Ketone-Catalyzed Asymmetric Epoxidation Reactions

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Received October 9, 2003

ABSTRACT
This Account summarizes our efforts in developing organic ketone catalysts for enantioselective and diastereoselective epoxidation of olefins. We have developed an efficient and general protocol for epoxidation of olefins using dioxiranes generated in situ from activated ketones and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in a homogeneous aqueous solvent system. We have also developed chiral ketone catalysts for highly enantioselective epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins. Excellent diastereoselectivities have been achieved for epoxidation of substituted cyclohexenes with ketone catalysts.

Introduction

Epoxides are an important class of functional groups that are widely employed in organic synthesis. Many natural products such as triptolide, epothilones, and cryptophycin A possess epoxide units as essential structural moieties for their biological activities (Figure 1). Moreover, epoxides are believed to be key intermediates in the biosynthesis of many natural products, such as brevetoxin-B (Figure 1), monensin, and glabrescol. Thus, the development of efficient epoxidation methods continues to receive considerable attention.

Epoxidation of olefins is typically performed with organic peracids (such as *m*-chloroperbenzoic acid and magnesium monoperoxyphthalate) or a combination of a transition metal catalyst and a co-oxidant (such as H_2O_2, *t*-BuOOH, PhIO, NaOCl, and even oxygen). It has been a great challenge to devise a generally applicable, environmentally benign epoxidation method that operates under mild and neutral conditions and, most importantly, furnishes epoxides with complete stereocontrol (enantioselectivity and diastereoselectivity).[1]

Dioxiranes represent a new generation of oxidants for olefin epoxidation, hydroxylation of C−H bonds, and heteroatom oxidation (Scheme 1).[2] Epoxidation mediated by dioxiranes is stereospecific and highly efficient toward both electron-rich and electron-deficient olefins under mild and neutral reaction conditions. The most commonly used dioxiranes are dimethyldioxirane and methyl(trifluoromethyl)dioxirane, which can be isolated by distillation from the reactions of ketones and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$). A more convenient procedure is to gener-

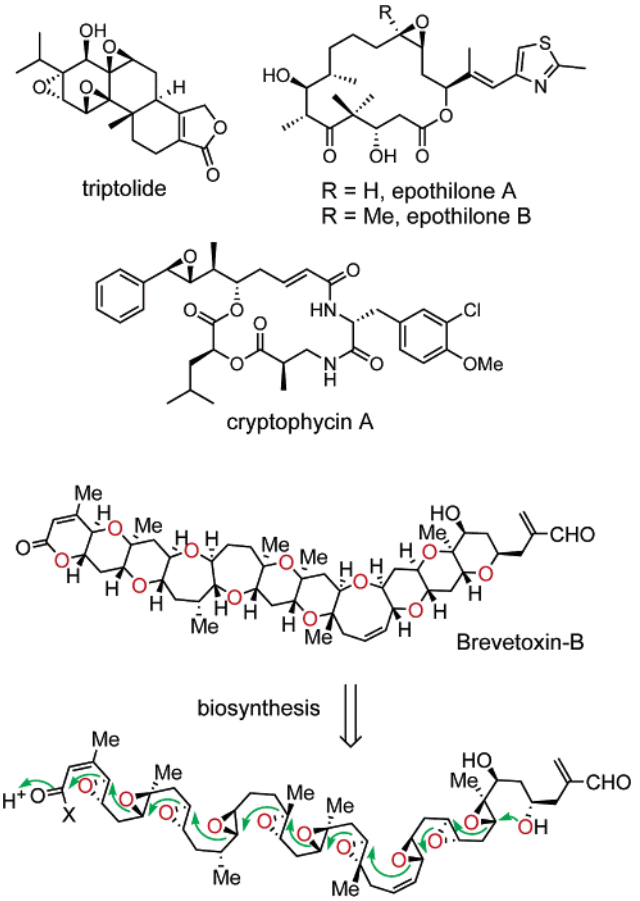
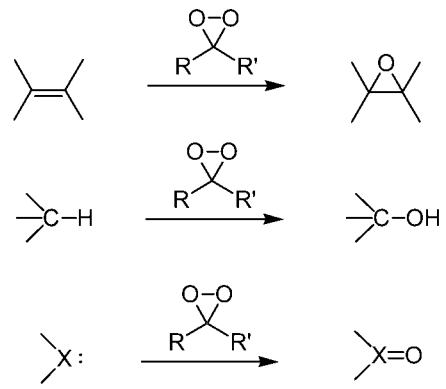
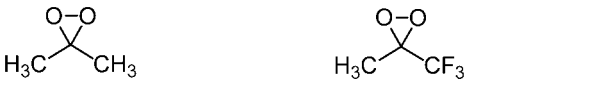


FIGURE 1. Examples of natural products containing epoxide groups or biosynthesized from epoxides.

Scheme 1



Most common dioxiranes used in epoxidation:



Dimethyldioxirane Methyl(trifluoromethyl)dioxirane

Dan Yang was born on October 20, 1965, in Sichuan, China. She received her B.Sc. degree in Chemistry from Fudan University, P. R. China, in 1985. Through the U.S.−China Chemistry Graduate Program, she obtained an M.A. degree in 1998 at Columbia with Professor Ronald Breslow and a Ph.D. from Princeton under the guidance of Professor Daniel Kahne in 1991. She then spent two years as a postdoctoral fellow with Professor Stuart Schreiber at Harvard. In 1993, she joined The University of Hong Kong, where she is currently a professor of chemistry. Her research interests include asymmetric catalysis and total synthesis, the design and synthesis of novel foldamers, and the chemical biology of natural products.

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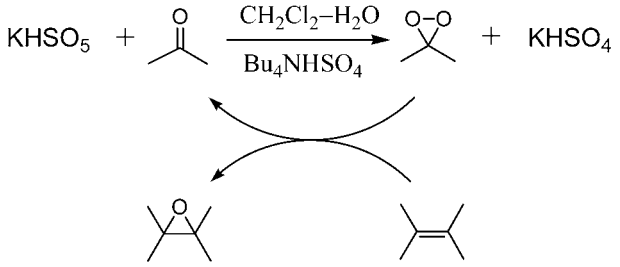
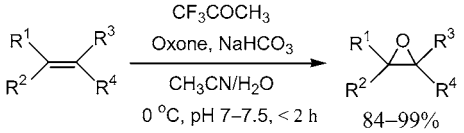
10.1021/ar030065h CCC: $27.50
Published on Web 04/22/2004

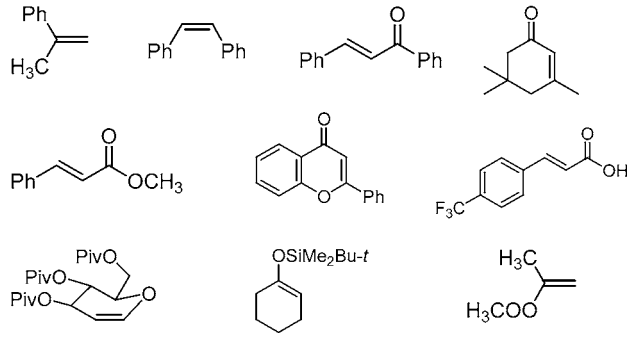
Scheme 2



Scheme 3



Substrates:

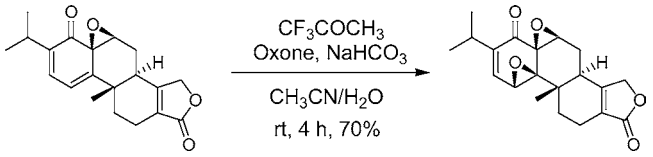


ate dioxiranes in situ from ketones and Oxone in a catalytic fashion (Scheme 2), as reported by Curci in 1984.[3] The potential of in situ epoxidation by dioxiranes was not explored, however, until recently. Several reviews covering chiral ketone-catalyzed epoxidation reactions have already appeared.[4] In this Account, we describe our efforts in developing organic ketone catalysts for epoxidation of unfunctionalized olefins with high enantioselectivities and diastereoselectivities.

An Efficient Epoxidation Method. Epoxidations of olefins with dioxiranes generated in situ from acetone, 2-butanone, and cyclohexanones proceed with slow reaction rates. We reasoned that the poor epoxidation efficiency might be attributable to the low reactivities of the ketones employed and, more importantly, to the biphasic solvent system (CH_2Cl_2–H_2O), which uncouples the process of dioxirane formation from that of oxygen-atom transfer.

As methyl(trifluoromethyl)dioxirane was reported to be ca. 1000 times more reactive than dimethyldioxirane, we reasoned that trifluoroacetone might be an excellent catalyst for the in situ dioxirane epoxidation. After a systematic investigation of the reaction parameters, we found that trifluoroacetone catalyzes epoxidation much faster when a homogeneous acetonitrile/water mixture is used as the solvent.[5] As Scheme 3 illustrates, unfunctionalized olefins having various substitution patterns, electron-deficient olefins (such as α,β-unsaturated ketones, acids, and esters), and electron-rich olefins (such as enol ethers and esters) were epoxidized in excellent yields at 0 °C. Here sodium bicarbonate was used as the buffer to neutralize the acidity of Oxone and sodium hydrogen sulfate formed as a byproduct, thus maintaining the pH of the reactions at 7.0−7.5. These virtually neutral conditions allow various acid- or base-labile epoxides (such as those of flavone and enol esters) to be isolated in excellent yields.

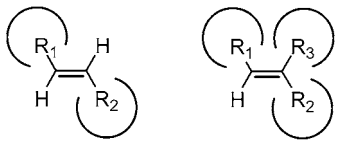
Scheme 4



We applied this method in our total synthesis of triptolide, a potent antitumor, antiinflammatory, and immunosuppressive agent isolated from *Tripterygium wilfordii* Hook F (Scheme 4).[6] When the dienone was treated with methyl(trifluoromethyl)dioxirane generated in situ from trifluoroacetone and Oxone, the bis-epoxide, which features the second epoxide positioned cis to the first, was obtained as a single diastereoisomer in 70% yield. This efficient epoxidation method has been applied by others to the total synthesis of epothilones.[7]

Developing C_2-Symmetric Cyclic Ketones as Catalysts for Asymmetric Epoxidation. Asymmetric epoxidation has attracted significant attention in the past two decades.[8] The Sharpless epoxidation method is a powerful tool for the asymmetric epoxidation of allylic alcohols; the hydroxyl group directs oxygen-atom transfer to the olefins in an enantioselective fashion.[8a] For the enantioselective epoxidation of unfunctionalized olefins,[8b] the chiral Mn-salen catalysts developed independently by Jacobsen and co-workers[9] and Katsuki and co-workers[10] are effective for a variety of olefin types, particularly *cis*-olefins. When we initiated our program in 1993, however, there was no general and effective method available for catalytic asymmetric epoxidation of *trans*-olefins and trisubstituted olefins.

We envisaged that chiral ketones could be ideal catalysts for asymmetric epoxidation of unfunctionalized olefins. When examining the structural features of trans-disubstituted and trisubsituted olefins, we noticed that both of them have one large and one small substituent on either one side or one terminus of the C=C double bond (Figure 2). Under either a spiro or planar transition state (Figure 3), chiral dioxiranes bearing large and small substituents, respectively, on each face of the dioxirane should have the potential to discriminate between the large and small groups on the C=C double bond and,



trans-olefin trisubstituted olefin

FIGURE 2. Recognizing olefin substitution patterns.

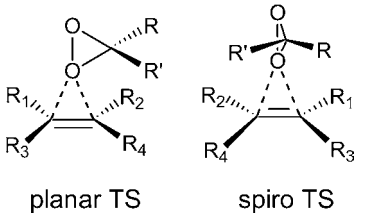


FIGURE 3. Transition-state geometries during epoxidation of olefins by dioxiranes.

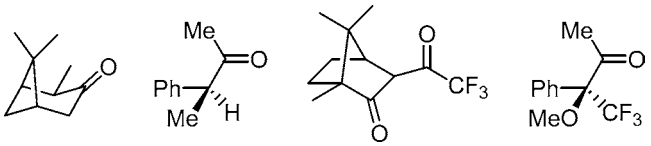


FIGURE 4. Curci's chiral ketone catalysts.

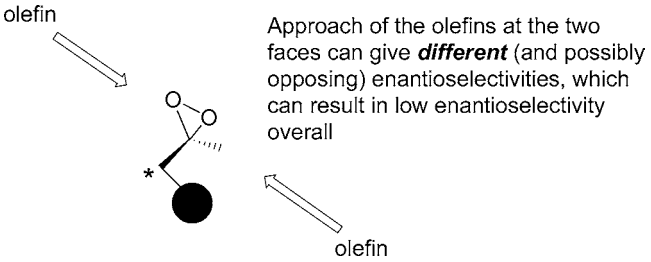


FIGURE 5. Asymmetric epoxidation by non-C_2 symmetric dioxiranes.

hence, could offer a promising solution to the problem of asymmetric epoxidation of trans-disubstituted and trisubstituted olefins.

The pioneering work by Curci et al. demonstrated the possibility of chiral dioxiranes being applied to the asymmetric epoxidation of unfunctionalized olefins.[3,11] The chiral ketones that they employed have one stereogenic center adjacent to the carbonyl group (Figure 4). The epoxidation by chiral dioxiranes generated in situ proceeded in good yield, but the enantioselectivity was low (<20% ee). One reason for these low enantioselectivities could be that, in each of those dioxiranes, the two apparently different faces of the dioxirane functional groups are both accessible to the olefins, which would result in differing (and potentially opposing) stereoselectivity during the oxygen-atom transfer process (Figure 5).

In principle, two approaches can be taken in designing chiral dioxiranes for use in asymmetric epoxidations. One is to block one face of the dioxirane to allow epoxidation to occur exclusively at the other face. The other approach is to use dioxiranes having C_2 symmetry, in which the two faces of a chiral dioxirane would have exactly the same chiral environment for oxygen-atom transfer (Figure 6). We chose to focus first on the design of C_2-symmetric chiral ketones.[12−14]

By comparing the catalytic activities of various ketones in epoxidation of *trans*-stilbene (Figure 7), we observed two general trends: (1) ketones having electron-withdrawing groups, such as F, Cl, and OAc, in their α positions display higher activities, and (2) steric hindrance at the α positions decreases their activities. Thus, both steric and electronic factors must be considered when designing efficient ketone catalysts.

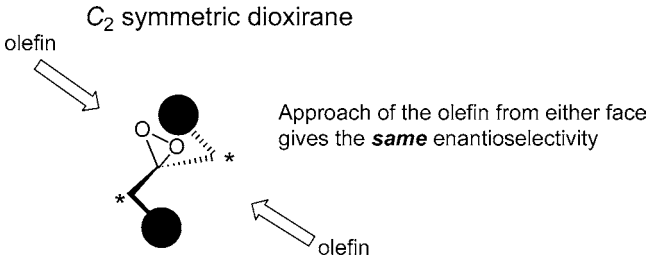


FIGURE 6. Asymmetric epoxidation by C_2 symmetric dioxiranes.

1,3-Diacetoxyacetone (**1**) has a 2-fold symmetry axis passing through its C═O bond. To obtain dioxiranes having rigid conformations, we designed and synthesized cyclic analogues of 1,3-diacetoxyacetone. We observed several interesting features in the subsequent epoxidation reactions (Figure 8): (1) With a 1:1 ketone:substrate ratio and the reaction conducted at room temperature, the epoxidation of *trans*-stilbene catalyzed by cyclic ketones **2**−**5** proceeded faster than those catalyzed by trifluoroacetone or **1**. (2) The activities of cyclic ketones increase in the order 9-membered-ring ketone **2** < 10-membered-ring ketone **3** < 11-membered-ring ketones **4** and **5**. Among the ketones we screened, **4** exhibited the highest catalytic activity: even 1 mol % ketone **4** can be employed for the epoxidation of *trans*-stilbene. (3) Cyclic ketones **2**−**5** are stable under the reaction conditions and can be recovered in high yield (>80%) and reused without loss of their catalytic activities.[15]

To introduce a chiral element to ketone **4**, we replaced the biphenyl unit with a chiral binaphthalene unit to provide the C_2-symmetric, 11-membered ring ketone (*R*)-**6** (Figure 9).[12] Similar to ketone **4**, chiral ketone **6** is highly active in catalyzing epoxidation reactions. We found that chiral ketone **6** gave moderate-to-good enantioselectivity in the epoxidation of *trans*-olefins and trisubstituted olefins, but not for *cis*-olefins or terminal olefins (Figure 10). It is significant that 87% ee was obtained for the epoxidation of (*E*)-4,4′-diphenylstilbene, with as little as 10 mol % ketone **6**. An ^{18}O labeling experiment proved that the enantioselective epoxidation of *trans*-stilbene catalyzed by chiral ketone (*S*)-**6** proceeded through its dioxirane intermediate.[14]

X-ray crystallographic analysis revealed that ketone **6** had a rigid and symmetric structure with the keto group lying on a C_2 axis (Figure 9).[12] We believe that the ester groups serve two roles. On one hand, they activate the ketone group by their electron-withdrawing effects. The corresponding ether-linked ketone is a much less efficient catalyst.[14,16] On the other hand, the ester groups add further rigidity to the chiral ketone, which results in a higher ee in the enantioselective epoxidation of *trans*-stilbene relative to that obtained with the ether-linked ketone. We expected that the H-3 and H-3′ atoms of the naphthalene rings act as the steric recognition element (steric sensor) and exert significant influence on the enantioselectivity. The distance between either H-3 or H-3′ of the binaphthyl group and the catalytic keto group is ca. 5 Å, which is a bit too far for effective recognition of olefin substitution patterns. Thus, we designed a series

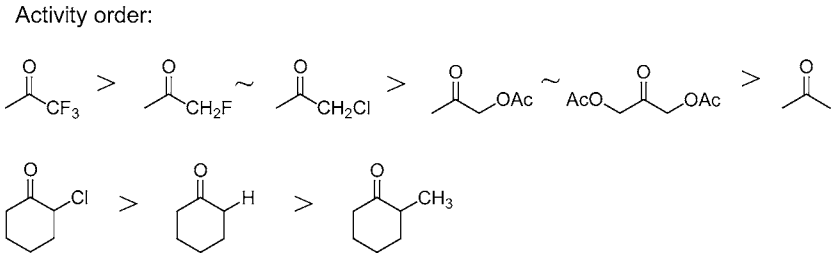


FIGURE 7. Activity order of ketones in catalyzing the in situ epoxidation of *trans*-stilbene.

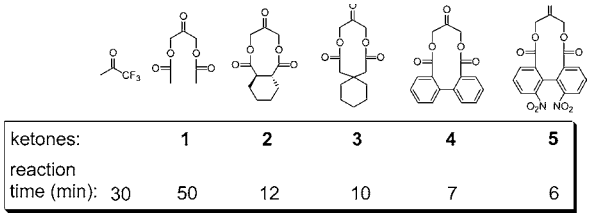


FIGURE 8. Activities of ketones designed for catalyzing the in situ epoxidation of *trans*-stilbene (ketone/substrate ratio 1:1).

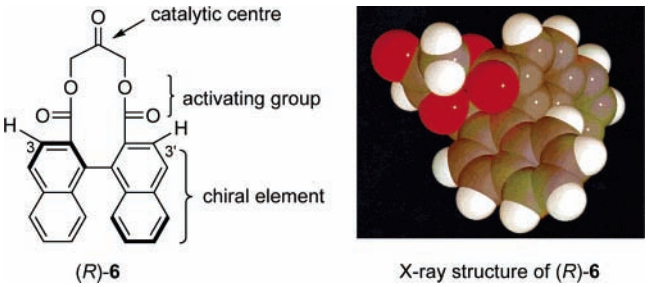


FIGURE 9. Structure of ketone (*R*)-**6**.

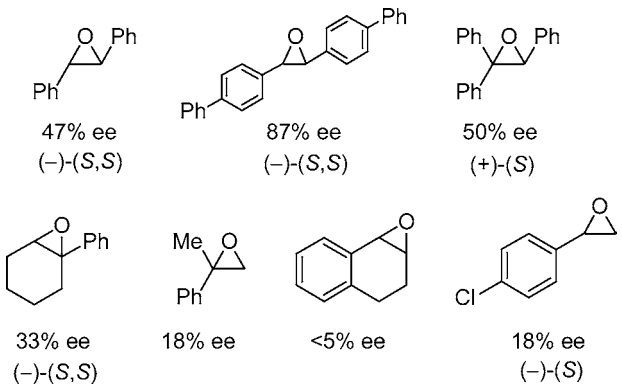
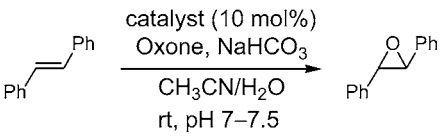


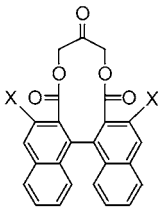
FIGURE 10. Asymmetric epoxidation of unfunctionalized olefins catalyzed by ketone (*R*)-**6**.

of ketones bearing different steric sensors.[13,14] As the size of the steric sensor X (i.e., the substituents at the 3 and 3′ positions) becomes larger (from H to Cl to Br to I; from H to Me to CH_2OCH_3 to acetal to $SiMe_3$), it was found that the enantioselectivity first increases and then decreases (Table 1). This result suggests that ketones having steric sensors of an appropriate size are desirable. With (*R*)-ketones as catalysts, the (*S*,*S*)-epoxide of *trans*-stilbene was obtained as the major enantiomer.

These chiral ketones proved to be useful probes for examining the transition-state geometry during dioxirane epoxidation.[13,14] There are two extreme transition states for this process: spiro and planar (Figure 3). When

Table 1. Asymmetric Epoxidation of *trans*-Stilbene Catalyzed by Ketones 6−13



	Catalyst	X	ee (%)	Epoxide Confg
	(R)-**6**	*H*	47	(–)-(*S*,*S*)
	(*R*)-**7**	Cl	76	(–)-(*S*,*S*)
	(*R*)-**8**	Br	75	(–)-(*S*,*S*)
	(*R*)-**9**	I	32	(–)-(*S*,*S*)
	(*S*)-**10**	Me	56	(+)-(*R*,*R*)
	(*R*)-**11**	CH_2OCH_3	66	(–)-(*S*,*S*)
	(*R*)-**12**		71	(–)-(*S*,*S*)
	(*S*)-**13**	$SiMe_3$	44	(+)-(*R*,*R*)

encountering *trans*-stilbene, the C_2-symmetric chiral dioxirane, generated in situ from ketone (*R*)-**6**, has two possible orientations based on steric considerations (favored and disfavored orientations) under either a spiro or a planar transition state (Figure 11). The favored orientation has the phenyl group of *trans*-stilbene positioned away from the naphthalene rings of the dioxirane. With (*R*)-ketones as catalysts, (*S*,*S*)-epoxides of *trans*-stilbenes are expected to be the major products under a spiro TS, whereas (*R*,*R*)-epoxides are expected under a planar TS. Consequently, the results of our epoxidations are consistent with a spiro TS. When 10 mol % of ketones **7**, **8** and **12** was used, we achieved high enantioselectivities for the asymmetric epoxidation of *trans*-stilbenes (up to 95% ee) and trisubstituted olefins (up to 81% ee) (Figure 12). A theoretical study by the Houk group has confirmed our experimental findings on epoxidation with chiral dioxiranes.[17]

It is worth noting that the chiral binaphthyl ketone **6** has been applied by Tanabe Seikayu Company in Japan to a large-scale asymmetric epoxidation of methyl *p*-methoxycinnamate (MPC) (Figure 13).[18] After optimization of the reaction parameters, the chiral epoxide can be obtained in 87% yield and 78% ee. Through a continuous extraction process, the chiral ketone can be readily precipitated and recovered in 88% yield, while the chiral epoxide can be isolated by recrystallization in 64% yield and >99% ee. This chiral epoxide product is an important intermediate in the synthesis of the chiral drug diltiazem

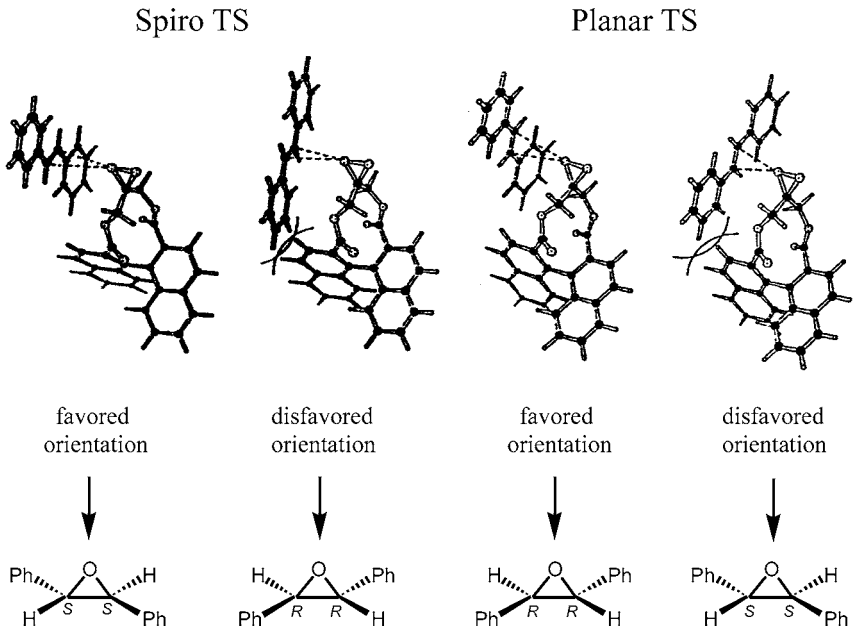


FIGURE 11. Proposed transition states for the epoxidation of *trans*-stilbene.

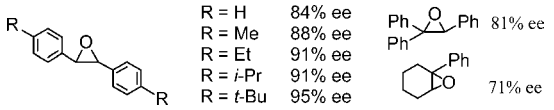


FIGURE 12. Asymmetric epoxidation of *trans*-stilbenes and trisubstituted olefins catalyzed by ketones **7**, **8**, and **12** (10 mol %).

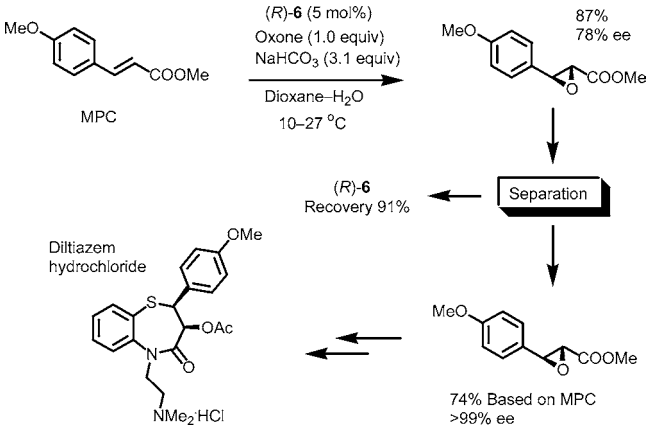


FIGURE 13. Asymmetric epoxidation of MPC catalyzed by (*R*)-**6**.

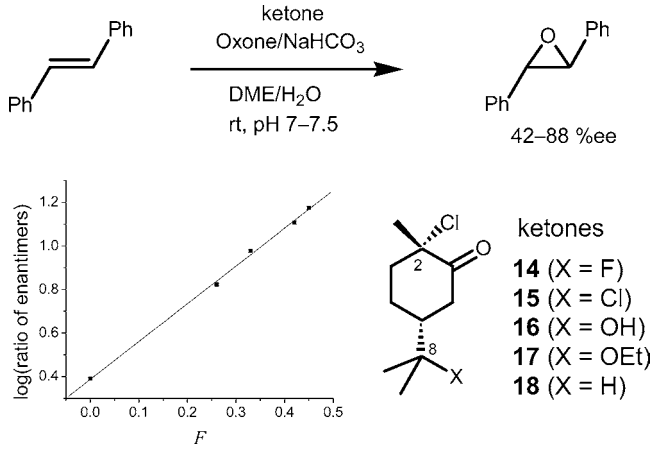


FIGURE 14. Catalyst electronic effects observed with ketones **14**–**18**.

hydrochloride, a coronary vasodilator for the treatment of angina pectoris and hypertension.

Electronic Effects in Chiral Ketone-Catalyzed Epoxidation Reactions. Since Jacobsen's pioneering studies of electronic effects in asymmetric epoxidation reactions,[19] electronic tuning has become an important tool in asymmetric catalysis. There is a lack of general understanding, however, of electronic effects in asymmetric catalysis. As reactions between dioxiranes and olefins follow a concerted one-step process, chiral dioxirane epoxidation offers an ideal system for understanding the electronic effects of remote substituents on enantioselectivity. In our case, we found that a series of (*R*)-carvone-derived chiral ketones (**14**−**18**) having different remote substituents exhibit interesting electronic effects during catalysis (Figure 14).[20] Epoxidations of *trans*-stilbene catalyzed by these ketones proceeded with 42−88% ee, with the most electron-withdrawing substituent giving the highest catalyst reactivity and also highest enantioselectivity for the epoxide. We obtained a linear Hammett plot of log (ratio of enantiomers) versus the field constants of those remote substituents (Figure 14). This study was the first in which nonconjugated remote substituents were observed to exert significant electronic effects in asymmetric catalysis.

To understand the electronic effect of the remote substituents, first we looked at the substrate electronic effect. When the dichloro ketone **15** was used as the catalyst, we observed that the Hammett plot for the epoxidation of symmetrical meta- or para-substituted *trans*-stilbenes displays a negative slope, i.e., the more electron-releasing substrates give higher enantioselectivity (Figure 15). The slope of a Hammett plot is the reaction constant ρ, which represents the charge distribution in the transition state. In enantioselective reactions, the ρ value corresponds to the difference in charge distribution

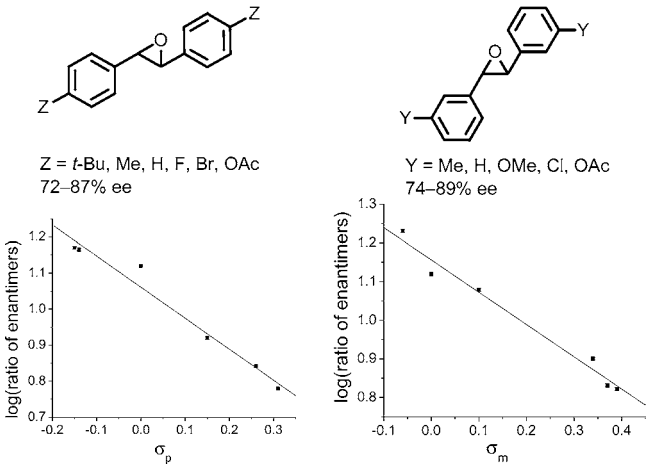


FIGURE 15. Substrate electronic effects observed with ketone **15** as the catalyst.

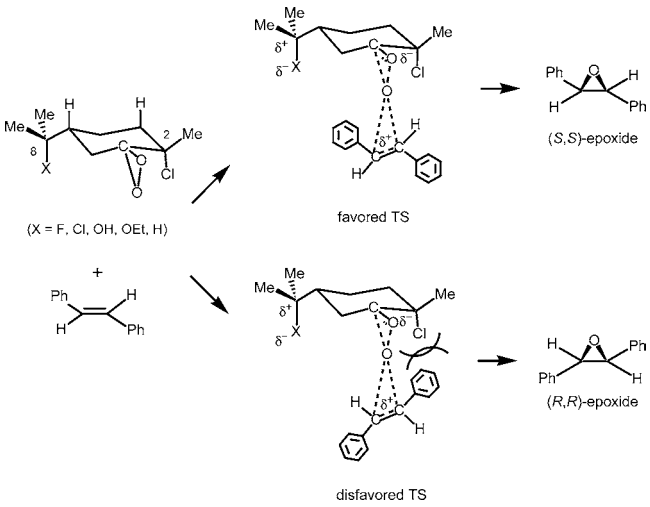


FIGURE 16. Electrostatic model proposed for epoxidation by dioxiranes.

of the two diastereomeric transition states that lead to the formation of two enantiomers, respectively. The negative slope of the Hammett plot, observed in our study of the substrate electronic effect, suggests that the favored transition state leading to the (*S*,*S*)-epoxide should feature more positive charge at the epoxide-forming carbon atoms than in the disfavored transition state leading to the (*R*,*R*)-epoxide (Figure 16). Therefore, the remote electronegative substituent at the C-8 position of the catalyst could be stabilizing the favored TS more than it does the disfavored one by through-space electrostatic interactions (i.e., a field effect), which leads to the increase in values of ee. This model offers insights for future design of catalysts for asymmetric epoxidation.

Designing Efficient Ketone Catalysts for Epoxidation by Use of the Field Effect. Next, we applied our understanding of the field effect to the design of efficient catalysts for the epoxidation of nonchiral olefins. It is known that the field effect of heteroatoms, i.e., through-space dipole−dipole or charge−dipole interactions, can be used to increase the electrophilicities of ketones. We found that the rates of epoxidation indeed increase dramatically upon increasing the field constants of the

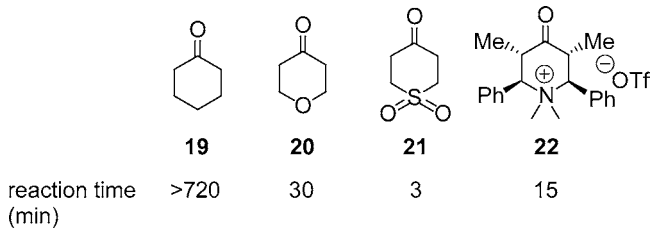
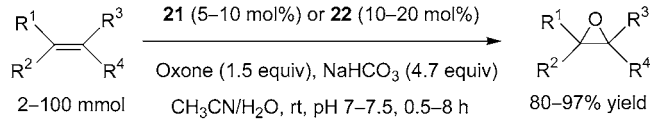


FIGURE 17. Activities of ketones **19**−**22** in catalyzing the in situ epoxidation of *trans*-stilbene in CH_3CN-H_2O (ketone/substrate ratio 1:1).



olefins:

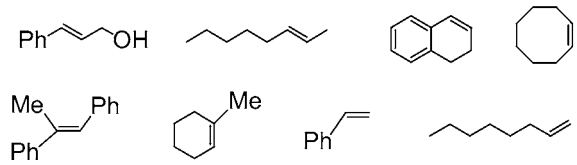


FIGURE 18. Epoxidation of olefins with either ketone **21** or **22** as catalyst.

Table 2. Diastereoselective Epoxidation of Cyclohexenes Bearing Allylic Substituents

oxidant	ratio of trans/cis-epoxide		
			
ketone **22** + Oxone	15.1/1	19.7/1	18.7/1
CH_3COCF_3 + Oxone	6.1/1	19.3/1	8.4/1
mCPBA	2.7/1	7.5/1	1.2/1

heteroatom substituents in 4-heterocyclohexanones **19**−**21** (Figure 17).[21] Because of the strong field effects exerted by sulfone and quaternary ammonium groups, we found ketones **21** and **22** to be the best catalysts for epoxidation in this series of compounds. By using either ketone **21** (5−10 mol %) or **22** (10−20 mol %) as catalyst, the epoxidation of various olefins (Figure 18) at room temperature was complete in a short period of time (0.5−8 h) with excellent yields for the isolation of epoxides (80−97%) and ketone recovery (ca. 80%). The epoxidation could be performed on a large scale (20−100 mmol) directly with 5 mol % commercially available tetrahydrothiopyran-4-one, which is oxidized by Oxone to ketone **21** during the epoxidation reactions.

Diastereoselective Epoxidation Catalyzed by Ketones. It is interesting to note that, for the epoxidation of cyclohexenes bearing allylic substituents, ammonium ketone **22** gives much higher diastereoselectivities (trans/cis ratio) than do either *m*-CPBA or trifluoroacetone under the in situ conditions (Table 2).[22] One important application of ketone catalysts is in the β-selective epoxidation of Δ^5-unsaturated steroids (Figure 19). Common organic oxidants, such as *m*-CPBA, give α-epoxides as the major product in the epoxidation of 3β-substituted Δ^5-steroids,

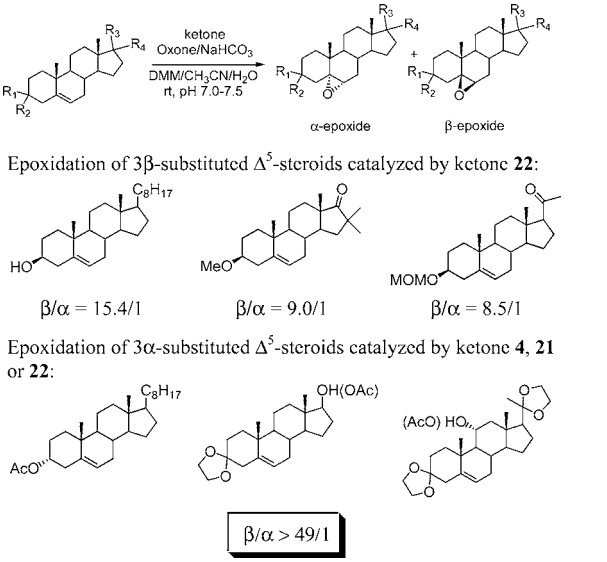
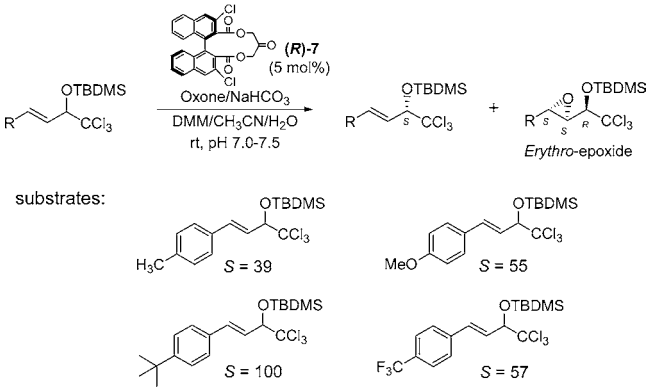


FIGURE 19. Ketone-catalyzed epoxidation of Δ^5-steroids.

Scheme 5. Kinetic Resolution of Acyclic Secondary Allylic Silyl Ethers Catalyzed by Chloroketone (*R*)-7



but they display poor selectivities for the epoxidation of 3α-substituted Δ^5-steroids other than *epi*-cholesterol. We found that for the epoxidation reactions of 3*β*-substituted Δ^5-steroids, only ketone **22** gave high *β*-selectivities (*β*/α-epoxide ratio > 8.5:1), and that in the epoxidation reactions of 3α-substituted Δ^5-steroids, ketones **4**, **21**, and **22** all afforded almost exclusively the 5*β*,6*β*-epoxides.[23]

Kinetic Resolution of Acyclic, Secondary Allylic Silyl Ethers Catalyzed by Chiral Ketones. On the basis of our understanding of the enantioselective and diastereoselective epoxidation reactions catalyzed by ketones, next we investigated the kinetic resolution of α-trichloromethyl allylic alcohols and their derivatives using chiral chloroketone **7** (5 mol %) as the catalyst (Scheme 5).[24] We found that the (*R*)-substrates were epoxidized preferentially over the (*S*)-substrates, with selectivity factors (*S* values) of up to 100. In addition, these kinetic resolutions exhibit excellent diastereoselectivities: almost a pure diastereoisomeric epoxide was formed with ratios of *erythro*/*threo*-epoxides of over 49:1.

Work Performed by Others in Chiral Ketone-Catalyzed Asymmetric Epoxidation of Unfunctionalized Olefins. Since we reported our initial work in early 1996 on the chiral ketone-catalyzed epoxidation, several other groups have communicated their results in this area.[4,25] Both C_2-symmetric and non-C_2-symmetric chiral ketones have been designed and tested. Some representative examples are shown in Figure 20.

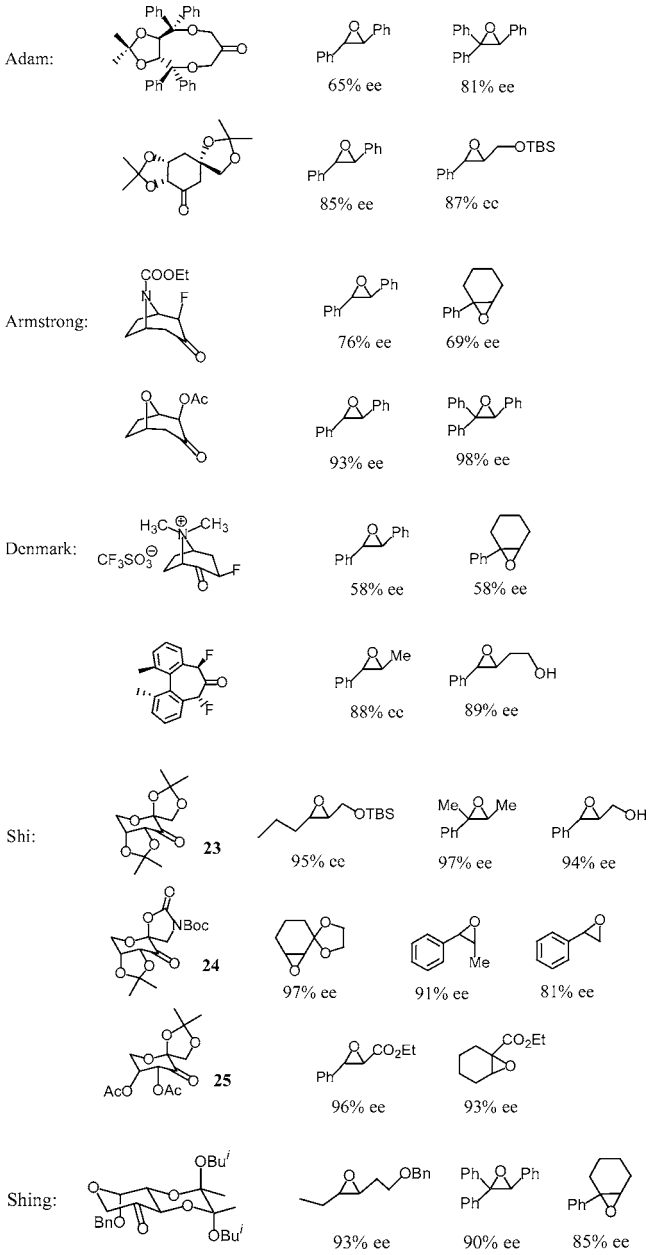


FIGURE 20. Representative chiral ketone catalysts developed by other research groups.

Among the considerable advances in the search for efficient chiral ketone catalysts, the fructose-derived ketones developed by Shi and co-workers have proved to be the best ketone catalysts in chiral dioxirane epoxidation. For example, ketone **23**, readily prepared from L-fructose in two steps, gave the highest ee values for epoxidation of substrates ranging from *trans*-olefins, trisubstituted olefins, conjugated dienes, enynes, silyl enol ethers, and esters to vinylsilanes, with 20−30 mol % catalyst loading at elevated pH (>10).[4b,c,25g−m] Further modification of the structure led to the discovery of ketone **24**, which efficiently catalyzed enantioselective epoxida-

tion of *cis*-olefins (83−97% ee) and terminal olefins (71−85% ee) at 15−30 mol % catalyst loading.[25p−r] More recently, Shi's group reported ketone catalyst **25** for highly enantioselective epoxidation of *trans*- and trisubstituted α,β-unsaturated esters with excellent ee values (82−97%) at 20−30 mol % catalyst loading.[25s] These exciting developments demonstrate perfectly that chiral ketones are excellent catalysts for the asymmetric epoxidation of unfunctionalized olefins.

Conclusions

We have established a general method for generating dioxiranes in situ under mild reaction conditions, which makes dioxiranes benchtop reagents for oxidation reactions. In addition, we have developed efficient ketone catalysts for olefin epoxidation in high enantioselectivity and diastereoselectivity, which, thus, has extended the scope of dioxirane chemistry in organic synthesis significantly. Our investigations on the steric and electronic effects in dioxirane epoxidation reactions provide insights for the further development of practical catalysts for pharmaceutical applications. Future efforts will be directed at exploring the potential of using ketones as catalysts for other oxidation reactions, such as C−H bond hydroxylation and heteroatom oxidation.

The University of Hong Kong and Hong Kong Research Grants Council provided financial support for the research described in this Account. I am very grateful to my co-workers Yiu-Chung Yip, Man-Kin Wong, Xue-Chao Wang, Man-Wai Tang, Jian-Hua Zheng, Jian Chen, and Guan-Sheng Jiao for their enthusiasm and hard work, which made this research program successful. I also thank Man-Kin Wong for help during the preparation of the manuscript.

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AR030065H