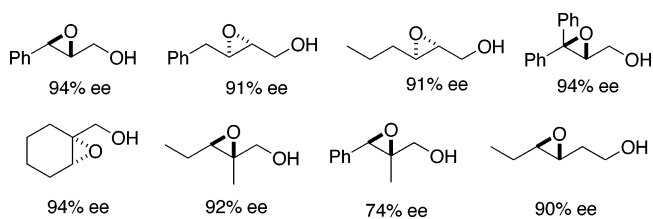


FIGURE 1. Plot of the conversion of *trans*- $\beta$ -methylstyrene against pH using ketone 1 (0.2 equiv) as catalyst in two solvent systems: (A) H<sub>2</sub>O–CH<sub>3</sub>CN (1:1.5, v/v); (B) H<sub>2</sub>O–CH<sub>3</sub>CN–DMM (2:1:2, v/v; ref 26).

Scheme 6. Epoxidation Examples of Trans and Trisubstituted Olefins with Ketone 1 (Refs 26 and 34)

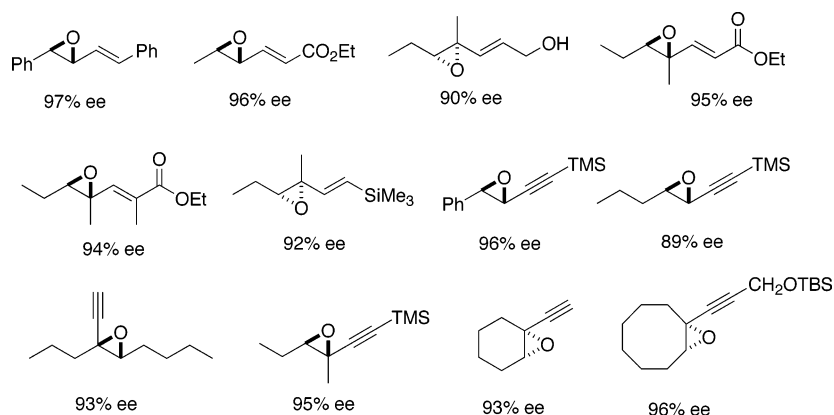


Scheme 7. Epoxidation Examples of Hydroxyalkenes with Ketone 1 (Ref 35)



(90–92% ee) at high pH. Performing the reaction at higher pH greatly reduces the amount of catalyst needed and leads to a catalytic asymmetric epoxidation process. The epoxidation is typically carried out around pH 10.5, and the reaction pH can be controlled by adding either K<sub>2</sub>CO<sub>3</sub> or KOH as the reaction proceeds. Furthermore, this catalytic procedure also requires substantially less Oxone (~30% of the previous amount), suggesting that ketone 1 is indeed reactive enough to compete with the autodecomposition of Oxone. In comparative studies, it was shown that the conversion also generally increased at higher pH when acetone and trifluoroacetone were used, although optimal pH varied with ketones.<sup>26,32,33</sup> A clearer mechanistic understanding of the pH effect on ketone-catalyzed epoxidation awaits further studies.

Scheme 8. Epoxidation Examples of Conjugated Dienes and Enynes with Ketone 1 (Refs 36 and 37)

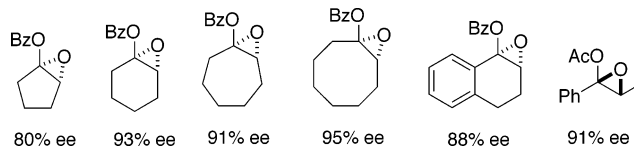


## Substrate Scope of Trans and Trisubstituted Olefins

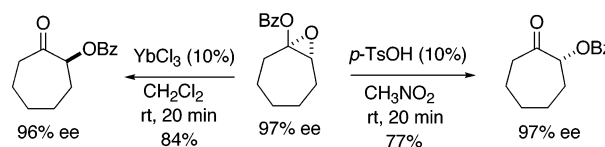
The generality of this epoxidation was subsequently investigated using a variety of olefins with a catalytic amount of ketone **1** (typically 20–30 mol %). High enantioselectivities are obtained for a variety of trans and trisubstituted olefins (Scheme 6).<sup>26</sup> Importantly, the high ee obtained with *trans*-7-tetradecene suggests that this epoxidation is quite general for simple trans olefins. The epoxidation conditions are also compatible with various functional groups such as ethers, ketals, esters, etc. (Scheme 6). A variety of 2,2-disubstituted vinyl silanes can also be enantioselectively epoxidized (Scheme 6).<sup>34</sup> Desilylation of the resulting epoxysilanes with tetrabutylammonium fluoride (TBAF) provides easy access to optically active 1,1-disubstituted terminal epoxides. The epoxidation can also be extended to allylic, homoallylic, and bishomoallylic alcohols with good enantioselectivity (Scheme 7).<sup>35</sup> Conjugated dienes can be regioselectively epoxidized to provide vinyl epoxides with high ee's (Scheme 8).<sup>36</sup> Monoepoxides are predominately produced if a proper amount of catalyst is used, since epoxidation of the remaining olefin is deactivated by the first epoxide introduced. The regioselectivity for the epoxidation of unsymmetrical dienes can be regulated by using steric or electronic effects or both. For conjugated enynes, the olefin can be chemo- and enantioselectively epoxidized to produce optically active propargyl epoxides (Scheme 8).<sup>37</sup>

Enol silyl ethers can be epoxidized to give enantioselectively enriched  $\alpha$ -hydroxy ketones,<sup>38a,39</sup> but the enantioselectivity is generally moderate, except for a few substrates. In addition, certain  $\alpha$ -hydroxy ketones are prone to racemization or dimerization. Enol esters, however, have been found to be more effective substrates for the current epoxidation. When a number of enol esters are epoxidized, the corresponding enol ester epoxides are obtained with high ee's (Scheme 9).<sup>38</sup> The resulting chiral enol ester epoxides can undergo stereoselective rearrangement to generate optically active  $\alpha$ -acyloxy ketones under acidic or thermal conditions.<sup>38,40,41</sup> As shown in Scheme 10, in some cases one enantiomer of an epoxide can be converted into either enantiomer of the  $\alpha$ -acyloxy ketones by judicious choice of reaction conditions.<sup>38,40</sup> In

Scheme 9. Epoxidation Examples of Enol Esters with Ketone 1 (Ref 38)



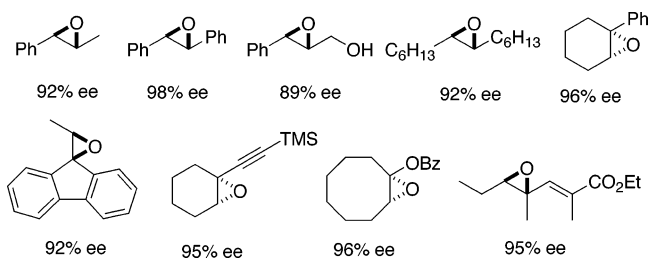
Scheme 10



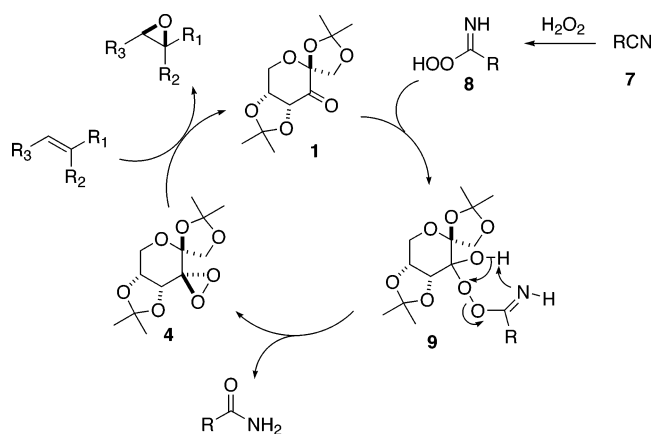
short, both the ready availability of ketone **1** and its high enantioselectivity for a wide variety of trans and trisubstituted olefins display its potential for practical use. The utilization of the ketone **1**-mediated epoxidation process has been reported by other researchers.<sup>42</sup>

## Hydrogen Peroxide as Primary Oxidant

Potassium peroxomonosulfate (KHSO<sub>5</sub>) is effective for the generation of dioxiranes and is almost exclusively used as oxidant for ketone-mediated epoxidations (Scheme 1). The ketone-mediated epoxidation using different oxidants has been largely unexplored. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is a particularly attractive oxidant due to its high active oxygen content with its reduction product being water. Studies have shown that a combination of hydrogen peroxide and a nitrile provides an effective system for epoxidation with a catalytic amount of ketone **1**.<sup>43,44</sup> Among nitriles investigated, CH<sub>3</sub>CN and CH<sub>3</sub>CH<sub>2</sub>CN were found to be the most effective for the epoxidation. A variety of olefins can be epoxidized in good yields and high enantioselectivity with CH<sub>3</sub>CN–H<sub>2</sub>O<sub>2</sub> (Scheme 11).<sup>44</sup> This epoxidation system proceeds under mild conditions and requires less solvent. Hydrogen peroxide is likely to be activated by the nitrile to form peroxyimidic acid **8** (an analogous intermediate of Payne oxidation<sup>45</sup>), which then reacts with the ketone to generate the dioxirane (Scheme 12). The RCN–H<sub>2</sub>O<sub>2</sub> system is also effective for some other ketones. For example, high yields of epoxides can be obtained when 10–30% trifluoroacetone is used as catalyst.<sup>33</sup>

Scheme 11. Epoxidation Examples of Olefins with Ketone 1 (0.1–0.3 equiv) Using CH<sub>3</sub>CN–H<sub>2</sub>O<sub>2</sub>

Scheme 12



## Transition State Analysis

Elucidation of the epoxidation mode of the dioxirane could provide valuable insights for predicting the stereochemical outcome of the reaction and designing new ketone catalysts. Figure 2 shows the two extreme transition state geometries (spiro and planar) for the epoxidation with dioxiranes.<sup>6c,d,11b,c,24,26,46–51</sup> Baumstark and co-workers observed that the epoxidation of cis hexenes with dimethyldioxirane occurred 7–9 times faster than that for the corresponding trans hexenes and proposed that the epoxidation rate difference was consistent with a spiro transition state being favored.<sup>46</sup> Computational studies also show that the spiro transition state is favored for the epoxidation of ethylene with dimethyldioxirane, presumably due to the stabilizing interaction of an oxygen lone pair with the  $\pi^*$  orbital of the alkene in the spiro transition state (such an orbital interaction is not geometrically feasible in the planar transition state) (Figure 2).<sup>47–49</sup>

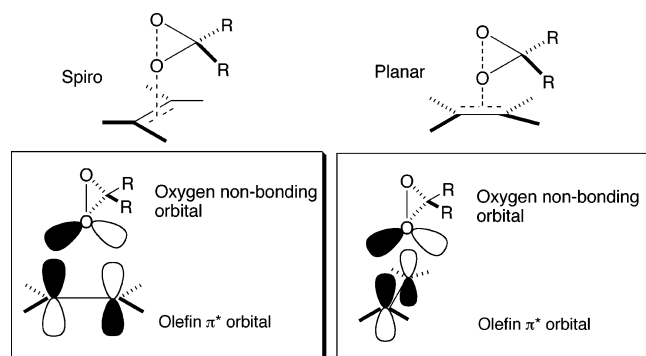


FIGURE 2. The spiro and planar transition states for the dioxirane epoxidation of olefins.

Analysis of the stereochemistry of the epoxide produced by chiral dioxiranes provides the opportunity for further understanding of the transition state. The corresponding dioxirane of ketone 1 has two diastereomeric oxygens, and the equatorial oxygen is likely to be sterically more accessible for olefin approach. Among possible spiro and planar transition states for the epoxidation with ketone 1,<sup>24,26</sup> spiro B–D and planar F–H are disfavored by destabilizing steric interactions (Figure 3). Spiro A and planar E are the two sterically favored transition states. Our studies show that the epoxidation of trans and trisubstituted olefins with ketone 1 proceeds mainly through spiro A, planar E being the major competing transition state.<sup>24–26,34–38</sup> Because spiro A and planar E result in opposite configurations of the epoxide product, factors influencing the competition of these two transition states would consequently affect the ee of the epoxide (Figure 4). The extent of involvement of planar E is subject to the electronic and steric nature of the substituents on the olefins. Higher ee's are usually obtained when the reacting alkenes are conjugated with groups, such as phenyl, alkene, or alkyne, since these groups can lower the energy of the  $\pi^*$  orbital of the reacting alkene and consequently enhance the stabilizing secondary orbital interaction, thus favoring spiro A. With regard to the steric effect, generally higher ee can be obtained by decreasing the size of R<sub>1</sub> (favoring spiro A), increasing the size of R<sub>3</sub> (disfavoring planar E) or both. Subsequent kinetic resolution study of racemic olefins with ketone 1 also validates the transition state model.<sup>52</sup>

## Structural Studies of Ketones on Catalysis and Substrate Scope

To further understand the structural requirement for ketone catalysts, a variety of ketone catalysts were prepared and investigated. Studies show that the exact nature of the ketone structure is important for catalytic properties. As shown in Scheme 13, the rigid five-membered spiro ketal of 1 was found to be better than the six-membered cyclic ketal of 10 and the acyclic groups of 11 and 12 for both reactivity and enantioselectivity of the epoxidation.<sup>53</sup> The size of the groups attached to the ketals was also shown to be important. Generally speaking, the smaller the group is, the higher the reactivity and selectivity become (1 vs 13).<sup>54</sup> The oxygen of the pyranose ring was found to be beneficial to catalysis.<sup>54</sup> The carbocyclic analogue 14 gave lower conversions and ee's than 1 (Scheme 13). The replacement of the oxygen with a carbon could have conformational and electronic effects on the catalyst.<sup>54</sup>

To further understand factors influencing the stability and reactivity of the ketone and to develop more robust ketone catalysts, the fused ketal of ketone 1 was replaced with a more electron-withdrawing oxazolidinone to reduce the presumed Baeyer–Villiger decomposition. The resulting ketone 15 was indeed found to be highly active (Scheme 14), giving good yields and enantioselectivities for a variety of olefin substrates.<sup>55</sup> For example, 100% conversion and 88% ee were obtained for *trans*- $\beta$ -meth-

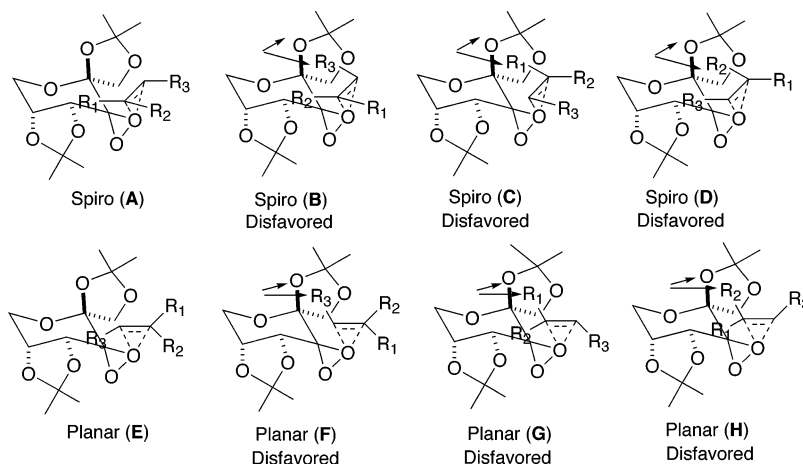
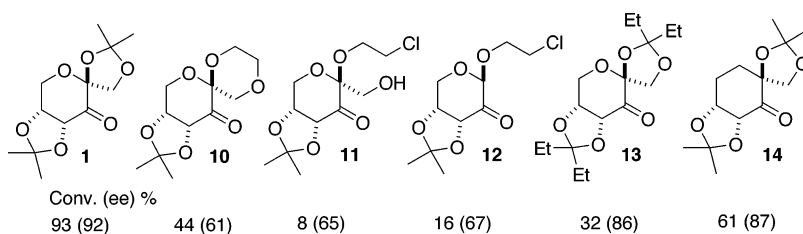
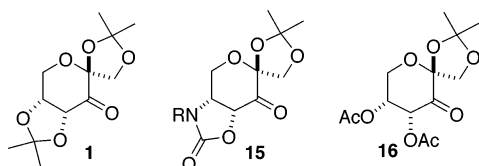


FIGURE 3. Possible spiro and planar transition states for the epoxidation with ketone **1**.

### Scheme 13. Asymmetric Epoxidation of *trans*- $\beta$ -Methylstyrene



### Scheme 14



ylstyrene with 5 mol % of **15**. In the case of 1-phenylcyclohexene, the epoxide was obtained with 93% yield and 97% ee using 2 mol % of the ketone. The information gained from this study is helpful for the further understanding of the ketone-catalyzed epoxidation and for the design of more efficient catalysts.

Being electrophilic in nature, dioxiranes epoxidize electron-deficient olefins sluggishly. When the epoxidation is slow, the dioxirane is consumed unproductively by reacting with Oxone to form the corresponding ketone, by self-decomposition, or both. A catalyst for this class of olefin needs to be highly active and enantioselective. Ketone **16**, readily available from **1**, was found to be effective for the epoxidation of  $\alpha,\beta$ -unsaturated esters.<sup>56</sup> High ee's and good yields can be obtained for a variety of  $\alpha,\beta$ -unsaturated esters using 20–30 mol % ketone **16** (Scheme 15).

While ketone **1** gives high ee's for a variety of *trans* and trisubstituted olefins, this epoxidation is not effective for

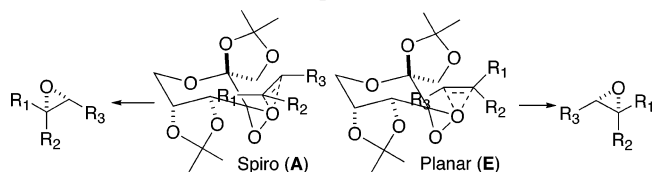
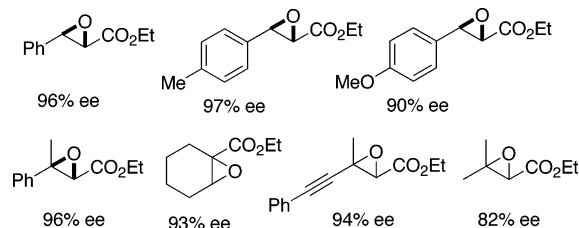
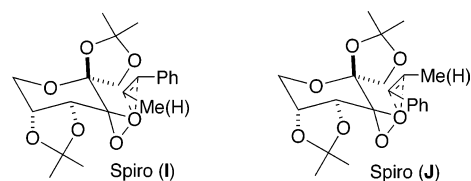


FIGURE 4. Competing spiro (A) and planar (E) transition states for the epoxidation with ketone **1**.

### Scheme 15. Epoxidation of $\alpha,\beta$ -Unsaturated Esters with Ketone **16** (Ref 56)



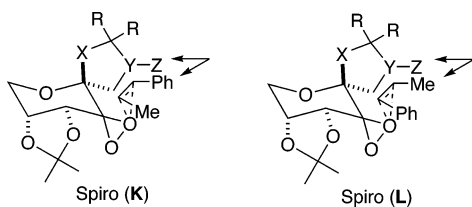
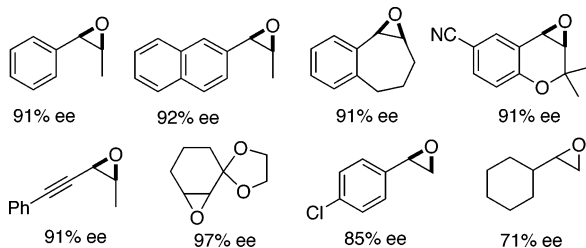
### Scheme 16



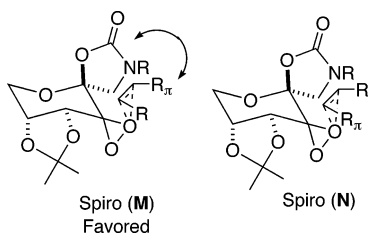
*cis* and terminal olefins.<sup>26,57</sup> For example, only 39% ee and 24% ee were obtained for *cis*- $\beta$ -methylstyrene and styrene with ketone **1**. As shown in the two main competing transition states spiro **I** and **J** (Scheme 16), the phenyl and methyl (or hydrogen) groups of the olefin cannot be effectively differentiated, thus giving poor enantioselectivity. Since the spiro ketal of ketone **1** is in close proximity to one of the substituents on the reacting olefin in the transition state, it was envisioned that replacement of the spiro ketal by other moieties would create an environment in which the olefin substituents could be sufficiently differentiated sterically, electronically, or both (Scheme 17).

Along this line, oxazolidinone-containing ketone **17** was examined and was found to be effective for the epoxidation of *cis* olefins.<sup>57–60</sup> High ee's have been obtained for a

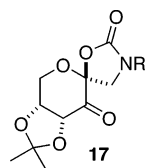
Scheme 17

Scheme 18. Epoxidation of Cis and Terminal Olefins with Ketone **17** (R = Boc; Refs 57–59)

Scheme 19



number of both acyclic and cyclic olefins (Scheme 18).<sup>57,59</sup> The epoxidation was stereospecific with no isomerization observed in the epoxidation of acyclic systems. Also, ketone **17** provides encouragingly high ee's for certain terminal olefins, particularly styrenes.<sup>58,59</sup> Overall the substrate scope of ketone **17** is complementary to that of ketone **1**.



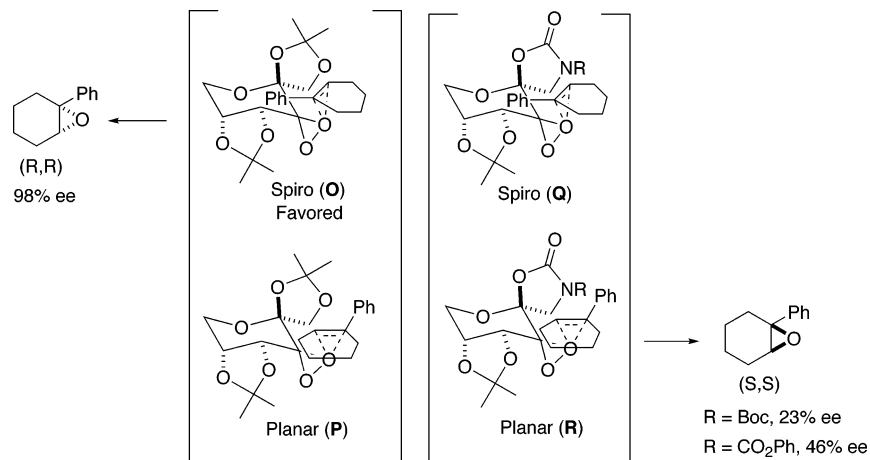
The origin of stereodifferentiation for ketone **17** for cis and terminal olefins is rather intriguing and may involve electronic interactions. Studies show that there appears to be an attraction between the  $R_\pi$  group of the olefin and the oxazolidinone of the ketone (Scheme 19).<sup>57–59</sup> As a result, groups with  $\pi$  systems ( $R_\pi$ ) could be significantly differentiated from those without  $\pi$  electrons (R), leading to high enantioselectivity for the reaction. Studies with *N*-aryl-substituted oxazolidinone-containing ketones show that the attractive interaction can be strengthened by a group that withdraws electrons from the oxazolidinone through conjugation.<sup>61</sup>

The above attractive interaction is also revealed in the epoxidation of 1-phenylcyclohexene. For example, when the epoxidation of 1-phenylcyclohexene was carried out with ketone **1**, the reaction predominately proceeded via spiro **O**, giving the epoxide with (*R,R*) configuration in 98% ee (Scheme 20).<sup>26</sup> However, when the epoxidation was carried out with ketone **17**, the reaction outcome varied dramatically with the substituents on the nitrogen of the ketone. In some cases, the (*S,S*) isomer was obtained, suggesting that planar **R** eventually became a major transition state. The favoring of planar **R** is consistent with the attractive interaction between the Ph group and the oxazolidinone in this transition state.

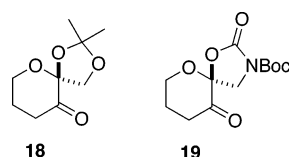
In another study, the epoxidation of 2,2-dimethylstyrene was carried out with ketones **18** and **19** (Scheme 21).<sup>59</sup> The removal of the fused ketals in these ketones encouraged the competing epoxidation pathway with the axial oxygen of the dioxirane, thus lowering enantioselectivity. Indeed, only 3% ee was obtained with ketone **18**, suggesting that there is little preference for spiro **S** over spiro **T**. In stark contrast, 78% ee was obtained with ketone **19**, suggesting spiro transition state **U** is greatly favored over spiro **V** due to the attraction between the Ph group and the oxazolidinone in spiro **U** (Scheme 22). At this moment, the exact nature of the interaction between  $R_\pi$  and the oxazolidinone is not clear and awaits further study. Synthetically, it is anticipated that the substrate scope of ketone **17** will be further expanded.

A similar transition state analysis could also be applied to terminal olefins such as styrenes (Scheme 23).<sup>58,59,61</sup>

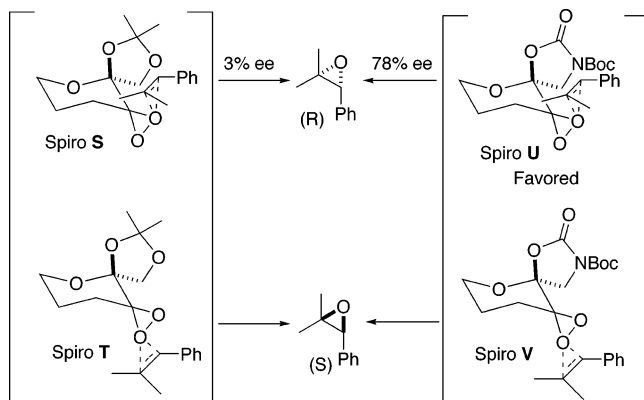
Scheme 20



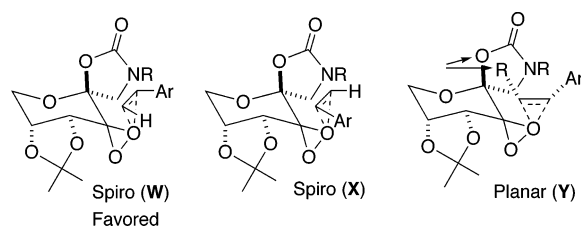
Scheme 21



Scheme 22



Scheme 23



Spiro transition state **W** is expected to be the major transition state. Compared to cis olefins, one difference is that planar transition state **Y** could also be operating ( $R = H$ ). On the other hand, the corresponding planar **Y** would be less feasible for cis olefins due to the steric effect, which could explain why higher ee's were obtained for cis olefins than terminal olefins with ketone **17**. Reducing the competition from planar **Y** is important to further improve the enantioselectivity for terminal olefins.

## Summary and Outlook

Chiral ketone-catalyzed asymmetric epoxidation has received intensive interest since the first chiral ketone-mediated epoxidation reported by Curci in 1984.<sup>8</sup> However, discovering highly enantioselective chiral ketone catalysts has proven to be challenging due to a number of undesired processes that compete with the catalytic cycle of the epoxidation as well as various conflicting factors.<sup>62</sup> The development of an efficient ketone catalyst thus requires delicately balancing the sterics and electronics of the chiral control elements around the carbonyl group, a task that is not at all trivial.

During the past few years, a variety of chiral ketones have been investigated in a number of laboratories, and significant progress has been made in the field. Chiral ketones have been shown to be effective organocatalysts for asymmetric epoxidation of olefins. A few favorable features for the ketone-catalyzed epoxidation are worth

noting: (1) The substrate scope appears to be very broad. For example, fructose-derived ketone **1** is found to be a highly general and enantioselective catalyst for the epoxidation of trans and trisubstituted olefins. Recent studies show that ketone **17**, a nitrogen analogue of **1**, gives high enantioselectivity for a number of cis olefins and useful levels of enantioselectivity for certain terminal olefins. It can be expected that the substrate scope will be further expanded. (2) The spiro transition state model allows one to rationalize and predict the stereochemical outcome for various olefin systems with a reasonable level of confidence. (3) The epoxidation conditions are mild and environmentally friendly. Water is used as cosolvent. (4) The workup is easy. In many cases, the epoxide can be obtained by simple extraction of the reaction mixture with hexane, leaving the ketone catalyst in the aqueous phase. The epoxidation is also amenable to a large scale. In summary, the ketone-catalyzed asymmetric epoxidation provides a viable synthetic method. Additional optimization of the reaction process and development of new ketone catalysts will bring further improvement.

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