CHEMICAL REVIEWS

Review

Organocatalytic Oxidation. Asymmetric Epoxidation of Olefins Catalyzed by Chiral Ketones and Iminium Salts

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Organocatalytic Oxidation. Asymmetric Epoxidation of Olefins Catalyzed by Chiral Ketones and Iminium Salts

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1. Introduction

Optically active epoxides are highly useful intermediates and building blocks for the synthesis of biologically active compounds. Various effective systems have been developed over the years for the preparation of chiral epoxides,[1,2] and asymmetric epoxidation of olefins has proven to be one of the most powerful approaches. Great success has been achieved in this area, including epoxidation of allylic alcohols with chiral titanium catalysts,[3] epoxidation of allylic[4] and homoallylic[5] alcohols using chiral vanadium catalysts, metal-catalyzed epoxidation of unfunctionalized olefins,[6–8] and the nucleophilic epoxidation of electron-deficient olefins.[9] Among the many powerful methods for the epoxidation of olefins, three-membered ring compounds containing two heteroatoms such as dioxiranes,[10] oxaziridines,[11] and oxaziridinium salts[10e] are remarkably versatile oxidation reagents. During recent years asymmetric epoxidation catalyzed by chiral ketones[12] and iminium salts[10e] has received much attention. Significant progress has been made toward the epoxidation of various types of olefins, particularly unfunctionalized trans- and trisubstituted olefins, which has been a long-standing challenge. This review describes progress in this area.

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2. Chiral Ketone-Catalyzed Epoxidation

2.1. Introduction

Dioxiranes can be generated *in situ*[10,13] from ketones and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (Scheme 1).[14] In principle, only a catalytic amount of ketone should be needed since the ketone is regenerated upon epoxidation of the olefin, and asymmetric epoxidation could also be possible with a chiral ketone catalyst. However, developing effective chiral ketone catalysts has proven to be challenging in practice. Balancing of steric and electronic effects on both the reactivity and enantioselectivity as well as overcoming various competing processes[12b] are not trivial matters.

2.2. Early Ketones

In 1984, Curci and co-workers reported the asymmetric epoxidation of 1-methylcyclohexene and *trans*-β-methylstyrene with (+)-isopinocamphone (**1**) and (*S*)-(+)-3-phenylbutan-2-one (**2**) as catalyst in a biphasic mixture of $CH_2Cl_2-H_2O$ (pH 7−8) (Figure 1).[15] These ketones provided good yields, and up to 12.5% ee was obtained (Table 1, entries 1−3, 6−7). Then in 1995, two ketone catalysts containing electron-withdrawing trifluoromethyl groups (**3** and **4**) (Figure 1) were reported by Curci and co-workers.[16] These ketones were much more active than **1** and **2**. High conversions were achieved with 0.8−1.2 equiv of ketone at 2−5 °C within 17−48 h (Table 1), and the ketones could be recovered from the reaction. Up to 20% ee was obtained for *trans*-2-octene (Table 1, entry 8) using this method. Also in 1995, Marples and co-workers reported the epoxidation using chiral 1-tetralones and 1-indanones bearing fluorines at α-positions (Figure 2).[17,18] The dioxiranes generated from these ketones were reactive toward olefins but provided no enantioselectivity.

2.3. C_2-Symmetric Binaphthyl-Based and Related Ketones

In 1996, Yang and co-workers reported a series of elegant binaphthylene-derived chiral ketones **8** (Figure 3).[19] C_2

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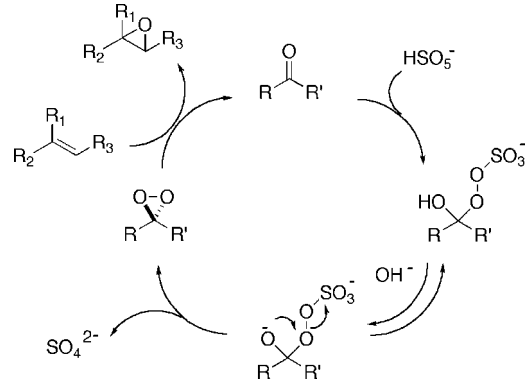
Yian Shi was born in Jiangsu, China, in 1963 and obtained his B.Sc. degree in chemistry from Nanjing University in 1983. Upon receiving his M.Sc. degree from University of Toronto with Professor Ian W. J. Still in 1987, he pursued his doctoral studies at Stanford University with Professor Barry M. Trost and obtained his Ph.D. degree in 1992. Subsequently, he carried out his postdoctoral studies at Harvard Medical School with Professor Christopher Walsh 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. His current research interests include the development of new synthetic methods, asymmetric catalysis, and synthesis of natural products. He has received a number of honors for research and teaching, including the Camille and Henry Dreyfus New Faculty Award (1995), Beckman Young Investigator Award (1997), National Science Foundation Career Award (1999), Alfred P. Sloan Research Fellowship (1999), Camille Dreyfus Teacher-Scholar Award (1999), DuPont Young Faculty Award (1999), Eli Lilly Grantee Award (1999), GlaxoWellcome Inc. Chemistry Scholar Award (2000), Researcher of the Year Award, Colorado State University (2000), Lectureship Award, The Society of Synthetic Organic Chemistry, Japan (2001), Monfort Professorship Award, Colorado State University (2002), and ACS Arthur C. Cope Scholar Award (2004).

symmetry was intended to limit the competing epoxidation pathways of the dioxirane, and a remote binaphthalene unit was used as the chiral control element instead of substituents at the α carbon of the carbonyl, thus eliminating the possible racemization of chiral centers and steric hindrance at the α carbon. The unhindered carbonyl plus electron-withdrawing esters at the α carbon made ketones **8** very active catalysts. High conversion for epoxidation can be obtained with as low

Scheme 1. Ketone-Catalyzed Epoxidation of Olefins



as 10 mol % catalyst in a few hours at pH 7−7.5 in a homogeneous solvent system (CH_3CN-H_2O).[13i,20] Studies with ketone **8a** showed that the enantioselectivity of the epoxidation increased as the size of the *para* substituents on *trans*-stilbenes increased from H to Ph (H, 47% ee; *p*-Me, 50% ee; *p*-Et, 60% ee; *p*-*i*-Pr, 71% ee; *p*-*t*-Bu, 76% ee; *p*-Ph, 87% ee).[19a,c] Ketone **8a** can be recovered in >80% yield.

The X-ray structure of ketone **8a** showed the hydrogens on carbons 3 and 3′ to be closest to the reacting center among

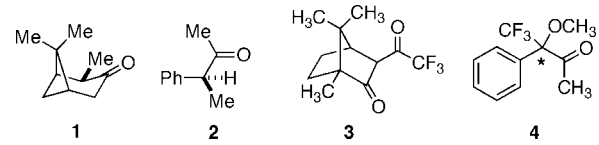
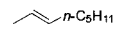
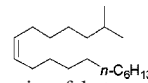
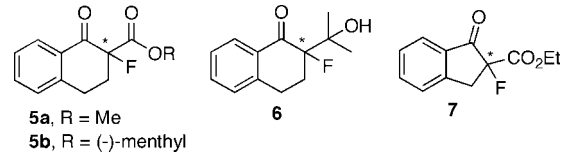


Figure 1.

Table 1. Asymmetric Epoxidation with Chiral Ketones 1−4

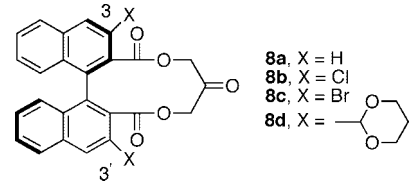
Entry	Substrate	Catalyst	Yield (%)[e]	ee (%)
1[a]		**1**	60	12.5 (1R, 2R)
2[b]		**1**	68	11.2 (1R, 2R)
3[a]		**2**	85	9.5 (1R, 2R)
4[c]		**3**	82	13 (1R, 2R)
5[c]		(S)-**4**	77	18 (1R, 2R)
6[a]		**1**	90	10.4 (1S, 2R)
7[d]		**2**	92	12 (1S, 2R)
8[c]		(S)-**4**	80	20 (2S, 3S)
9[c]		(S)-**4**	80	16 (7R, 8S)

[a] 1.0 equiv of ketone used. [b] 0.2 equiv of ketone used. [c] 0.8−1.2 equiv of ketone used. [d] 0.5 equiv of ketone used. [e] All yields based on olefins reacted except entry 1.



5a, R = Me
5b, R = (-)-menthyl

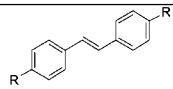
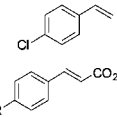
Figure 2.



8a, X = H
8b, X = Cl
8c, X = Br
8d, X =

Figure 3.

Table 2. Asymmetric Epoxidation with Ketones 8

Entry	Substrate	Catalyst	Yield (%)	ee (%)
				
1[a]	R = H	**8b**	>90	76 (S,S)
2[a]		**8c**	>90	75 (S,S)
3[a]		**8d** (0 °C)	>90	84 (S,S)
4[a]	R = Et	**8b**	>90	85 (S,S)
5[a]		**8c**	>90	88 (S,S)
6[a]		**8d** (0 °C)	>90	91 (S,S)
7[a]	R = *t*-Bu	**8b**	>90	91 (S,S)
8[a]		**8c**	>90	93 (S,S)
9[a]		**8d** (0 °C)	>90	95 (S,S)
10[a]		**8c**	82	81 (S)
11[a]		**8d**	90	71 (S,S)
12[a]		**8a**	85	<5
13[a]		**8a**	70	18
14[a]		**8a**	83	18
15[b]	R = H	**8a**	75	74 (2R, 3S)
16[b]	R = Me	**8a**	95	72 (2R, 3S)
17[b]	R = OMe	**8a**	92	80
18[c]		**8b**	74	85
19[b]	R = *t*-Bu	**8a**	81	92 (2R, 3S)

[a] Ketone (0.1 equiv), Oxone (5 equiv), $NaHCO_3$ (15.5 equiv), MeCN−aq EDTA at rt or 0 °C. [b] Ketone (0.05 equiv), Oxone (1.0−2.0 equiv), $NaHCO_3$ (3.1−6.2 equiv), dioxane−H_2O. [c] Ketone (0.05 equiv), Oxone (1.0 equiv), $NaHCO_3$ (3.1 equiv), DME−H_2O.

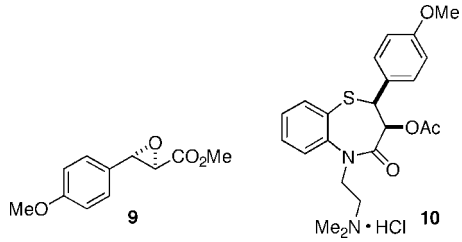


Figure 4.

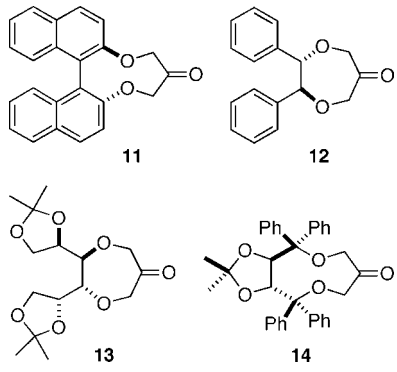
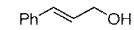
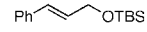


Figure 5.

all the atoms on the binaphthylene unit, and likely to be the steric sensors for the epoxidation.[19b,c] Various substitutents

Table 3. Asymmetric Epoxidation with Ketones 11−14

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1[a]		**11**	95	29 (S,S)
2[a]		**12**	61	20 (S,S)
3[a]		**11**	79	26 (S,S)
4[a]		**12**	72	59 (S,S)
5[b]		**13**	72	38 (R,R)
6[a]		**14**	67	65 (R,R)
7[a]		**14**	51	80 (R,R)
8[c]		**14**	80	79 (R,R)
9[a]		**14**	70	81 (R,R)

[a] 1 equiv of ketone used. [b] 2 equiv of ketone used. [c] 0.5 equiv of ketone used.

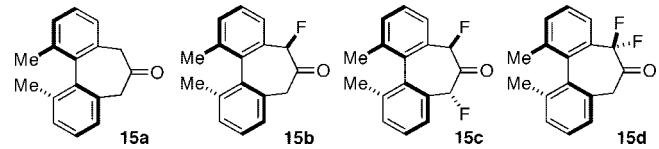
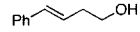
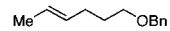
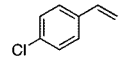
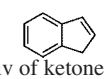


Figure 6.

Table 4. Asymmetric Epoxidation with Ketones 15 and 16

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1[a]		**15a**	6[e]	nd
2[a]		**15b**	33[e]	79
3[b]		**15c**	80	88 (R,R)
4[a]		**15d**	100[e]	85
5[c]		**16a**	35[e]	46
6[c]		**16b**	57[e]	80
7[c]		**16c**	100[e]	86
8[c]		**16d**	100[e]	83
9[c]		**16e**	32[e]	40
10[b]		**15c**	46	94 (R,R)
11[b]		**15c**	93	89
12[d]		**15c**	72	68
13[b]		**15c**	78	59 (R,R)
14[b]		**15c**	55	43 (R)
15[b]		**15c**	67	12

[a] 1.0 equiv of ketone used. [b] 0.3 equiv of ketone used. [c] 0.1 equiv of ketone used. [d] 0.5 equiv of ketone used. [e] Conversion (%).

were subsequently introduced in place of hydrogens at the 3 and 3′ positions (selected examples are shown in Figure 3). As the substituents became larger going from H (47% ee) to Cl (76% ee) to Br (75% ee) to I (32% ee), the enantioselectivity toward *trans*-stilbene first increased and then decreased.[19b,c] It appears that an appropriate size substituent is required to achieve optimal enantioselectivity. Among the ketones examined, **8d** was found to be the most reactive. Apparently the electron-withdrawing ketal groups

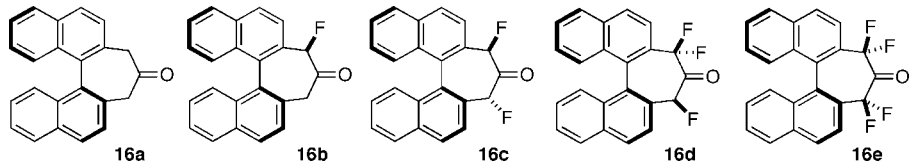


Figure 7.

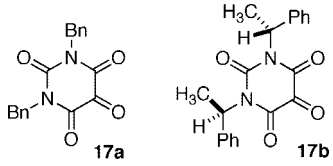


Figure 8.

provide further activation to the carbonyl. As shown in Table 2, *para*-substituted *trans*-stilbenes proved to be very effective substrates for the epoxidation with ketones **8**, and the ee's increased as the size of the substituents on the phenyl groups of the olefins increased (Table 2, entries 1−9). On the other hand, increasing the size of the *meta*-substituent of stilbene had little effect on enantioselectivity.[19c] Seki and co-workers made extensive efforts to improve the synthesis of ketone **8**,[21] and also extended the epoxidation to cinnamates (Table 2, entries 15−19).[22] Epoxide **9** (Figure 4), a key intermediate for calcium antagonist diltiazem hydrochloride (**10**), could be obtained in up to 85% ee using ketone **8b** (Table 2, entry 18).

In 1997, Song and co-workers reported the use of ether-linked C_2-symmetric ketones **11** and **12** (Figure 5).[23] Up to 59% ee was obtained for *trans*-olefins (Table 3, entries 1−4). These ketones showed both lower reactivity and enantioselectivity when compared to ketones **8**, possibly due to the weaker electron-withdrawing ability of the ether as compared to the ester. In the same year, Adam and co-workers also reported the synthesis of two ether-linked C_2-symmetric ketones **13** and **14**, which are derived from mannitol and (+)-tartaric acid, respectively (Figure 5).[24] Up to 81% ee was obtained with these ketones (Table 3, entries 5−9).

In 1999 and 2002, Denmark and co-workers reported asymmetric epoxidations using 7-membered C_2-symmetric carbocyclic biaryl ketones **15** (Figure 6).[12a,25] Having chiral control elements closer to the reacting carbonyl may further increase the stereodifferentiation for the epoxidation as compared to 11-membered ketone **8**. While nonfluorinated ketone **15a** displayed low reactivity, the epoxidation efficiency was greatly enhanced by fluorine substitution at the α-carbon. Difluoroketones **15c** and **15d** were found to be highly active, and a variety of *trans*-olefins can be epoxidized with good to high enantioselectivity (Table 4, entries 3, 4, 10−12). In 2002, Behar and co-workers reported structurally related fluorinated binaphthyl ketones **16** (Figure 7).[26] Ketones **16c** and **16d** were found to be most reactive and enantioselective for the epoxidation of *trans*-β-methylstyrene (Table 4, entries 7, 8).

In 1999, Carnell and co-workers reported that *N*,*N*-dialkylalloxans such as **17a** were very robust catalysts for epoxidation and can be recovered without decomposition (Figure 8).[27] No enantioselectivity was obtained for the epoxidation of *trans*-stilbene with chiral ketone **17b**. It appears that the chiral center was not close enough to the reacting carbonyl.

In 2001, Tomioka and co-workers reported several seven-membered cycloalkanones bearing 1,2-diphenylethane-1,2-diamine and cyclohexane-1,2-diamine backbones such as ketones **18** and **19** (Figure 9). Up to 30% ee was obtained for the epoxidation of *trans*-stilbene with ketone **18b**.[28a,b] Ketones **20** and **21** bearing the 11-membered ether and sulfonylamide (Figure 9) were also investigated by Tomioka and co-workers. While almost no enantioselectivity was observed, relatively high yields were obtained for stilbene oxide.[28b] Subsequently, they reported that higher ee's were obtained with tricyclic ketone **22** and bicyclic ketone **23** (Figure 10).[28c] For example, stoichiometric amount of ketones **22** and **23** gave *trans*-stilbene oxide in high yields with 64% ee and 57% ee respectively. 1-Phenylcyclohexene oxide was obtained in quantitative yield and 83% ee with a catalytic amount (20 mol %) of ketone **22**.

2.4. Ammonium Ketones

In 1995, Denmark and co-workers reported that 4-oxopiperidinium salt **24** (Figure 11) is an effective catalyst for epoxidation. The electron-withdrawing ammonium ion not only inductively activates the carbonyl but also acts as phase transfer mediator, thus allowing efficient partitioning of the ketone and its dioxirane between the organic and aqueous phases.[13h] The partitioning ability between two phases can be regulated by the choice of alkyl groups on the nitrogen. Based on this study, a number of chiral ketones bearing ammonium ions were investigated (Figure 11).[12a,13h,j,l,25,29] Sterically congested ammonium ketones **25** and **26** displayed low reactivity for the epoxidation. 1-Phenylcyclohexene oxide and *trans*-β-methylstyrene oxide could be obtained in 58% and 34% ee, respectively, using ammonium salt **26** as the epoxidation catalyst.[12a] Tropinone-based rigid ammonium ketone **27** with fluorine as an additional activating group was found to be highly reactive. The epoxidation of *trans*-stilbene with 10 mol % of ketone **27** provided the epoxide in 79% yield and 58% ee.[25,29] Bis(ammonium) ketones **28**, **30**−**32** were also found to be active catalysts. For example, >95% conversion was obtained with 10 mol % of **31** and **32** for

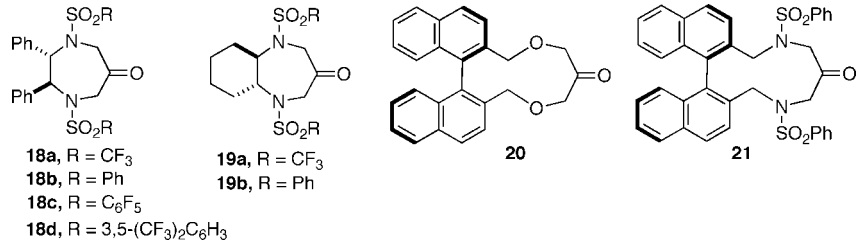


Figure 9.

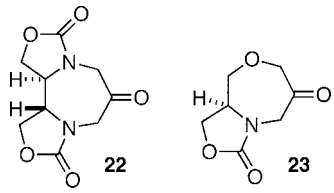


Figure 10.

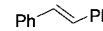
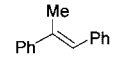
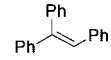
the epoxidation of *trans*-β-methylstyrene. Up to 40% ee was obtained for *trans*-β-methylstyrene with ketone **30**.

2.5. Bicyclo[3.2.1]octan-3-ones and Related Ketones

In 1998, Armstrong and co-workers reported tropinone-based ketone **33a**, which contains a bridgehead nitrogen at the β position and a fluorine atom at the α position, was a highly active catalyst for epoxidation (Figure 12).[30] A variety of olefins could be epoxidized in good conversions with a short reaction time, and up to 83% ee was obtained for phenylstilbene (Table 5, entry 16). Similar enantioselectivities were observed with α-fluorotropinone immobilized on silica compared to the nonsupported catalyst.[31] Further studies showed that replacing the fluorine of **33a** with an acetate and/or replacing the bridgehead nitrogen with an oxygen increased the enantioselectivity for epoxidation (Figure 12).[30b,32] Up to 98% ee_{max} was obtained for phenylstilbene with ketone **34b** (Table 5, entry 17).

Recently, Armstrong and co-workers investigated chiral tetrahydropyran-4-ones **35** for asymmetric epoxidation reactions to test the role of the two-carbon bridge contained in bicyclic ketones **33** and **34**.[33] These monocyclic pyranones were found to be stable under epoxidation conditions as only 10 mol % was needed to obtain satisfactory conversions, and gave only slightly lowered enantioselectivities for *E*-alkenes (Table 5, entries 5−7, 18, 22). These results for ketones **35** suggested that the α ester group seems to play an important role in reactivity and selectivity in this reaction. Armstrong and co-workers also investigated bicyclo[3.2.1]-octanones **36** and **37** bearing two electronegative substituents at the α positions.[34] Studies showed that these α-disubstitutions in ketones **36** and **37** proved to be nonbeneficial for enantioselectivity in asymmetric epoxidations (Table 5, entries 8−11). Epoxidation with 2-substituted-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones **38** was also reported by Klein and co-workers (Figure 12).[35] Ketone **38c** bearing a fluorine atom was found to be the most reactive, and up to 68% ee was obtained for stilbene (Table 5, entries 12 and 19).

Table 5. Asymmetric Epoxidation with Ketones 33−38

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1[a]		**33a**	100	76 (R, R)
2[b]		**33b**	100	86[d]
3[b]		**34a**	100	83[d]
4[b]		**34b**	85	93[d] (R,R)
5[a]		**35a**	100	81 (S,S)
6[a]		**35b**	52	43 (S,S)
7[a]		**35c**	100	83 (S,S)
8[b]		**36**	100	64 (S,S)
9[b]		**37a**	92	77[d] (R,R)
10[b]		**37b**	84	68[d] (R,R)
11[b]		**37c**	80	63[d] (R,R)
12[c]		**38c**	67	68
13[a]		**33a**	100	29 (R)
14[b]		**34b**	100	48[d] (R)
15[a]		**33a**	100	73 (R,R)
16[a]		**33a**	100	83 (R)
17[b]		**34b**	71	98[d] (R)
18[a]		**35c**	60	82 (S)
19[c]		**38c**	47	66 (R)
20[a]		**33a**	100	69 (R)
21[b]		**34b**	89	82[d] (R,R)
22[a]		**35c**	100	74 (S,S)

[a] 0.1 equiv of ketone used. [b] 0.2 equiv of ketone used. [c] 0.3 equiv of ketone used. [d] ee_{max} (100 × product ee/ketone ee).

2.6. Carbohydrate-Based and Related Ketones

2.6.1. Catalyst Development

In 1996, a fructose-derived ketone (**41**) was reported to be a highly reactive and enantioselective asymmetric epoxidation catalyst for *trans*- and trisubstituted olefins.[36] This ketone can be readily obtained *via* a two-step synthesis (ketalization then oxidation) from D-fructose (Scheme 2)[37–39] The enantiomer of this ketone (*ent*-**41**) can also be easily

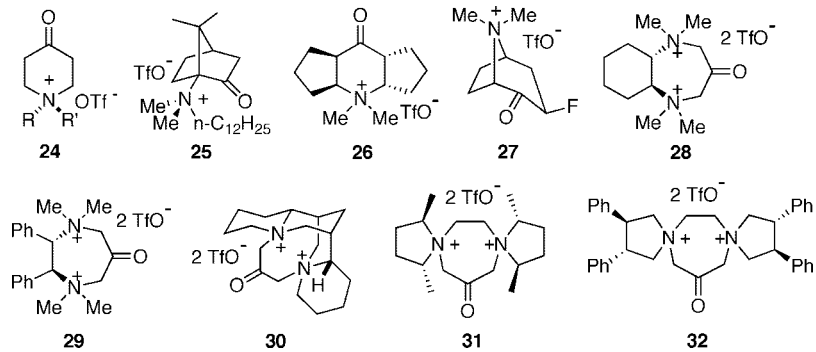


Figure 11.

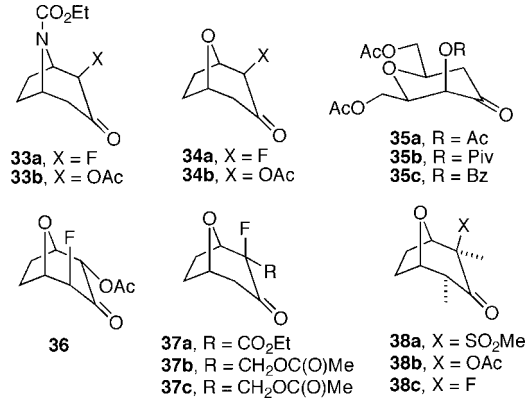
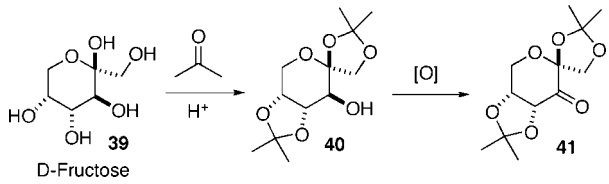


Figure 12.

Scheme 2. Synthesis of Ketone 41



obtained from L-fructose, which can be synthesized from L-sorbose.[40]

Ketone **41** belongs to a class of ketones designed on the basis of the following general considerations (Figure 13): (1) the chiral control elements being placed close to the reacting carbonyl to enhance the stereochemical interaction between substrate and catalyst; (2) fused ring(s) and/or a quaternary center α to the carbonyl group being used to minimize the potential epimerization of the stereogenic centers; (3) the approach of an olefin to the reacting dioxirane being directed by sterically blocking one face or by a C_2- or pseudo-C_2-symmetric element; (4) the carbonyl being inductively activated by introduction of electron-withdrawing substituents.[36,37]

The reaction pH often has a large impact on the epoxidation with dioxiranes generated *in situ*.[13a,h] At high pH, Oxone autodecomposes rapidly,[41] resulting in poor conversion for the epoxidation. Therefore, earlier epoxidations using *in situ* generated dioxirane were usually carried out at pH 7−8.[13] At this pH, the epoxidation with ketone **41** gave high enantioselectivities for a variety of trans- and trisubstituted olefins, but required an excess amount of ketone for good conversion of olefin substrates.[36] Apparently, ketone **41** readily decomposes at this pH, and Baeyer−Villiger oxidation was assumed to be one of the possible decomposition pathways although the corresponding lactones **45** and **46** had not been isolated as they might be rapidly hydrolyzed under the reaction conditions (Scheme 3). The reaction pH was then raised with the hope that, at higher reaction pH, the formation of anion **43** and subsequent formation of the

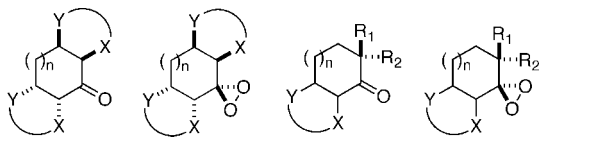


Figure 13.

Scheme 3. Catalytic Cycle of Ketone 41-Mediated Epoxidation

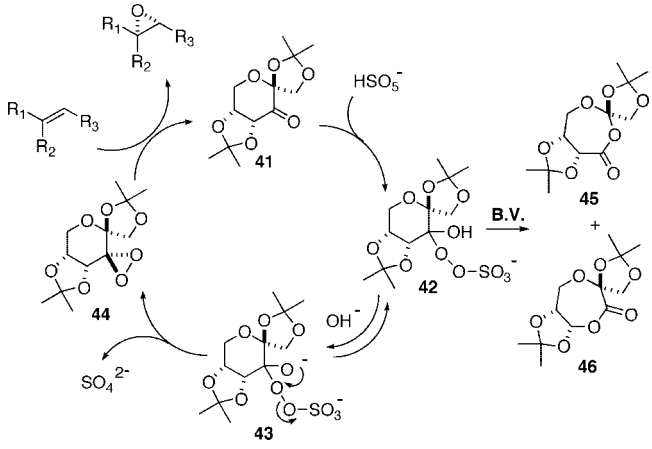
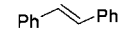
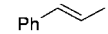
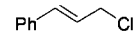
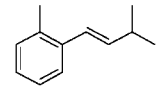
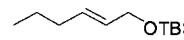
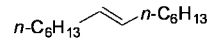
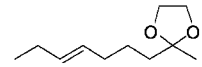
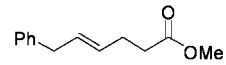
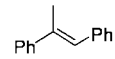
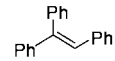
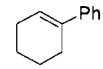
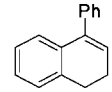
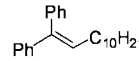
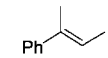
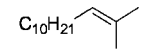
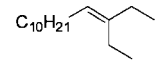
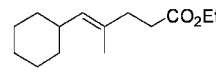
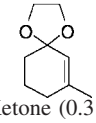
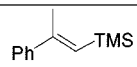
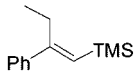
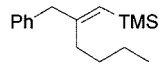
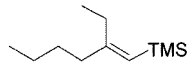
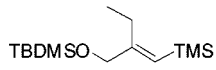
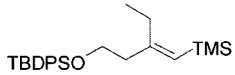
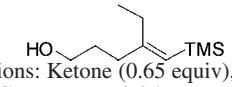


Table 6. Asymmetric Epoxidation of trans- and Trisubstituted Olefin with Ketone 41[a]

Entry	Substrate	Yield (%)	ee (%)
1		85	98 (R,R)
2		94	96 (R,R)
3		49	96 (2S,3R)
4		78	96 (R,R)
5		83	95 (R,R)
6		89	95 (R,R)
7		92	92 (R,R)
8		68	92 (R,R)
9		89	96 (R,R)
10		54	97 (R)
11		94	98 (R,R)
12		98	95 (1S,2R)
13		92	97 (R)
14		89	97 (R,R)
15		97	87 (R)
16		94	89 (R)
17		89	94 (R,R)
18		41 (*ent*-**41**)	97 (R,R)

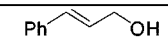
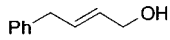
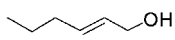
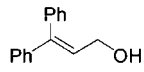
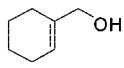
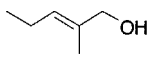
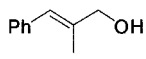
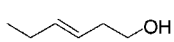
[a] Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN−DMM−0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq Na_2EDTA (1:2:2 v/v).

Table 7. Asymmetric Epoxidation of 2,2-Disubstituted Vinylsilanes with Ketone 41[a]

Entry	Substrate	Yield (%)	ee (%)
1		74	94 (R,R)
2		82	92 (R,R)
3		66	93 (R,R)
4		51	90 (R,R)
5		67	84 (R,R)
6		67	92 (R,R)
7[b]		71	93 (R,R)

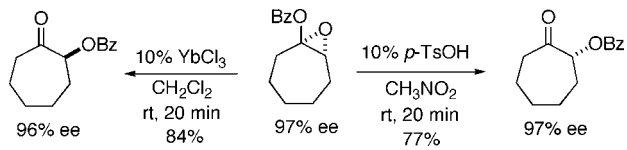
[a] Conditions: Ketone (0.65 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN−DMM−0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq Na_2EDTA (1:2:2 v/v), 0 °C. [b] 0.3 equiv of ketone used.

Table 8. Asymmetric Epoxidation of Hydroxyalkenes with Ketone 41[a]

Entry	Substrate	Yield (%)	ee (%)
1		85	94 (R,R)
2		45	91 (R,R)
3		68	91 (R,R)
4		87	94 (R)
5		93	94 (R,R)
6		85	92 (R,R)
7		75	74 (R,R)
8		82	90 (R,R)

[a] Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN−DMM−aq K_2CO_3/AcOH (1:2:2 v/v).

Scheme 4. Rearrangement of Enol Ester Epoxide to α-Acyloxy Ketones



Scheme 5. Kinetic Resolution of Racemic Enol Ester Epoxide

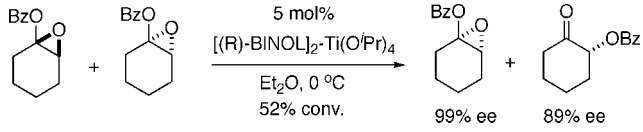
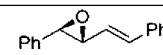
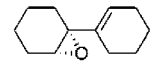
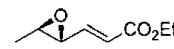
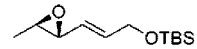
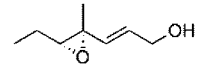
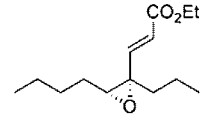
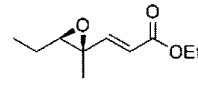
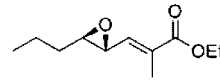
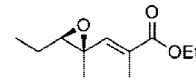
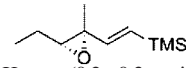
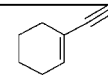
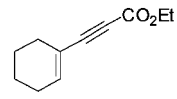
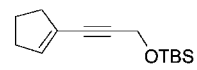
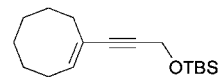
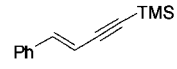
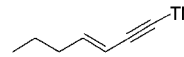
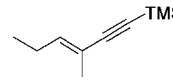
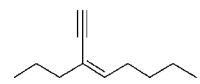


Table 9. Asymmetric Epoxidation of Conjugated Dienes with Ketone 41[a]

Entry	Epoxide	Yield (%)	ee (%)
1		77	97
2		54	95
3		41	96
4		68	96
5		68	90
6		68	95
7		82	95
8		61	94
9		89	94
10		60	92

[a] Conditions: Ketone (0.2−0.3 equiv), Oxone (1.12−1.38 equiv), K_2CO_3 (5.0−6.2 equiv), MeCN−DMM−0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq Na_2EDTA (1:2:2 v/v).

Table 10. Asymmetric Epoxidation of Conjugated Enynes with Ketone 41[a]

Entry	Substrate	Yield (%)	ee (%)
1		78	93 (R,R)
2		71	93 (R,R)
3		97	77 (R,R)
4		98	96 (R,R)
5		59	96 (R,R)
6		71	89 (R,R)
7		84	95 (R,R)
8		60	93 (R,R)

[a] Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN−DMM−aq K_2CO_3/AcOH (1:2:2 v/v).

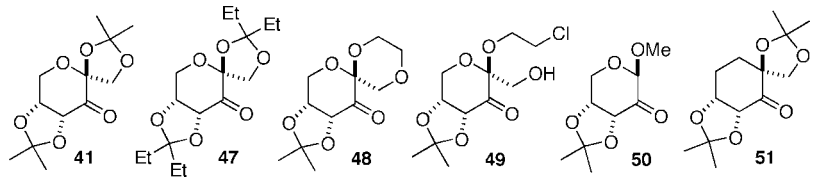
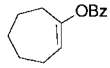
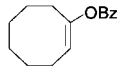
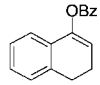
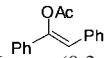


Figure 14.

Table 11. Asymmetric Epoxidation of Enol Esters with Ketone 41[a]

Entry	Substrate	Yield (%)	ee (%)
1		82	93 (R,R)
2		79	80 (R,R)
3		87	91 (R,R)
4		82	95 (R,R)
5		92	88 (R,R)
6		66	91 (2S,3R)
7		46	91 (2S,3R)

[a] Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), org solv/aq buffer (3:2, v/v), 0 °C

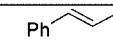
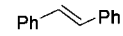
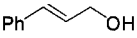
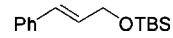
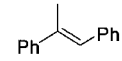
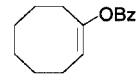
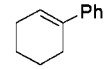
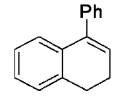
Table 12. Asymmetric Epoxidation with Ketones 41, 47−51[a]

Entry	Substrate	Ketone	Conv. (%)	ee (%)
1		**41**	75	97 (R,R)
2		**47**	16	96 (R,R)
3		**48**	34	90 (R,R)
4		**49**	2	nd
5		**50**	10	88 (R,R)
6		**51**	10	88 (R,R)
7		**41**	93	92 (R,R)
8		**47**	32	86 (R,R)
9		**48**	44	61 (R,R)
10		**49**	8	65 (R,R)
11		**50**	15	59 (R,R)
12		**51**	61	87 (R,R)

[a] Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN/0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq EDTA (4×10^{-4} M) solution (1.5:1, v/v), 1.5 h. For entries 6 and 12, Oxone (2.07 equiv) and K_2CO_3 (8.66 equiv) in DMM–MeCN–buffer (0.1 M K_2CO_3–AcOH, pH 9.3) (1.5:1.5:2 v/v) for 8 h.

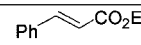
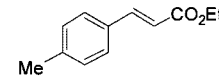
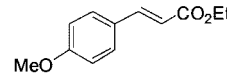
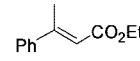
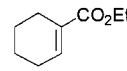
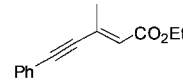
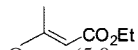
desired dioxirane **44** could further be favored over the undesired Baeyer−Villiger oxidation from **42**. It was also hoped that ketone **41** could react with Oxone fast enough before its autodecomposition at high pH.

Table 13. Asymmetric Epoxidation with Ketone 52[a]

Entry	Substrate	Yield (%)	ee (%)
1		100[b]	88 (R,R)
2		67	96 (R,R)
3		89	87 (R,R)
4		73	94 (R,R)
5		80	93 (R,R)
6		93	90 (R,R)
7		74	92 (R,R)
8		80	93 (R,R)

[a] Conditions: Ketone (0.01−0.05 equiv), Oxone (1.49−2.13 equiv), K_2CO_3 (3.12−4.45 equiv), DMM−MeCN−buffer (2:1:2 v/v), 0 °C. [b] Conversion (%).

Table 14. Asymmetric Epoxidation with Ketone 53[a]

Entry	Substrate	Yield (%)	ee (%)
1[b]		73	96 (2S,3R)
2[c]		91	97
3[d]		57	90 (2S,3R)
4[c]		93	96 (2S,3R)
5[c]		77	93
6[c]		96	94
7[b]		64	82

[a] Conditions: Oxone (5.0 equiv), $NaHCO_3$ (15.5 equiv), MeCN−aq Na_2EDTA (1.5:1 v/v), 0 °C. [b] 0.3 equiv of ketone used. [c] 0.25 equiv of ketone used. [d] 0.2 equiv of ketone used.

The epoxidation of *trans*-β-methylstyrene was then carried out to investigate the effect of reaction pH on the epoxidation.[37,42] A higher pH was indeed beneficial to the catalyst efficiency, with the substrate conversion being increased from ca. 5% at pH 7−8 to >80% at pH >10. As

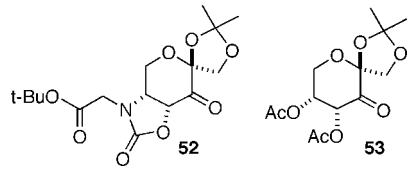


Figure 15.

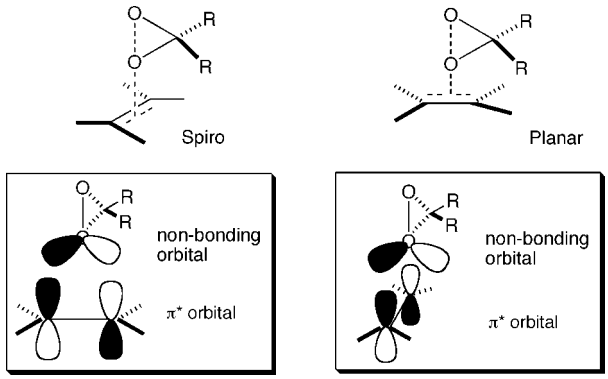


Figure 16.

Scheme 6. Catalytic Cycle of Ketone 41 Catalyzed Epoxidation Using H_2O_2

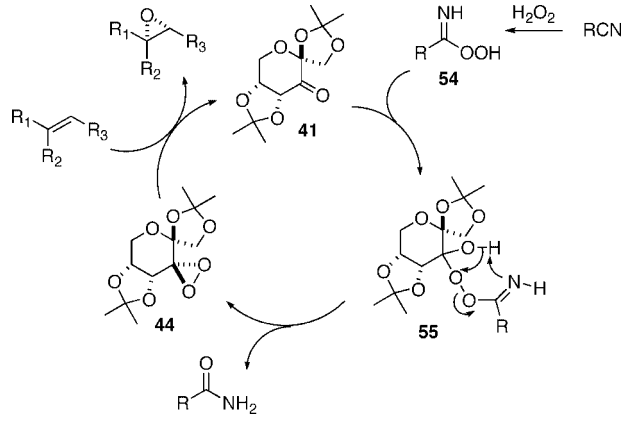
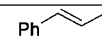
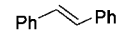
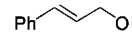
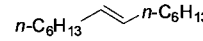
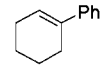
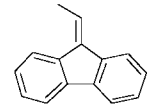
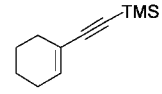
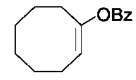
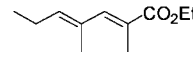
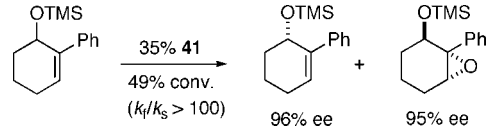


Table 15. Asymmetric Epoxidation with Ketone 41 and H_2O_2 as Oxidant

Entry	Substrate	Yield (%)	ee (%)
1[a]		93	92
2[b]		90	98
3[a]		71	89
4[b]		97	92
5[a]		90	96
6[b]		77	92
7[a]		93	95
8[a]		75	96
9[a]		76	95

[a] Conditions: Ketone (0.1−0.3 equiv), H_2O_2 (4.0 equiv) in MeCN−2.0 M aq K_2CO_3 in aq EDTA. [b] Conditions: Ketone (0.3 equiv), H_2O_2 (4.0 equiv), in MeCN−EtOH−CH_2Cl_2 (1:1:2, v/v)−2.0 M aq K_2CO_3 in aq EDTA.

Scheme 7. Kinetic Resolution of 1,6-Disubstituted Cyclohexene



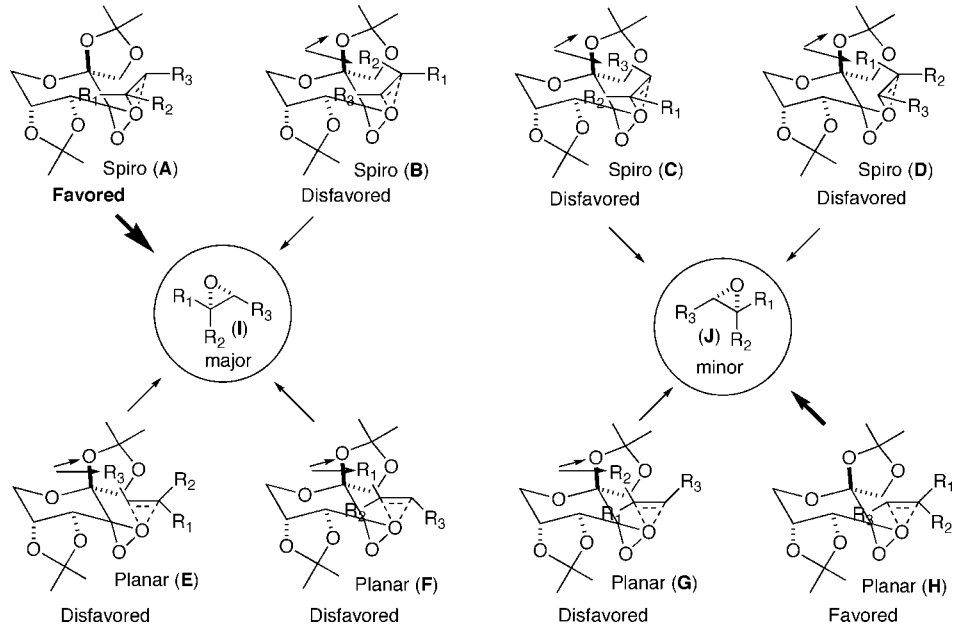
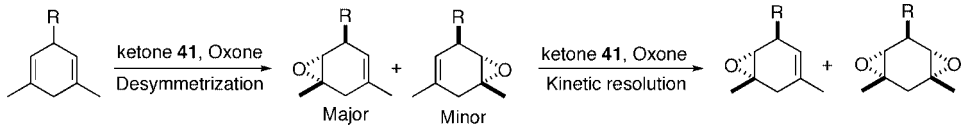
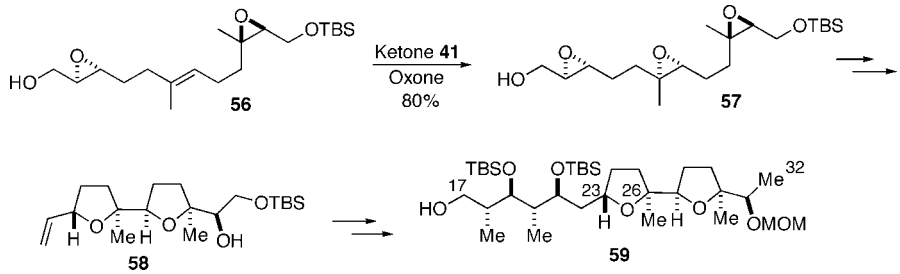


Figure 17.

Scheme 8. Desymmetrization and Kinetic Resolution of Substituted 1,4-Cyclohexadiene



Scheme 9. Synthesis of Bistetrahydrofuran C17−C32 Fragment (59)



a result, a catalytic asymmetric epoxidation process became feasible for ketone **41**. The epoxidation is typically performed at pH around 10.5 by adding either K_2CO_3 or KOH as the reaction proceeds. It is crucial to keep the reaction pH steady throughout the reaction to maximize the reaction efficiency. Further studies showed that greater conversions were also obtained for the epoxidation with acetone and trifluoroacetone at higher pH.[43,44] For example, 80% conversion was obtained for *trans*-β-methylstyrene at pH 10 with only 5 mol % of CF_3COCH_3. It appears that higher pH not only suppresses the possible Baeyer−Villiger decomposition pathway but also enhances the nucleophilicity of Oxone toward ketone catalysts, thus increasing the overall epoxidation efficiency. A better mechanistic understanding awaits further study.

The substrate scope of asymmetric epoxidation with ketone **41** was explored with a variety of olefins using a catalytic amount of ketone (Tables 6–11). High enantioselectivities can be obtained for a wide range of unfunctionalized trans- and trisubstituted olefins (Table 6).[37] The fact that *trans*-7-tetradecene can be epoxidized in high yield and ee's indicated that this epoxidation is general for simple *trans*-olefins (Table 6, entry 6). A variety of 2,2-disubstituted vinyl silanes can be epoxidized in high ee's (Table 7).[45] The resulting epoxide can be desilylated to give enantiomerically enriched 1,1-disubstituted terminal epoxides. Allylic, homoallylic, and bishomoallylic alcohols are effective substrates as well (Table 8).[46] The epoxidation of conjugated dienes[47] and enynes[48] can be accomplished with high ee's to obtain vinyl epoxides and propargyl epoxides (Tables 9 and 10). A variety of silyl enol ethers and esters were also studied.[49,50] The epoxide of a silyl enol ether rearranges to give an α-hydroxyl ketone under epoxidation conditions. Some α-hydroxyl ketones are prone to racemization and might act as catalyst for the epoxidation during the reaction process, thus lowering the overall enantioselectivity of the resulting compounds. Generally, enol esters are more effective substrates and can be

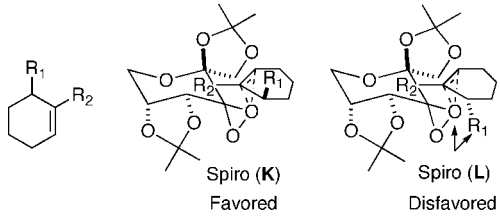
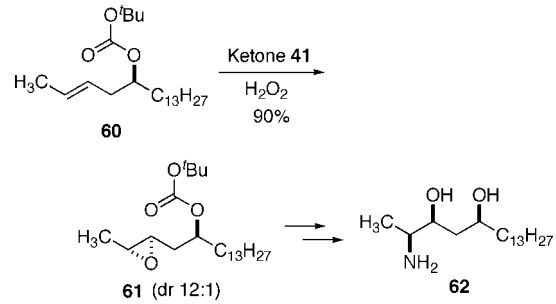


Figure 18.

Scheme 10. Synthesis of Aminodiol 62

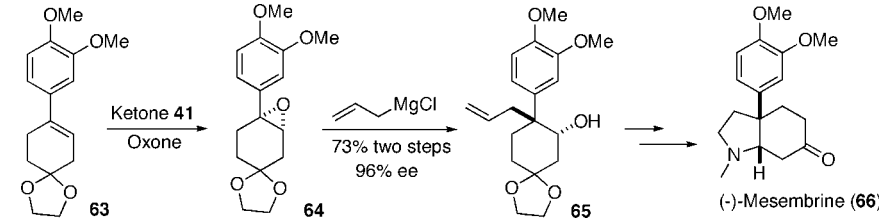


epoxidized in high enantioselectivities (Table 11). Optically active α-hydroxyl or α-acyloxy ketones can be obtained by hydrolysis or stereoselective rearrangement of the resulting chiral enol ester epoxides (Scheme 4). This rearrangement can operate through two different pathways, resulting in either retention or inversion of configuration. As a result, both enantiomers of α-acyloxy ketones can be readily accessed.[49b–d] It was also found that racemic enol ester epoxide can be kinetically resolved using chiral Lewis acids. Good enantiomeric excess can be obtained for both the α-acyloxy ketone and the unreacted enol ester epoxide using 5% [(R)-BINOL]$_2$-Ti(O^{i}Pr)$_4$ in ether (Scheme 5).[49c]

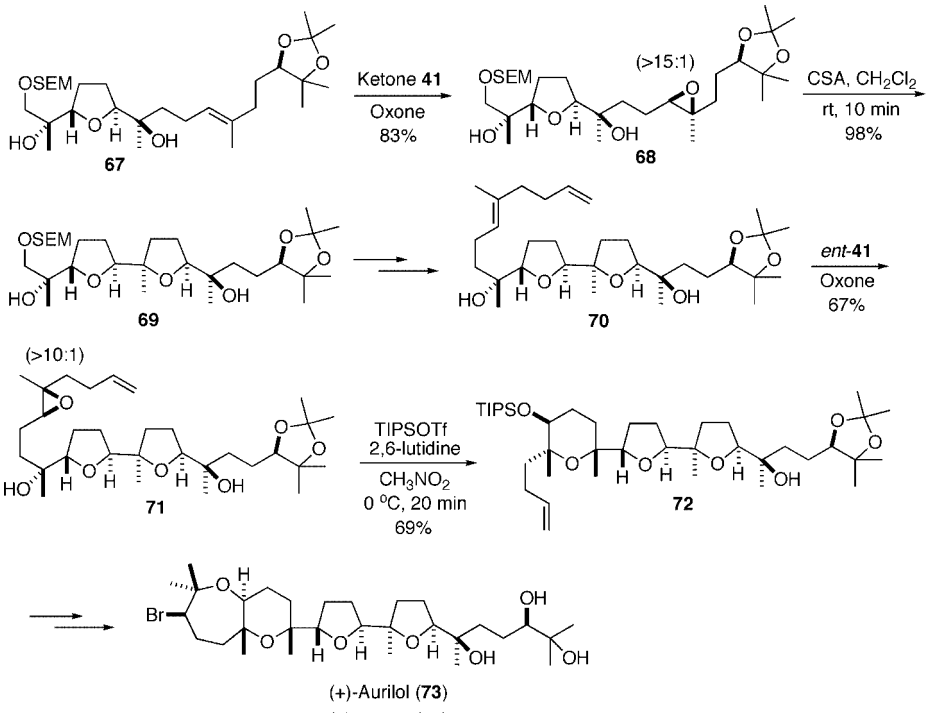
Further studies with a variety of ketone catalysts illustrated the structural requirements of the chiral ketone catalyst for asymmetric epoxidations.[51,52] As shown in Figure 14 and Table 12, the spiro 5-membered ketal group of **41** appears to be better than both the six-membered ketal and the acyclic groups (**41** vs **48**, **49** and **50**). Methyl ketals also seem to give better epoxidation reactivity and enantioselectivity compared to ethyl ketals (**41** vs **47**). The epoxidation results also indicated that the pyranose oxygen is beneficial to catalysis since ketone **41** gave better epoxidation results compared to its carbocylic counterpart (**51**).[52]

Baeyer−Villiger oxidation is believed to be one of the major decomposition pathways for ketone **41** under the epoxidation conditions (Scheme 3); therefore, a high catalyst loading is required (typically 20−30 mol %). During the search for a more robust catalyst, ketone **52** (Figure 15) was synthesized with the hope that the replacement of the fused ketal of **41** by a more electron-withdrawing oxazolidinone would reduce the decomposition of this catalyst *via* Baeyer−Villiger oxidation (Scheme 3).[53] Indeed, only 5 mol % (1 mol % in some cases) of ketone **52** is needed to get comparable epoxidation results with 20−30 mol % of ketone

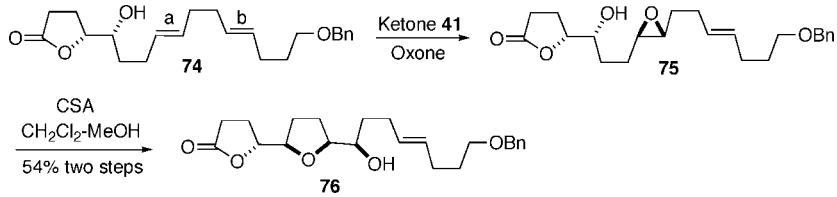
Scheme 11. Synthesis of (-)-Mesembrine (66)



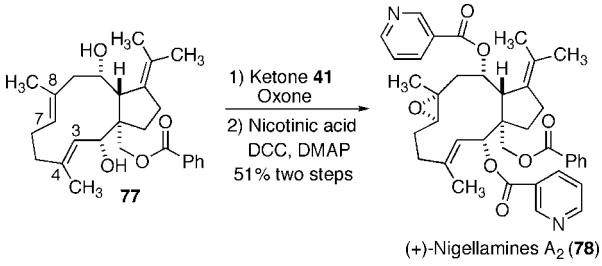
Scheme 12. Synthesis of (+)-Aurilol (73)



Scheme 13. Synthesis Tetrahydrofuran Lactone 76



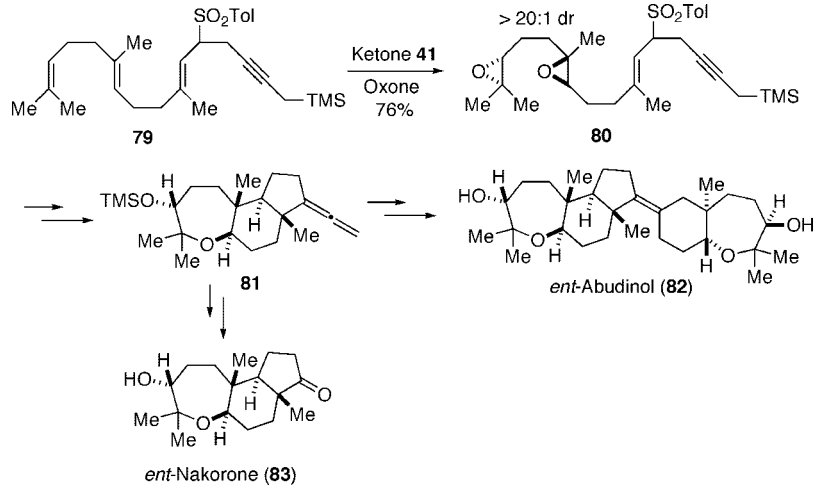
Scheme 14. Synthesis of (+)-Nigellamine A_2 (78)



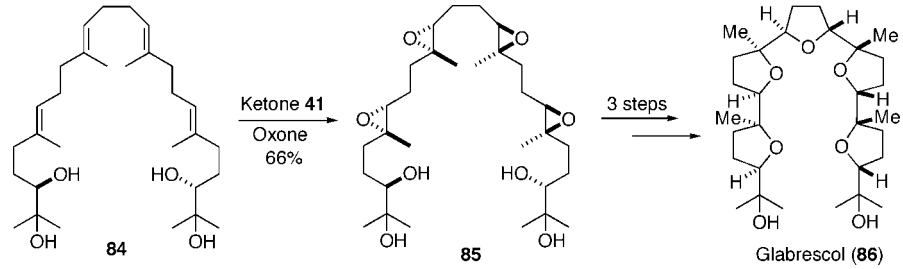
41 (Table 13). Besides using oxazolidinone to suppress the undesired Baeyer−Villiger oxidation of the catalysts, acetate groups were also tested for this purpose. Ketone **41** epoxidizes electron-deficient α,β-unsaturated esters sluggishly since dioxiranes are electrophilic reagents. Ketone **53**, readily available from ketone **41**, was found to be an effective catalyst toward these esters (Figure 15).[54,55] High ee's and good yields can be obtained for a number of α,β-unsaturated esters (Table 14). High reactivity and enantioselectivity should make ketone **53** useful for other olefins as well. The information obtained with ketones **52** and **53** should be useful for the design of more effective catalysts in the future.

Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), a commonly used source for peroxymonosulfate ($KHSO_5$), is effective toward the generation of dioxirane from ketones, presumably because the sulfate moiety is a good leaving group (Scheme 3).[56,57] Hydrogen peroxide (H_2O_2) is an attractive substitute for Oxone because it has a high active oxygen content and its reduction product is water.[58,59] Studies with ketone **41** showed that a combination of RCN and H_2O_2 can be used as oxidant (Scheme 6).[60–62] Peroxyimidic acid **54** is likely to be the active oxidant. CH_3CN and CH_3CH_2CN were proven to give the best results among the nitriles tested. This epoxidation system is milder; the amount of solvent and salts needed are significantly reduced and the slow addition of oxidant is unnecessary. The epoxidation results are very comparable to that of using Oxone (Table 15). A mixed solvent such as $CH_3CN-EtOH-CH_2Cl_2$ can be used for olefins with poor solubility.[60b] In addition to ketone **41**, the

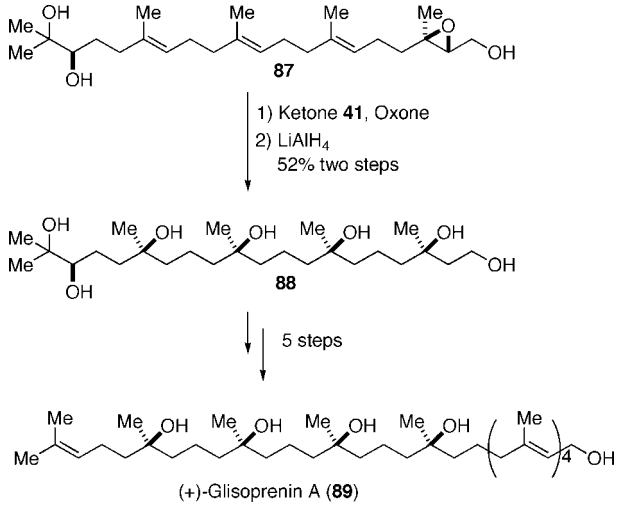
Scheme 15. Synthesis of *ent*-Abudinol (82) and *ent*-Nakorone (83)



Scheme 16. Synthesis of Glabrescol (86)



Scheme 17. Synthesis of (+)-Glisoprenin A (89)

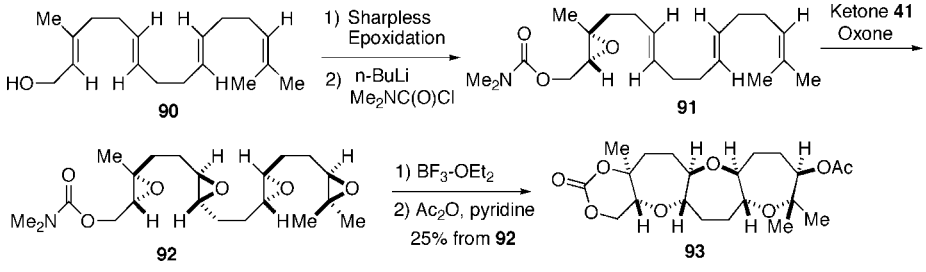


$RCN-H_2O_2$ system can be extended to other ketones, such as trifluoroacetone.[44,63]

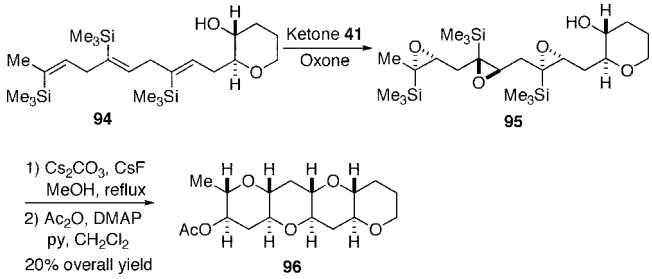
Elucidation of the transition states of the epoxidation would facilitate the rationalization of the stereochemistry of the formed epoxide and the design of new catalysts. Two extreme epoxidation modes of dioxiranes (spiro and planar) are shown in Figure 16.[10c,d,18,19b,c,36,37,64–66] Based on the observation that the epoxidation of *cis*-hexene with dimethydioxirane was 7−9 times faster than that of *trans*-hexene, Baumstark and co-workers proposed that spiro transition state is the major operating transition state.[64] Computational studies also show that spiro transition state is the favored transition state for the oxygen transfer from dimethyldioxirane to ethylene, possibly due to the stabilizing interaction between the oxygen nonbonding orbital and the olefin π^* orbital, which is not feasible geometrically in the planar transition state.[65]

The stereochemical outcome of the epoxidation by chiral dioxirane provides a new dimension to study the transition state. Of the two diastereomeric oxygens of the dioxirane derived from ketone **41**, the sterically more accessible equatorial oxygen is likely to be transferred onto the olefin being epoxidized. Figure 17 lists a few possible transition states for the epoxidation with ketone **41**. For trisubstituted olefins, transition states **B** to **G** are sterically disfavored and are unlikely to be major contributors (for trans-disubstituted olefins where R_2 = H, **B** and **G** are sterically feasible). Studies show that the epoxidation of trans- and trisubstituted olefins are consistent with the notion that the epoxidation proceeds mainly through sterically favored spiro **A**, giving

Scheme 18. Polyepoxide Cyclization



Scheme 19. Polyether Synthesis *via* Cascade Epoxide Opening



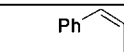
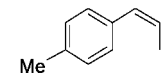
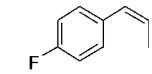
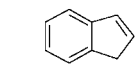
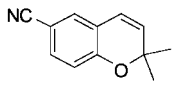
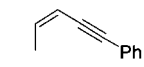
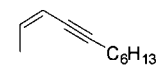
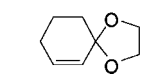
epoxide **I** as major enantiomer. However, planar **H** also competes with spiro **A**, giving the opposite enantiomer of the epoxides.[36,37] The competition between **A** and **H** thus will have an impact on the ee's obtained for epoxides and is influenced by the electronic and steric nature of the olefin substitutents. Electronically, the enantioselectivity of epoxides is usually increased by conjugating aromatic rings, alkenes, or alkynes since these conjugating groups can lower the π^* orbital of the reacting C−C double bond and enhance the stabilizing secondary orbital interaction, consequently further favoring spiro **A** transition state. Sterically, higher ee's are generally obtained with a smaller R_1 (favoring spiro **A**) and/or a larger R_3 (disfavoring planar **H**).[36,37]

The aforementioned transition state model for the epoxidation with **41** is further validated by subsequent study on kinetic resolution of racemic cyclohexene derivatives and desymmetrization of 1,4-cyclohexadiene derivatives. A number of 1,6- and 1,3-disubstituted cyclohexenes can be resolved with ketone **41** (Scheme 7).[67] Transition states spiro **K** and spiro **L** illustrate the major transition state of the epoxidation of each enantiomer of racemic 1,6-disubstituted cyclohexenes (Figure 18). The unfavorable steric interaction between the substrate and the catalyst in spiro **L** makes the epoxidation of this enantiomer slower. This kinetic resolution method also provides a convenient way to obtain chiral 1,3- and 1,6-disubstituted cyclohexenes and its epoxides. More recent studies have shown that ketone **41** is able to desymmetrize 1,4-cyclohexadienes and kinetically resolve the resulting monoepoxides. Depending on the diene system, the ee of the initially formed monoepoxide can be increased or decreased as the epoxidation proceeds (Scheme 8).[68] The observed reaction outcome can be effectively rationalized by the above transition state analysis.

2.6.2. Synthetic Applications of Ketone **41**

Fructose-derived ketone **41** is readily available and is effective for a wide variety of trans- and trisubstituted olefins. The epoxidation with ketone **41** has been used to synthesize optically active molecules by other researchers. Some of these syntheses will be highlighted in this section.

Table 16. Asymmetric Epoxidation of *cis*-Olefins with Ketone 104[a]

Entry	Substrate	Yield (%)	ee (%)
1		87	91 (1R,2S)
2		76	92 (1R,2S)
3		74	92 (1R,2S)
4		88	83 (1R,2S)
5		61	91 (3R,4R)
6		82	91 (2S,3R)
7		77	87 (2S,3R)
8		61	97

[a] Ketone (0.15−0.3 equiv), Oxone (1.78 equiv), K_2CO_3 (4.02 equiv), DME−DMM (3:1, v/v), buffer, 0 or −10 °C.

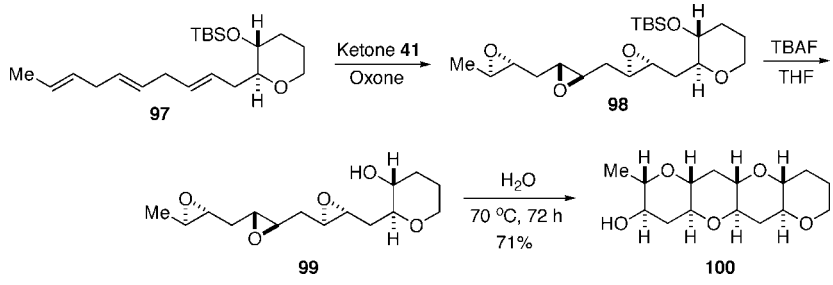
In 2006, Marshall and co-workers employed ketone **41** in the synthesis of the bistetrahydrofuran C17−C32 segment of antibiotic ionomycin.[69] Epoxide **56** was obtained by Sharpless epoxidation of allylic alcohols, and the internal trisubstituted olefin was epoxidized with ketone **41** and Oxone to give epoxide **57** in 80% yield (Scheme 9).

In 2005, McDonald and co-workers reported that the epoxidation of **60** with ketone **41** gave epoxide **61** in 90% yield with high diastereoselectivity (dr 12:1) (Scheme 10).[70] Epoxide **61** was subsequently converted into 1-deoxy-5-hydroxy-sphingolipid analogue **62** by a highly stereo- and regioselective synthetic route. Hydrogen peroxide (H_2O_2) was used as the stoichiometric oxidant for the epoxidation. When Oxone was used as stoichiometric oxidant, higher diastereoselectivity (dr 19:1) was obtained, but requiring additional catalyst for complete conversion of the substrate.

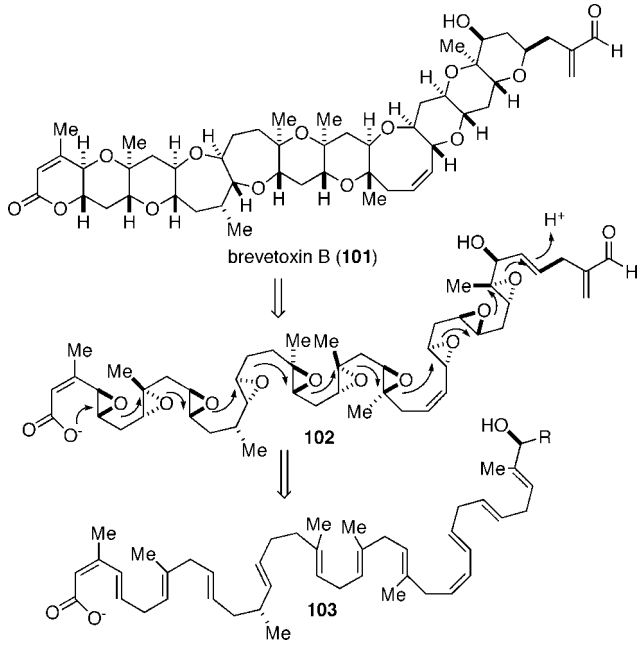
In 2005, Taber and co-workers reported that the epoxidation of **63** with **41** followed by regioselective ring opening of crude epoxide **64** with allylmagnesium chloride gave alcohol **65** in overall 73% yield and 96% ee. Alcohol **65** was subsequently converted into (−)-mesembrine (**66**) (a natural product with anxiolytic properties) in five steps (Scheme 11).[71]

In 2005, Morimoto and co-workers accomplished the first total synthesis of cytotoxic bromotriterpene polyether (+)-

Scheme 20. Water Promoted Cascade Epoxide Cyclization

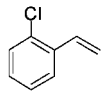
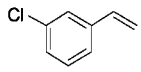
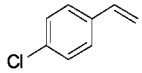
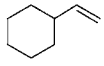
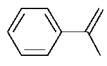
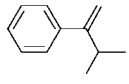
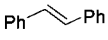


Scheme 21. Biosynthetic Pathway of Brevitoxin B



aurilol (**73**) *via* biogenetic-like regioselective ether ring formation to establish the complete stereochemistry assignment (Scheme 12).[72] Epoxidation of **67** with **41** gave epoxide **68** with high diastereoselectivity. Epoxide **68** underwent acid-catalyzed 5-exo-tet cyclization to produce tetrahydrofuran with the desired stereochemistry. Subsequently, diene **70** was selectively epoxidized only at the trisubstituted olefin with

Table 17. Asymmetric Epoxidation of Terminal, trans-, and Trisubstituted Olefins with Ketone 104[a]

Entry	Substrate	Yield (%)	ee (%)
1		92	81 (R)
2		61	81 (R)
3		74	83 (R)
4		90	85 (R)
5		93	71
6		88	30 (S)
7		87	58
8		65	94 (R,R)
9		91	77 (R,R)
10		78	95
11		68	42 (S,S)

[a] Ketone (0.15−0.3 equiv), Oxone (1.78 equiv), K_2CO_3 (4.02 equiv), DME−DMM (3:1, v/v), buffer, 0 or −10 °C.

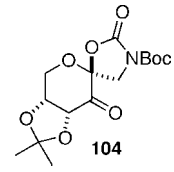


Figure 19.

ent-**41** to give epoxide **71** which underwent an unusal silyl triflate-promoted 6-endo-tet cyclization to form the corresponding tetrahydropyran with the desired stereochemistry. Epoxides **68** and **71** play important roles in setting stereocenters in the final product.

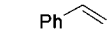
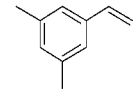
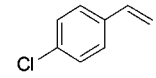
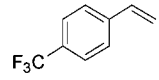
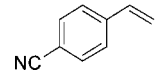
In 2005, Sinha and co-workers reported syntheses of thirty-six stereoisomers of bifunctional adjacent bis-THF lactones using a combination of oxidation methods such as Sharpless asymmetric dihydroxylation, rhenium(VII) oxide-mediated oxidative cyclization, and asymmetric epoxidation with ketone **41** and *ent*-**41**.[73] The thirty-six stereoisomers can provide a complete library (64 isomers) of annonaceous bis-THF acetogenins after some transformations. It is particularly interesting to note that substrate **74**, that contains two trans-double bonds, can be selectively epoxidized at olefin **a** using **41**, giving mono-THF lactone **76** in 54% overall yield after cyclization with CSA (Scheme 13).

In 2006, Ready and co-workers reported that compound **77**, which contains three double bonds, was selectively epoxidized at the desired C_7-C_8 double bond with the desired stereochemistry. The resulting epoxide was converted into (+)-nigellamine A_2 (**78**) in 51% yield over two steps (Scheme 14).[74]

Ketone **41** was also employed in McDonald and co-workers' total synthesis of nakorone, and abudinol B.[75] Triene-yne **79** was selectively epoxidized on the two more electron-rich double bonds, leaving the olefin next to the electron-withdrawing sulfone group unreacted (Scheme 15). Bis-epoxide **80** was transformed into both *ent*-nakorone (**83**) and *ent*-abudinol B (**82**).

In 2000, in efforts to verify the structure of glabrescol, a chiral C_2-symmetric pentacyclic oxasqualenoid, Corey and co-workers reported the tetraepoxidation of tetraene **84** to form epoxide **85**, which was transformed into glabrescol (**86**) in three steps (Scheme 16).[76]

Table 18. Asymmetric Epoxidation of Styrenes with Ketone 105[a]

Entry	Substrate	Yield (%)	ee (%)
1		63	90 (R)
2		62	89
3		76	91 (R)
4		69	93
5		56	93 (R)

[a] Ketone (0.2 equiv), Oxone (3.4 equiv), K_2CO_3 (7.7 equiv), DME−DMM (5:1, v/v), buffer, −10 °C.

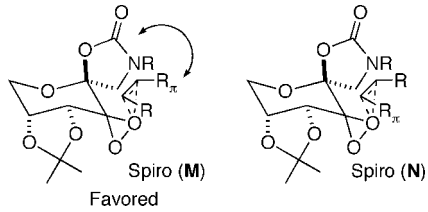


Figure 20.

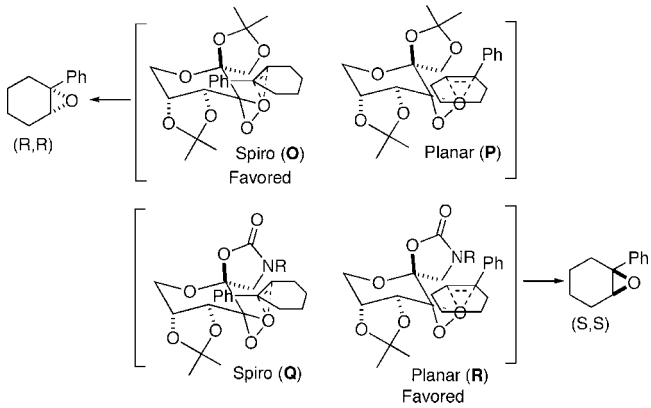


Figure 21.

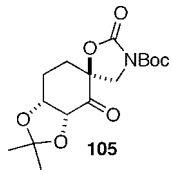


Figure 22.

In 2004, Kishi and co-workers reported that the epoxidation of triene **87** with ketone **41** and subsequent epoxide opening with $LiAlH_4$ gave compound **88** in 52% yield over two steps. Compound **88** was transformed into (+)-gliosoprenin A (**89**) in five steps (Scheme 17).[77]

McDonald and co-workers studied a series of biomimetic syntheses of fused polycyclic ethers.[78] For example, acyclic polyene **91** was epoxidized with ketone **41** to give polyepoxide **92** (Scheme 18). Fused polycyclic ether **93** can be obtained in good yield from **92** *via* the BF_3-Et_2O promoted *endo*-regioselective tandem oxacyclization.[78d]

Recently, Jamison and co-workers reported a ladder fused polyether synthesis *via* cascade epoxidation and cyclization.[79] For example, vinylsilane **94** was epoxidized with ketone **41** to give triepoxide **95**, which was cyclized with Cs_2CO_3/CsF in MeOH to give tetracyclic tetrahydropyran **96** in 20% overall yield after acetylation (Scheme 19).[80] The $SiMe_3$ group acts as a "disappearing" directing group in the cyclization.

In more recent studies by Jamison and co-workers, water was found to be the optimal reaction promoter. The desired fused tetrahydropyran rings can be obtained selectively with no need for directing groups when the epoxide-opening reactions were done in water (Scheme 20).[81]

Polyethers such as brevitoxin B (**101**) are a class of compounds possessing important biological activities. It has been proposed that some naturally occurring polyethers are biosynthetically derived from the cyclization of polyepoxides which result from the epoxidation of polyene precursors (Scheme 21).[82,83] Such biomimetic cyclization of polyepoxides is a potentially powerful and versatile strategy for the synthesis of polyethers because of the simplicity with which the stereochemically complex segments are assembled from achiral polyolefinic precursors. The epoxidation with ketone **41** should provide a valuable method to investigate the hypothesis and application of the polyene−polyepoxide−polyether biosynthetic pathway. The effectiveness and simplicity of this epoxidation should make it useful in organic synthesis.[84]

Table 19. Asymmetric Epoxidation with Ketones 106−110[a]

Entry	Ketone	Substrate	Conv. (%)	ee (%)
1	**106**	Ph	76	96 (R,R)
2	**107**		91	76 (R,R)
3	**108**		66	73 (R,R)
4	**109**		76	83 (R,R)
5	**110**		100	80 (R,R)
6	**106**	Ph	87	12 (1R,2S)
7	**107**		100	45 (1R,2S)
8	**108**		55	61 (1R,2S)
9	**109**		89	70 (1R,2S)
10	**110**		100	68 (1R,2S)
11	**106**	Ph	100	97 (R,R)
12	**107**		96	38 (R,R)
13	**108**		45	18 (S,S)
14	**109**		89	88 (R,R)
15	**110**		100	87 (R,R)
16	**106**	Ph	50	19 (R)
17	**107**		100	41 (R)
18	**108**		34	60 (R)
19	**109**		93	63 (R)
20	**110**		100	52 (R)

[a] Ketone (0.30 equiv), Oxone (1.38 equiv), K_2CO_3 (5.80 equiv), CH_3CN/DMM (1:2, v/v) and buffer (0.1 M K_2CO_3−AcOH, pH 9.3) at 0 °C, 1.5 h.

2.6.3. Developing Catalysts for cis-Olefins, Styrenes, and Other Olefins

Thus far, only trans- and trisubstituted olefins have effectively been epoxidized with high ee's. Efforts were made to develop ketone catalysts for other types of olefins. In 2000, glucose-derived ketone **104** was reported to be a highly enantioselective catalyst for the epoxidation of *cis*-olefins (Figure 19) (Table 16).[85,86] No isomerization was observed in the epoxidation of acyclic systems (the epoxidation of *cis*-olefin only afforded *cis*-epoxide). Encouragingly high ee's were also obtained for certain terminal olefins with ketone **104** (Table 17). From the absolute configuration of several epoxides, it was revealed that the substitution with a π system, regardless of the size, prefers to be next to the spiro oxazolidinone of ketone **104** (spiro **M**, Figure 20). It seems that there exists some type of attraction between the R_π group of the olefin and the oxazolidinone of the ketone catalyst in the transition state. A prominent example is illustrated in Figure 21. When the epoxidation of 1-phenylcyclohexene

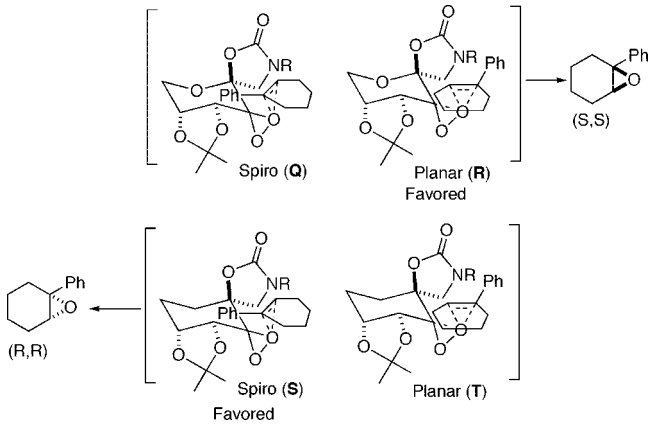


Figure 23.

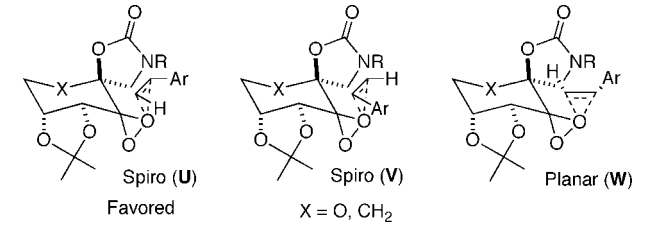


Figure 24.

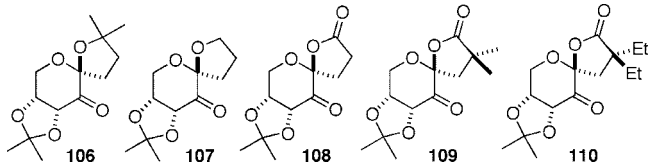


Figure 25.

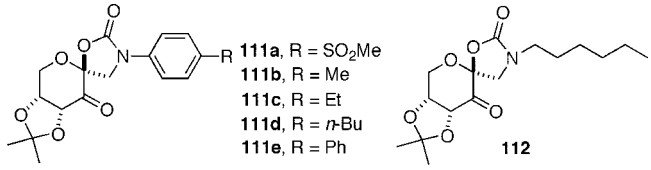


Figure 26.

was carried out with ketone **41**, the epoxide with absolute configuration (*R*,*R*) was obtained in 98% ee. This result indicated that spiro **O** is favored over planar **P**. However, when the same epoxidation was carried out with ketone **104**, the epoxide with absolute configuration (*S*,*S*) was obtained instead. The absolute configuration of the epoxide suggested that planar **R** is favored over spiro **Q**, which supports the proposal of the existence of an attraction between R_π of the olefin and the oxazolidinone of the catalyst in the transition state.[85]

During studies of electronic and conformational effects of ketone catalysts on epoxidation, ketone **105**, a carbocylic analogue of ketone **104** (Figure 22), was found to give higher ee's (89−93% ee) for styrenes (Table 18) and the opposite enantiomer (*R*,*R*) for the epoxidation of 1-phenylcyclohexene (Figure 23) as compared to **104**.[87]

These results suggest that the replacement of the pyranose oxygen with a carbon has a noticeable effect on the competition between the spiro and planar transition states. The X-ray studies show that ketones **104** and **105** have similar conformations (at least in the solid state), suggesting that the pyranose oxygen influences the transition states possibly *via* an electronic effect rather than a conformational

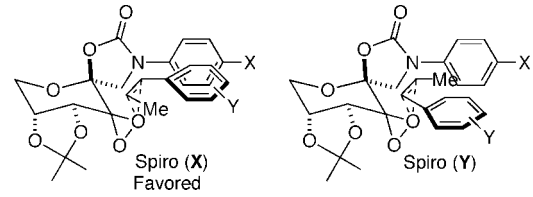


Figure 27.

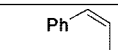
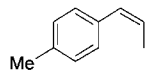
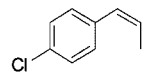
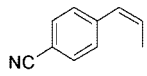
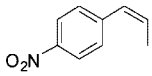
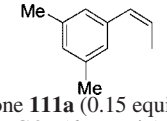
effect. It is likely that the replacement of the pyranose oxygen in ketone **104** with a carbon in ketone **105** increases the interaction of the nonbonding orbital of the dioxirane with the π^* orbital of the alkene by raising the energy of the nonbonding orbital of the dioxirane, consequently favoring the spiro transition state over the planar one. As a result, spiro **S** is favored over planar **T** for the epoxidation of 1-phenylcyclohexene, giving the (*R*,*R*) epoxide (Figure 23). For styrenes, the replacement of an oxygen with a carbon in ketone **105** further favors desired spiro **U** and undesired spiro **V** over undesired planar **W** (Figure 24), thus reducing the amount of the minor enantiomer generated *via* planar **W** pathway and enhancing the enantioselectivity of the reaction overall. Further increase in the enantioselectivity for styrenes may require a catalyst that can suppress both undesired spiro **V** and undesired planar **W** to a greater extent.

An electron-withdrawing substituent may increase the reactivity and/or stability of a ketone catalyst. However, such a substituent may also lower the energy of the nonbonding orbital of the dioxirane, thus disfavoring the main spiro transition state and decreasing the epoxide ee's. The results obtained with ketones **104** and **105** indicate that an effective catalyst should have proper substitutents that can provide a delicate balance between reactivity and enantioselectivity.

The spiro rings have been shown to be extremely important for the stereodifferentiation of the epoxidation for ketones **41** and **104**. To further probe the effects of different spiro ring substitution patterns on enantioselectivity of epoxidation, ketone catalysts with spiro ethers and lactones (**106**−**110**) (Figure 25) were investigated.[88] Studies showed that substituents on the spiro ring of ketone catalysts have large effects on the enantioselectivity both sterically and electronically (Table 19). Substituents smaller than methyl groups on the spiro ring of the catalyst decreased the ee for *trans*-olefins, likely due to increased competition from undesired spiro and/or planar transition states. The results obtained with lactone-containing ketones suggest that the carbonyl group of the oxazolidinone of ketone **104** is at least partially responsible for the observed enantioselectivity for conjugated *cis*-olefins. In addition, nonbonding interactions such as van der Waals forces and/or hydrophobic interactions between the olefin substituents and the nitrogen substituents of the oxazolidinone are also significant contributing factors for stereodifferentiation.

In an effort to further understand the effect of the *N*-substituent of the ketone catalyst on epoxidation and to develop more practical catalysts, a series of *N*-aryl-substituted ketones (**111**) were investigated. A few examples are shown in Figure 26.[89–91] Ketones such as **111b**−**e** are readily available in four steps from glucose and anilines (Scheme 22). Among the different aryl groups tested, phenyl groups substituted with hydrocarbons consistently gave better results than aryl groups with ethers or halogens.[90] Ketones **111b** and **111c** provide high enantioselectivity for a variety of olefins and can be prepared from inexpensive anilines in large quantities,[91] which makes them practically useful catalysts.

Table 20. Asymmetric Epoxidation of *cis*-β-Methylstyrenes with Ketones 111[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**111a**	100	90
2		**111b**	99	84
3		**111a**	96	92
4		**111b**	100	88
5		**111a**	90	95
6		**111b**	79	92
7		**111a**	98	96
8		**111b**	94	96
9		**111a**	91	97
10		**111b**	86	98
11		**111a**	100	94
12		**111b**	98	92

[a] Ketone **111a** (0.15 equiv) or ketone **111b** (0.10 equiv), Oxone (1.6 equiv), K_2CO_3 (6.7 equiv), DME:DMM (3:1, v/v), buffer, −10 °C.

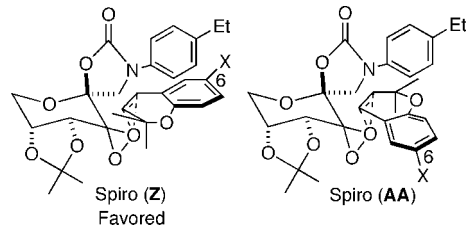
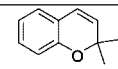
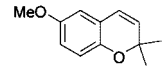
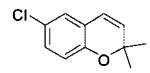
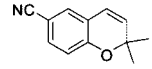
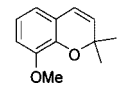
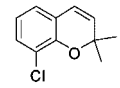
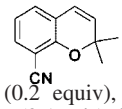


Figure 28.

The electronic nature of the *N*-phenyl substitution can also affect the outcome of the epoxidation with electron-withdrawing substitution (e.g., SO_2Me, as in ketone **111a**) generally giving the best ee's.[89]

The epoxidation with ketones **111** provides high ee's for a variety of olefins. As shown in Table 20, *cis*-β-methylstyrenes can be epoxidized with ketone **111a** and **111b** in high conversions and ee's.[92] Interestingly, the ee's increased across the board from the electron-donating Me group to the electron-withdrawing NO_2 group. These results indicate that substituents on the phenyl group of the olefins further enhance the interaction between the phenyl group of the olefin and the phenyl group of the ketone catalyst, thus further favoring desired spiro transition state **X** and increasing the enantioselectivity (Figure 27).

Table 21. Asymmetric Epoxidation of 2,2-Dimethyl Chromenes with Ketones 111c and 112[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**111c**	100	84 (R,R)
2		**112**	100	84 (R,R)
3		**111c**	100	90
4		**112**	100	88
5		**111c**	100	93
6		**112**	58	93
7		**111c**	83	93 (R,R)
8		**112**	71	89 (R,R)
9		**111c**	100	82
10		**112**	100	82
11		**111c**	85	83
12		**112**	76	86
13		**111c**	95	88
14		**112**	87	89

[a] Ketone (0.2 equiv), Oxone (2.7 equiv), K_2CO_3 (10.6 equiv), DME−DMM (3:1, v/v), buffer, 0 °C.

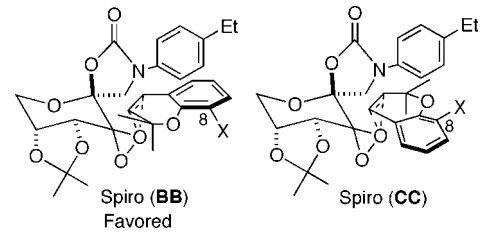
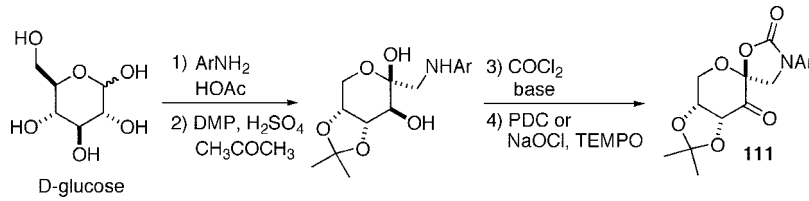


Figure 29.

To further investigate this substituent effect by restricting reacting approaches for the olefin substrate, cyclic olefins such as 6- and 8-substituted 2,2-dimethylchromenes were examined for the epoxidation using ketone **111c** and **112** (Figure 26, Table 21).[93] For 8-substituted chromenes, the ee's increase with electron-withdrawing groups such as cyano, but decrease with electron-donating groups such as methyl. The substituents at the 8-position influence the enantioselectivity likely *via* an electronic effect. However, for 6-substituted chromenes, the ee's increase (5−9%) with

Scheme 22. Synthesis of Ketone 111



Scheme 23. Synthesis of Chiral 2-Aryl Cyclopentanones

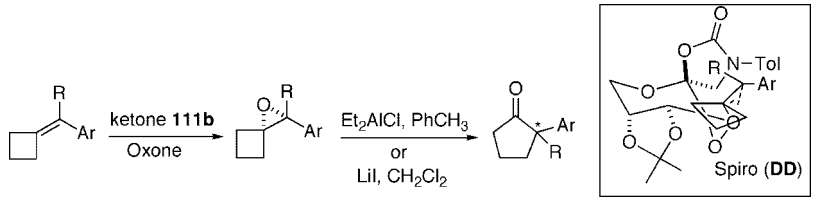
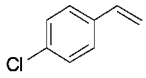
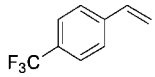
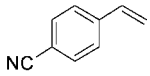
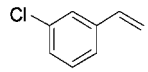
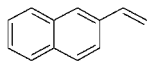
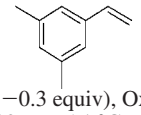
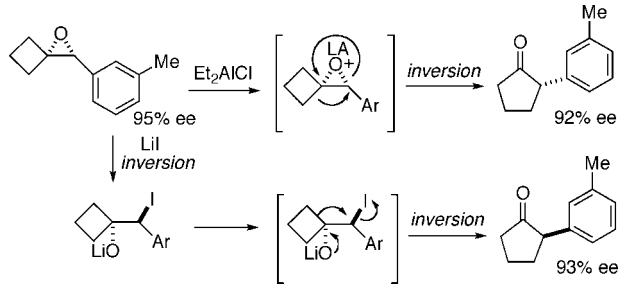


Table 22. Asymmetric Epoxidation of Styrenes with Ketone 111c[a]

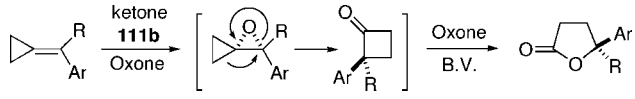
Entry	Substrate	Yield (%)	ee (%)
1		72	86 (R)
2		85	86 (R)
3		73	92
4		86	90 (R)
5		72	86
6		91	87
7		86	90

[a] Ketone (0.15−0.3 equiv), Oxone (2.7 equiv), K_2CO_3 (10.6 equiv), DME, buffer, −10 to −15 °C.

Scheme 24. Rearrangement of Epoxide



Scheme 25. Synthesis of Chiral γ-Aryl-γ-butyrolactones



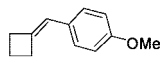
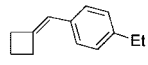
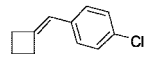
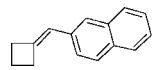
either an electron-donating or electron-withdrawing substituent, with electron-withdrawing groups giving generally higher ee's. Besides the electronic effect, the substituent at 6-position might cause additional beneficial nonbonding interactions between the substituent at the 6-position of the substrate and the phenyl group of the catalyst due to their proximity in spiro transition state **Z**, further favoring this transition state (Figure 28). On the other hand, such interaction is not involved for 8-substituted chromenes since the substituents are not proximal to the phenyl group of the catalyst in the favored spiro **BB** transition state (Figure 29). Since both *N*-aryl and alkyl substituted ketones give similar results, van der Waals forces and/or hydrophobic effects possibly play important roles in the beneficial interaction between the substituent of the substrate and the *N*-substitutent of the catalyst.

Epoxidation of styrenes with a wide variety of *N*-substituted oxazolidinone ketones was also investigated.[90] Among various ketone catalysts, **111c** was found to be one of the most effective catalysts. High ee's have been obtained for various styrenes (Table 22).

Trisubstituted benzylidenecyclobutanes (R = H) can be epoxidized with readily available ketone **111b** in high enantioselectivity *via* favored transition state spiro **DD** (Scheme 23).[94a] The resulting epoxides can be rearranged to 2-aryl cyclopentanones with either inversion or retention of configuration using Et_2AlCl or LiI (an example shown in Scheme 24). High ee's have been obtained for 2-aryl cyclopentanones in most cases (Table 23). This two-step process provides a viable entry to optically active 2-aryl cyclopentanones, which have not been easily obtained otherwise. The epoxidation can also be extended to tetrasubstituted benzylidenecyclobutanes to give optically active 2-alkyl-2-aryl cyclopentanones (70−90% ee) after epoxide rearrangement (Table 24), allowing generation of chiral all-carbon quaternary stereocenters.[94b] When benzylidenecyclopropanes are subjected to epoxidation conditions, optically active γ-aryl-γ-butyrolactones and γ-aryl-γ-methyl-γ-butyrolactones can be obtained in reasonable yields and good enantioselectivities (71−91% ee) *via in situ* epoxide rearrangement and Baeyer−Villiger oxidation (Scheme 25, Table 25).[95,96] Chiral cyclobutanones can also be obtained by supressing the Baeyer−Villiger oxidation with more ketone catalyst and less Oxone.

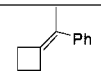
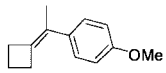
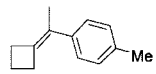
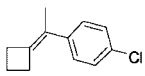
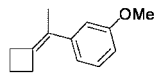
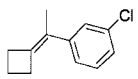
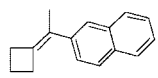
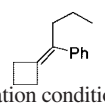
Conjugated *cis*-dienes[97] and *cis*-enynes[98] can also be epoxidized in high ee's, and no isomerization was observed

Table 23. Enantioselective Synthesis of 2-Aryl Cyclopentanones

Entry	Substrate	Epoxide Yield (%) (ee %)[a]	Rearrangement Conditions[b,c]	Cyclopentanone Yield (%) (ee %)
1		93 (90)	Et_2AlCl	90 (90) (S)
			LiI	81 (90) (R)
2		95 (91)	Et_2AlCl	98 (82) (S)
			LiI	81 (40) (R)
3		67 (94)	Et_2AlCl	99 (91) (S)
			LiI	86 (92) (R)
4		78 (96)	Et_2AlCl	89 (94) (S)
			LiI	87 (84) (R)
5		88 (95)	Et_2AlCl	94 (96) (S)
			LiI	84 (87) (R)

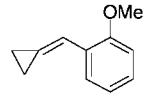
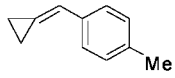
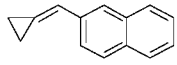
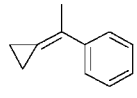
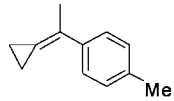
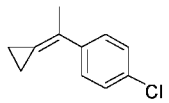
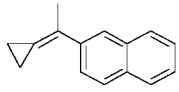
[a] Epoxidation conditions: ketone **111b** (0.2 equiv), Oxone (1.6 equiv), K_2CO_3 (6.7 equiv), DME:DMM (3:1 or 1:1, v/v), buffer, 0 or −10 °C. [b] Rearrangement conditions (Et_2AlCl): epoxide (1 equiv), Et_2AlCl (1 equiv), in $PhCH_3$ at −78 °C. [c] Rearrangement conditions (LiI): epoxide (1 equiv), LiI (1.0−3.0 equiv), in CH_2Cl_2 at rt or 0 °C.

Table 24. Enantioselective Synthesis of 2-Alkyl-2-aryl Cyclopentanones

Entry	Substrate	Epoxide Yield (%) (ee %)[a]	Cyclopentanone Yield (%) (ee %)[b]
1		94 (84)	93 (84)
2		95 (87)	92 (88)
3		86 (88)	78 (88)
4		77 (89)	98 (90)
5		98 (88)	73 (87)
6		79 (88)	99 (89)
7		nd	65 (90)
8		67 (77)	88 (77)
9		48 (70)	99 (70)

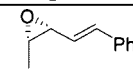
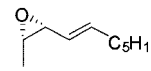
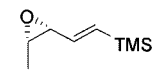
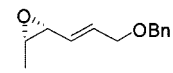
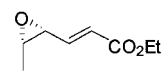
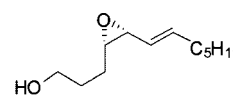
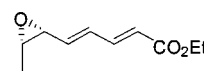
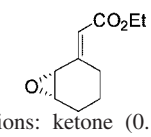
[a] Epoxidation conditions: ketone **111b** (0.2 equiv), Oxone (1.6 equiv), K_2CO_3 (6.7 equiv), DME:DMM (3:1, v/v), buffer, 0 or −10 °C. [b] Rearrangement conditions: epoxide (1 equiv), Et_2AlCl (0.5−1.0 equiv), in $PhCH_3$ at −78 °C for 15−60 min.

Table 25. Enantioselective Synthesis of γ-Aryl-γ-butyrolactones[a]

Entry	Substrate	Yield (%)	ee (%)
1		54	80
2		68	90 (S)
3		48	91
4		50	84 (S)
5		64	79 (S)
6		45	84
7		54	87 (S)

[a] Conditions: ketone **111b** (0.2 equiv), Oxone (3.2 equiv), K_2CO_3 (13.4 equiv), DME:DMM (3:1, v/v), buffer.

Table 26. Asymmetric Epoxidation of Conjugated *cis*-Dienes with Ketones 111[a]

Entry	Epoxide	Catalyst	Yield (%)	ee (%)
1		**111b**	66	85
2		**111d**	47	89
3		**111e**	58	92
4		**111e**	62	90
5		**111b**	64	94
6		**111d**	80	89
7		**111b**	74	94
8		**111b**	67[b]	91

[a] Conditions: ketone (0.1−0.3 equiv), Oxone (0.96−1.6 equiv), K_2CO_3 (4.0−10.1 equiv), DME−DMM (3:1, v/v), buffer. [b] A mixture of cis/trisubstituted epoxied (3.3:1).

during the reaction, giving *cis*-epoxides exclusively from *cis*-olefins (Table 26 and Table 27). Alkenes and alkynes appear to be effective directing groups to favor the desired transition states spiro **EE** and spiro **GG** (Figure 30 and Figure 31). Nonbonding interactions such as hydrophobic interactions between the substituents on the diene and enyne and the oxazolidinone moiety of the ketone catalyst (possibly *N*-aryl group) also significantly influence the enantioselectivity. Further studies show that asymmetric epoxidation with ketones **111** can also be carried out with H_2O_2 as primary oxidant (Table 28).[99]

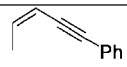
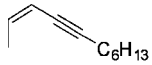
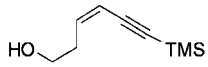
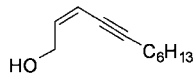
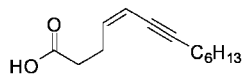
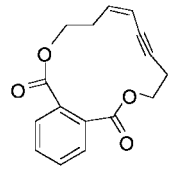
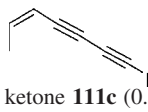
2.6.4. Other Carbohydrate-Based Catalysts

In 2002, Shing and co-workers reported three glucose-derived ketones (**113**−**115**) (Figure 32), and up to 71% ee was obtained for *trans*-stilbene oxide with ketone **113**.[100] In 2003, Shing and co-workers also reported a series of L-arabinose-derived ketones (**116**−**122**); up to 90% ee was obtained for *trans*-stilbene with ketone **119** (Figure 33). High yield was obtained for epoxidation with the ester substituted ketones **120**−**122**, and up to 68% ee was obtained for phenylstilbene.[101]

Later, Shing and co-workers also described ketone **123** and demonstrated that the enantioselectivity increased with the size of the R group (Figure 34). Up to 90% ee was obtained for phenylstilbene with ketone **123b**.[102] However, when *cis*-ethyl cinnamate was used as the substrate, the ee's had an inverse relationship with the size of the R group. Epoxide **125** can be obtained in 68% ee using ketone **123a**, and it could be readily converted into a protected side chain of paclitaxel (Scheme 26).[103]

In 2003, Zhao and co-workers reported the use of fructose-derived ketone and aldehydes **127**−**129** for asymmetric

Table 27. Asymmetric Epoxidation of Conjugated *cis*-Enynes with Ketone 111c[a]

Entry	Substrate	Yield (%)	ee (%)
1		78	93
2		84	90
3		46	94
4		68	97
5[b]		61	96
6		54	87
7[c]		76	93

[a] Conditions: ketone **111c** (0.25 equiv), Oxone (1.6 equiv), K_2CO_3 (6.7 equiv), DME, buffer (1.5:1, v/v). [b] The corresponding lactone was obtained. [c] Ketone **111b** (0.3 equiv) with DME−dioxane as solvent.

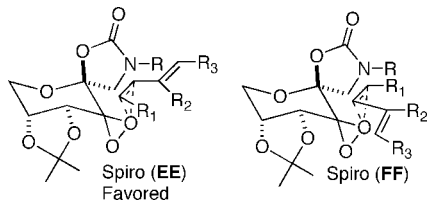


Figure 30.

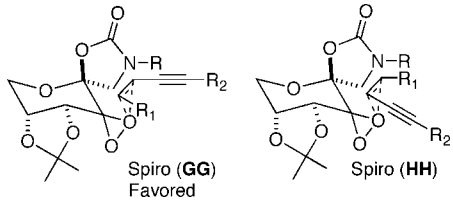


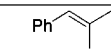
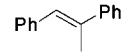
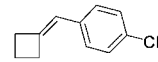
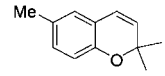
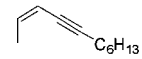
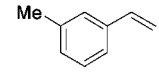
Figure 31.

epoxidation reactions (Figure 35). Up to 94% ee was obtained for *trans*-stilbene with aldehyde **129**.[104]

2.7. Carbocyclic Ketones

Ketones such as **41** and **111** use a fused ring and a quaternary carbon α to the carbonyl group as chiral control elements (Figure 36). In 1997, a series of pseudo-C_2-symmetric ketones bearing two fused rings at each side of the carbonyl group such as **130** was reported.[105] Among the ketones studied, ketones such as **130a** (R = CH_2OAc) and **130b** (R = CMe_2OH) were found to be very active for the epoxidation using 5−10 mol % catalyst, and even electron-deficient olefins could be epoxidized (Table 29). Overall, ketone **130** is less enantioselective than **41** for the epoxidation of trans- and trisubstituted olefins.

Table 28. Asymmetric Epoxidation with Ketone 111c and H_2O_2[a]

Entry	Substrate	Yield (%)	ee (%)
1		82	92
2		78	88 (R,R)
3		92	96 (R)
4		89	91
5		65	90 (2S,3R)
6		93	83

[a] Conditions: ketone **111c** (0.1−0.3 equiv), MeCN (3.8 equiv), *n*-BuOH/aq 0.30 M K_2CO_3 in 4×10^{-4} M EDTA (1:1 v/v), 30% H_2O_2 (3.0 equiv), 0 °C.

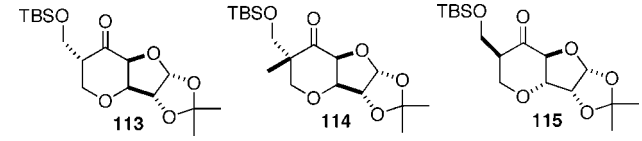


Figure 32.

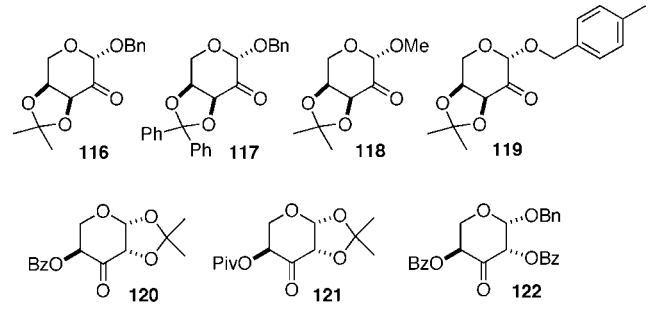


Figure 33.

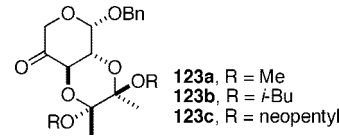
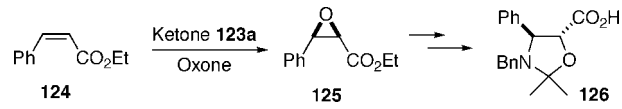


Figure 34.

Scheme 26. Synthesis of Paclitaxel Side Chain



Ketones **131** and **132**, having one of the ketals away from the α position (Figure 37), lowered the enantioselectivity and reactivity for the epoxidation. It appears that having the chiral control element close to the reacting carbonyl is important for an efficient stereodifferentiation.[106] Zhao and

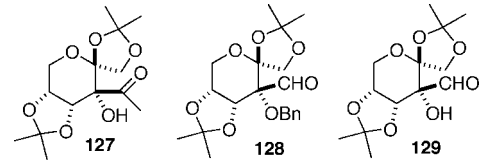
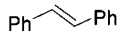
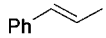
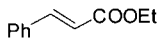
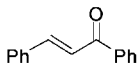
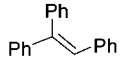
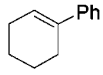


Figure 35.

Table 29. Asymmetric Epoxidation with Ketones 130b[a]

Entry	Substrate	Yield (%)	ee (%)
1		91	96 (R,R)
2		94	80 (R,R)
3		35	89 (2S,3R)
4		85	96 (2S,3R)
5		95	92 (R)
6		94	85 (R,R)
7		79	69 (R)

[a] Conditions: ketone (0.05−0.1 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), at −15 to 0 °C.

co-workers also reported their studies on ketones **131** and **133**, and 85% ee was obtained for stilbene with **131**.[107]

In 1999, Armstrong and co-workers reported two C_2-symmetric 5-membered ketones **134** and **135** (Figure 38).[108] Ketone **134** was shown to be completely unreactive in the epoxidation of *trans*-stilbene and could be recovered from the reaction mixture. This may be due to the steric hindrance

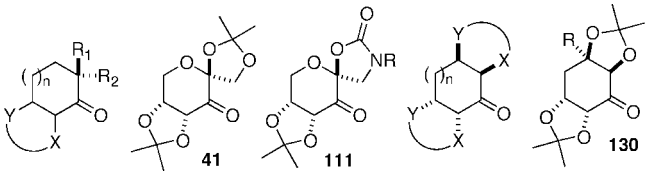


Figure 36.

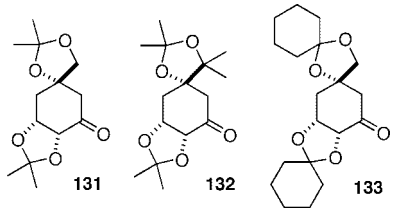


Figure 37.

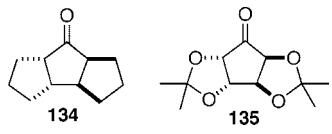


Figure 38.

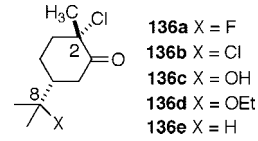


Figure 39.

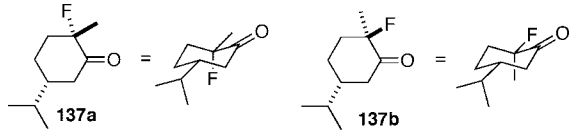
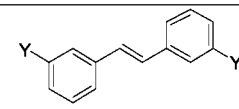
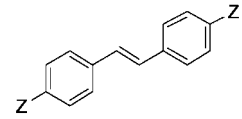


Figure 40.

Table 30. Asymmetric Epoxidation of Stilbene with Ketones 136b[a]

Entry	Substrate	ee (%)
		
1	Y = Me	88.9
2	Y = H	85.9
3	Y = F	77.7
4	Y = Cl	74.3
5	Y = OAc	73.8
		
6	Z = *t*-Bu	87.3
7	Z = Me	87.2
8	Z = F	78.5
9	Z = Br	74.8
10	Z = OAc	71.5

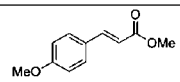
[a] Ketone (3.0 equiv) at rt.

of the carbonyl group. Studies showed that ketone **135** underwent rapid Baeyer−Villiger oxidation under reaction conditions to form the corresponding lactone.

In 1998, Yang and co-workers reported a series of ketones (**136**) containing a quarternary carbon at the C_2 position and various substituents at the C_8 position (Figure 39).[109] It was observed that the ee's for the epoxidation of *meta*- and *para*-substituted *trans*-stilbenes changed with the substituent on the phenyl group of the olefin using ketone **136b** as catalyst. The n−π electronic repulsion between the Cl atom of the catalyst and the phenyl group of the substrate is likely to be the major reason for the observed ee difference (Table 30). Moreover, the substitutents at C_8 significantly influence enantioselectivity through an electrostatic effect between the polarized C−X bond and the phenyl group on the stilbene (**136a**, 87.4% ee; **136b**, 85.4% ee; **136c**, 80.9% ee; **136d**, 73.8% ee; **136e**, 42.0% ee).

In 2000, Solladié-Cavallo and co-workers reported fluorinated ketones **137** (Figure 40) which are derived from (+)-dihydrocarvone.[110] Higher conversion and ee were obtained for *p*-methoxycinnamate with **137a** than with **137b** (99% vs 43% conversion, 40% vs 6% ee), suggesting that axial fluorine (as in **137a**) is a more effective activating substituent than equatorial fluorine (as in **137b**) (Figure 40) (Table 31, entries 1, 2).[111–113] Related cyclohexanones **138**−**141** (Figure 41) provide epoxides in high yields and good to high ee's (Table 31, entries 3−8).[114–117] These ketones are not prone to Baeyer−Villiger oxidation under the reaction conditions as they were quantitatively recovered after epoxidation. Rigid *trans*-decalones **142** and **143** (Figure 41), whose dioxiranes do not undergo chair inversion, have been synthesized to investigate the role of axial and equatorial α-fluorine effect.[118] Decalone **142**, having an axial α-fluorine, gave complete conversion and 70% ee for the

Table 31. Asymmetric Epoxidation with Ketones 137−143[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**137a**	99	40 (2R,3S)
2		**137b**	43	6 (2S,3R)
3[b]		**138**	74	60 (2R,3S)
4		**139**	90	66 (2R,3S)
5[b]		**138**	90	90 (S,S)
6[b]		**139**	95	90 (S,S)
7		**140**	100	88 (S,S)
8		**141**	100	86 (S,S)
9		**142**	100	86 R,R)
10		**143**	0	-
11		**142**	100	70 (R,R)
12		**143**	88	22 (R,R)

[a] Ketone (0.3 equiv) at rt. [b] Ketone (0.3 equiv) at 0 °C.

epoxidation of *trans*-β-methylstyrene. On the other hand, equatorial α-fluorine-containing decalone **143** only gave 88% conversion and 22% ee for the same substrate (Table 31, entries 11, 12). This result correlates with the results obtained using ketones **137**.

In 2001, Bortolini and co-workers reported asymmetric epoxidation using a series of keto bile acids as dioxirane precursors (**144**, Figure 42).[119] *p*-Methylcinnamic acid can be epoxidized in good yield and high ee's with **144b**−**e**(Table 32, entries 2−5). To investigate the effect of substitution on carbons 7 and 12, a number of 3-keto-bile acid derivatives (**145** and **146**) were synthesized and studied for the epoxidation (Figure 43).[120] Up to 98% ee was obtained for *trans*-stilbene (Table 32, entries 6−9). The study has shown that substitutions on carbons 7 and 12 are important for the reactivity and enantioselectivity of the epoxidation. In particular, 3-keto-12-substituted bile acids generally afforded epoxides with higher enantiomeric excess compared to their 7-substituted counterparts (Table 32, entries 8, 9 vs entries 6, 7).[121]

2.8. Ketones with an Attached Chiral Moiety

In 1999, Armstrong and co-workers reported the epoxidation of several olefins with chiral oxazolidinone trifluoromethyl ketone **147**, and up to 34% ee was obtained for 1-phenylcyclohexene (Figure 44).[108b] Ketone **147** underwent Baeyer−Villiger oxidation readily.

In 2003, Wong and co-workers reported a β-cyclodextrin-modified ketoester (**148**) as epoxidation catalyst (Figure 45),[122] and up to 40% ee was obtained for 4-chlorostyrene. In 2004, Bols and co-workers reported three cyclodextrins containing an acetone moiety or bridge (**149**−**151**) as catalysts (Figure 45).[123] In many cases, substantial amounts of corresponding diols would also be obtained, and up to 12% ee was obtained for styrene with ketone **150**.

3. Chiral Iminium Salt-Catalyzed Epoxidation

3.1. Introduction

In 1976 and 1981, Lusinchi and co-workers reported the formation of steroidal oxaziridinium salt **152** by methylation of the corresponding oxaziridine with FSO_3Me or by oxidation of the corresponding iminium salt with peracid (Figure 46).[124] In 1987, Hanquet and co-workers prepared another example of an oxaziridinium salt (**153**) by oxidation of an *N*-methyl isoquinolinium fluoroborate salt with *p*-nitrobenzoyl peroxide or methylation of its corresponding oxaziridine with trimethyloxonium fluoroborate.[125,126] In 1988, Hanquet and co-workers reported that oxaziridinium salt **153** can efficiently epoxidize various olefins.[127,128] They further reported that the epoxidation can be carried out with *in situ* generated oxaziridinium salt **153** with catalytic amount of its corresponding iminium salt using Oxone−$NaHCO_3$ in CH_3CN-H_2O[128a,129] or *m*CPBA−$NaHCO_3$ in CH_2Cl_2.[128b] A reaction pathway for iminium salt-catalyzed epoxidation is shown in Scheme 27. The iminium salt catalyst is regenerated upon epoxidation of the olefin. Asymmetric epoxidation using chiral oxaziridinium salts have also been extensively investigated.

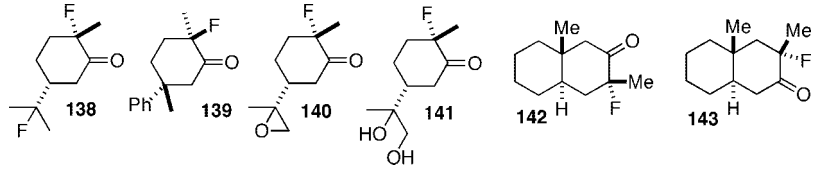


Figure 41.

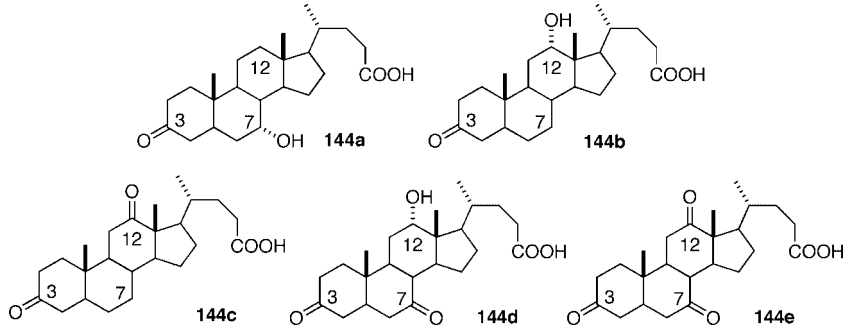


Figure 42.

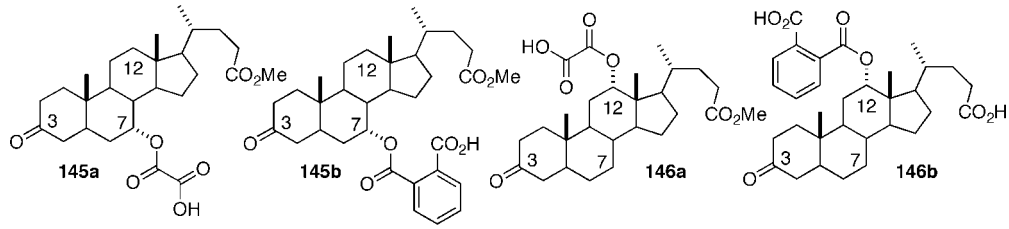


Figure 43.

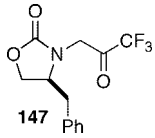
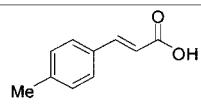
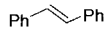


Figure 44.

Table 32. Asymmetric Epoxidation with Ketones 144−146[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**144a**	45	26 (2R,3S)
2		**144b**	94	95 (2S,3R)
3		**144c**	93	74 (2S,3R)
4		**144d**	89	87 (2S,3R)
5		**144e**	94	75 (2S,3R)
6		**145a**	90	80 (S,S)
7		**145b**	80	60 (S,S)
8		**146a**	90	90 (R,R)
9		**146b**	50	98 (R,R)

[a] Ketone (1.0 equiv) at 0 °C.

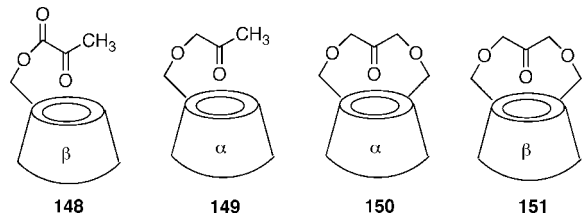


Figure 45.

3.2. Chiral Cyclic Iminium Salts

3.2.1. Dihydroisoquinoline-Based Iminium Salts

In 1993, Bohé and co-workers reported their studies on asymmetric epoxidation of olefins with enantiomerically pure oxaziridinium salt **161** (Scheme 28).[130] Dihydroisoquinoline **158**, prepared from benzaldehyde and (1*S*,2*R*)-(+)-norephedrine **156**, was converted into oxaziridinium salt **161** *via* two pathways: by methylation with Meerwein's salt to form iminium salt **159** and subsequent oxidation with *m*CPBA, or by oxidation with *m*CPBA to form oxaziridine **160**

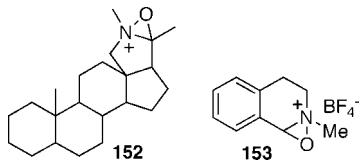
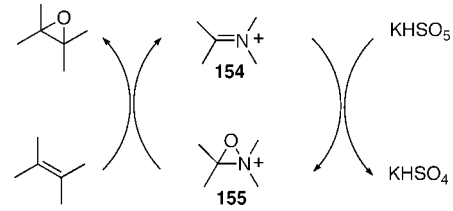
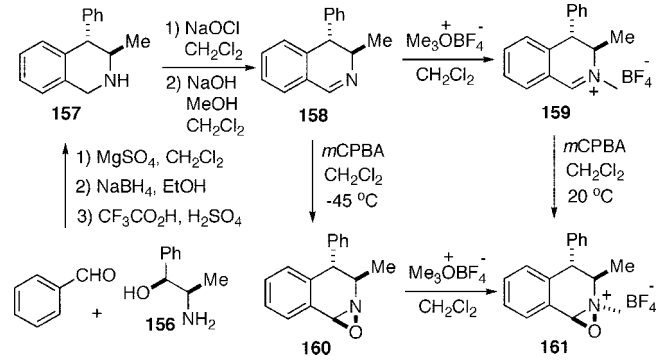


Figure 46.

Scheme 27. Catalytic Cycle for Iminium Salt-Catalyzed Epoxidation



Scheme 28. Synthesis of Oxaziridinium Salt 161



followed by methylation with Meerwein's salt. Oxaziridinium **161** was isolated by crystallization and characterized including X-ray diffraction.

Several olefins were effectively epoxidized with either isolated or *in situ* generated oxaziridinium **161**. For example, epoxidation of *trans*-stilbene with recrystallized **161** (1.1 equiv) at room temperature gave the (*R*,*R*)-stilbene oxide in 63% yield and 42% ee.[130b] The epoxidation of *trans*-stilbene with *in situ* generated oxaziridinium salt using a catalytic amount (5 mol %) of iminium salt **159** and Oxone−$NaHCO_3$ in CH_3CN-H_2O gave 80−90% conversion and 35% ee. Significant solvent effects on the rate of the epoxidation were observed. The epoxidation rate is the slowest in nonpolar solvents such as benzene and toluene, presumably due to the low solubility of oxaziridinium salt **161**. When a polar aprotic solvent, such as nitrobenzene or nitromethane, was used, the epoxidation rate increased, suggesting that the transition states of such reactions have strong ionic character.

In 1998, Page and co-workers reported a series of dihydroisoquinoline related iminium salt catalysts readily prepared from a chiral primary amine in a typical 30−65% overall yield (Scheme 29).[131a,b] The catalyst design can be versatile using this synthetic route since the chiral primary amine can be easily replaced. More hindered amines generally give lower catalyst yields, presumably because they can act as a base to produce the observed 2-vinylbenzaldehyde in the last step of the catalyst synthesis. The epoxidations are usually carried out using 0.3−10 mol % iminium salt, Oxone, and Na_2CO_3 in MeCN−H_2O. For catalyst **162a**, the best result was obtained for *trans*-stilbene with 78% yield and 73% ee (Table 33, entry 10).

Scheme 29. Synthesis of Iminium Salt 162

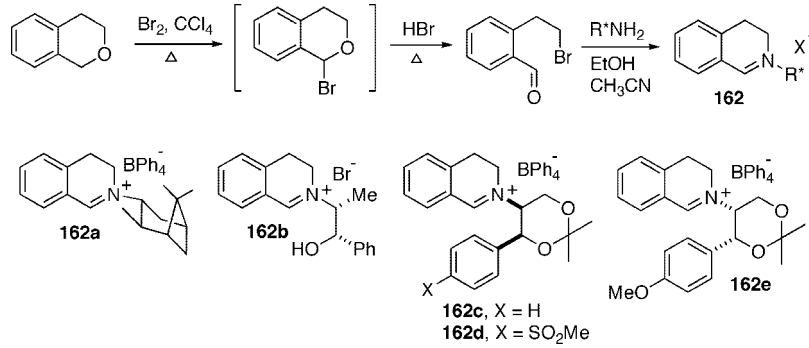
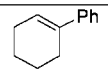
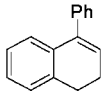
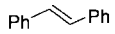
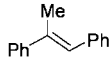
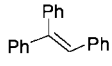
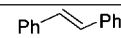
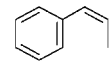
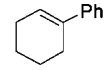
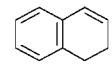
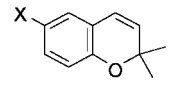


Table 33. Asymmetric Epoxidation with Iminium Salts 162[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**162a**[b]	68	40 (R,R)
2		**162b**[c]	64	30 (R,R)
3		**162c**[b]	55	41 (S,S)
4		**162d**[c]	100[d]	39 (S,S)
5		**162a**[b]	73	63
6		**162b**[c]	61	33
7		**162c**[b]	64	49 (1S,2R)
8		**162d**[c]	100[d]	47 (1S,2R)
9		**162e**[c]	62[d]	63 (1R,2S)
10		**162a**[c]	78	73 (R,R)
11		**162a**[b]	72	15 (R,R)
12		**162c**[b]	52	52 (1S,2R)
13		**162e**[c]	55	60 (1R,2S)
14		**162c**[b]	54	59 (S)
15		**162d**[c]	100[d]	50 (S)
16		**162e**[c]	60[d]	71 (R)

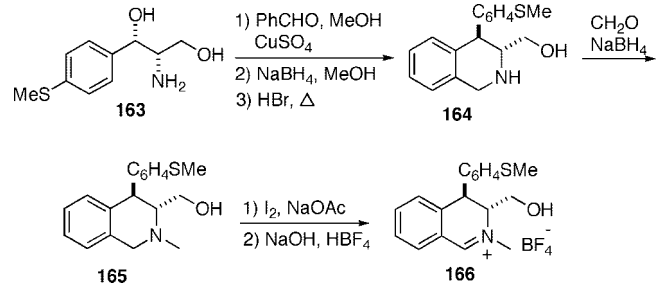
[a] Reactions were carried out at 0 °C. [b] 0.05 equiv of catalyst used. [c] 0.1 equiv of catalyst used. [d] Conversion (%).

Table 34. Asymmetric Epoxidation with Iminium Salt 162d[a]

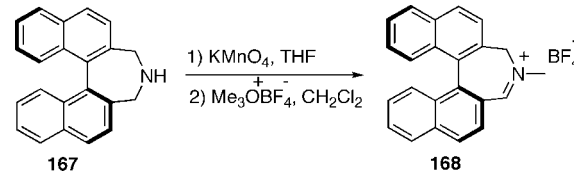
Entry	Substrate	Yield (%)	ee (%)
1		31	67 (R,R)
2		85	70 (1S,2R)
3		77	48 (1R,2R)
4		89	82 (1S,2R)
			
5	X=NO_2	52	88 (1S,2S)
6	X=Cl	76	93 (1S,2S)
7	X=CN	59	97 (1S,2S)

[a] Iminium salt **162d** (0.1 equiv), TPPP (2.0 equiv) in $CHCl_3$, at –40 °C.

Scheme 30. Synthesis of Iminium Salt 166



Scheme 31. Synthesis of Iminium Salt 168



A number of chiral iminium catalysts containing a secondary hydroxyl group were obtained by the same method (Scheme 29) using 1,2-amino alcohols as the chiral amine.[131c] These catalysts, such as **162b**, provided better enantioselectivities than their primary hydroxyl counterparts, suggesting that the substituent at this position may play an important role in the interaction between the olefin and the catalyst. Acetal-containing iminium salt **162c** gave higher enantioselectivity than catalyst **162a** for some olefins (Table 33, entry 12 vs 11).[131c,132] The results obtained with catalysts **162d** (Table 33, entries 4, 8, 15) and **162e** (Table 33, entries 9, 13, 16) showed that the epoxidation enantioselectivity can be influenced by the substituent on the phenyl ring.[133]

Due to Oxone solubility, most iminium salt-mediated epoxidations use water as solvent. As a result, the lowest temperature that the epoxidation can be performed at is about −8 °C since the solvent system freezes under that temperature. In 2004, Page and co-workers introduced nonaqueous conditions for iminium salt-mediated asymmetric epoxidation using organic solvent-soluble stoichiometric oxidant tetraphenylphosphonium monoperoxysulfate (TPPP), which is synthesized by treating Oxone with tetraphenylphosphonium

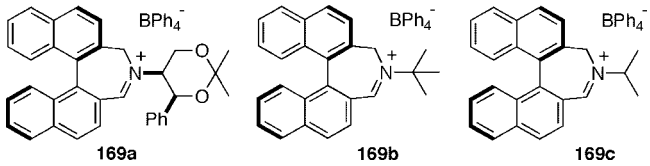


Figure 47.

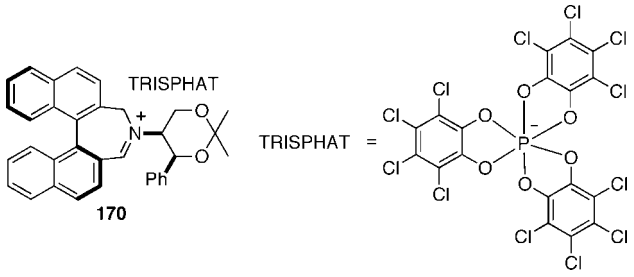


Figure 48.

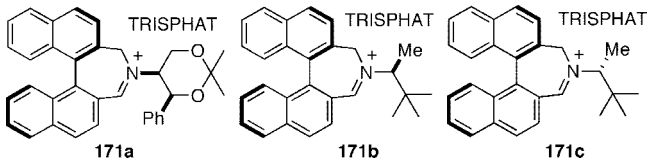
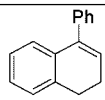
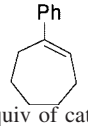


Figure 49.

Table 35. Asymmetric Epoxidation with Iminium Salts 169[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**169a**	66	95 (1R,2S)
2		**169c**	68	83 (1R,2S)
3[b]		**169a**	64	91 (1S,2S)
4		**169b**	54	84 (1S,2S)
5		**169c**	73	82 (1S,2S)
6[b]		**169a**	57	76 (1S,2S)
7		**169c**	60	65 (1S,2S)

[a] 0.05 equiv of catalyst. [b] 0.01 equiv of catalyst.

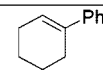
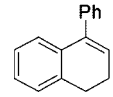
chloride.[134] When the epoxidation was carried out with iminium salt **162d** using TPPP in $CHCl_3$ at –40 °C, high ee's were obtained for a variety of *cis*-olefins, and up to 97% ee was obtained for 2,2-dimethyl-6-cyanochromene (Table 34, entry 7).[135] It was found that the reactions performed in $CHCl_3$ gave higher ee's than those in CH_3CN.

Rozwadowska and co-workers reported the synthesis of the enantiomer of **159** (*ent*-**159**) from an industrial waste product, (+)-thiomicamine **163**, in several steps. This iminium salt *ent*-**159** produced enantioselectivities similar to those of **159** reported by Bohé and co-workers. A hydroxymethyl analogue of *ent*-**159** (**166**) was also prepared from **163** and epoxidized *trans*-stilbene in 70% yield and 45% ee with *m*CPBA as oxidant (Scheme 30).[136]

3.2.2. Binaphthylazepinium-Based Iminium Salts

In 1996, Aggarwal and co-workers reported binaphthyl-based iminium salt **168**, prepared from binaphthylamine **167** in two steps (Scheme 31).[137] The epoxidation with **168** (5 mol %) and Oxone−$NaHCO_3$ in CH_3CN-H_2O gave 71% ee for 1-phenylcyclohexene, 45% for *trans*-α-methylstilbene, and 31% for *trans*-stilbene in 60−80% yield. Iminium salt **168** was found to epoxidize trisubstituted olefins faster than disubstituted olefins.

Table 36. Asymmetric Epoxidation with Iminium Salts 170 and 171[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**170**	98	81 (R,R)
2		**171a**	64	79 (S,S)
3		**171b**	67	84 (S,S)
4		**171c**	48	86 (S,S)
5		**170**	99	83 (1S,2R)
6		**171a**	34	71 (1R,2S)
7		**171b**	85	86 (1R,2S)
8		**171c**	61	87 (1R,2S)

[a] 0.05 equiv of catalyst, 0 °C.

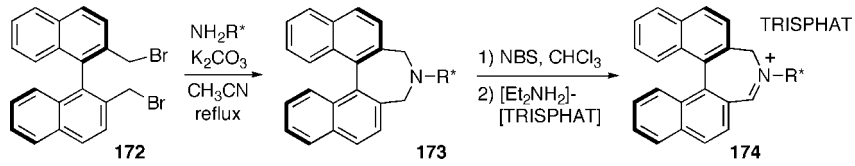
In 2004, Page and co-workers reported a highly active and selective binaphthyl-based iminium salt catalyst **169a** (Figure 47).[138] This catalyst gave good to excellent ee's for several substrates (Table 35, entries 1, 3, 6). The reaction time is short for this epoxidation and the catalyst loading can be as low as 0.1 mol % with only a slight loss of enantioselectivity and almost no loss in yield using 1-phenylcyclohexene as a test substrate. Recently, catalyst **169a** was also employed in nonaqueous epoxidation conditions. 1-Phenylcyclohexene was found to be one of the best substrates and CH_3CN was found to be the best solvent. When the epoxidation was carried out with 5 mol % **169a** and TTTP (2.0 equiv) as oxidant in CH_3CN at −40 °C, (*S*,*S*)-1-phenylcyclohexene oxide was obtained in 81% yield and 89% ee.[139] In 2007, Page and co-workers reported another set of binaphthalene-fused azepinium salts. Among these catalysts, **169b** and **169c** (Figure 47) gave the best results (Table 35, entries 2, 4, 5, 7).[140]

Recently, Lacour and co-workers reported several catalysts (**170** and **171**) structurally similar to iminium salts **169** with TRISPHAT as the counterion (Figure 48 and Figure 49).[141] They can be synthesized in three steps in good yields (Scheme 32) and provide good enantioselectivities for some trisubstituted olefins (Table 36). Iminium catalyts **170** and **171a**, having opposite binaphthyl configuration, gave epoxides of opposite configuration (Table 36, entries 1 vs 2 and 5 vs 6); and catalysts **171b** and **171c**, having the same binaphthyl configuration and opposite configuration on the *N*-substituent, gave epoxides with same absolute configuration (Table 36, entries 3 vs 4 and 7 vs 8). This result suggested that the binaphthyl framework is more effective in inducing chirality in the epoxidation process. However, the conversion for the epoxidation is affected by the "matched"/"mismatched" configurations of the binaphthyl framework and the *N*-substituent.[138,141]

3.2.3. Biphenylazepinium-Based Iminium Salts

In 2002, Page and co-workers reported a series of biphenylazepinium salt catalysts (**175**) that are synthesized in the same manner as the dihydroisoquinoline-based iminium catalysts (Figure 50, Scheme 29).[142,133] In some cases, the enantioselectivity can be improved by using nonaqueous

Scheme 32. Synthesis of Iminium Salt 174



Scheme 33. Intramolecular Epoxidation with Iminium Salt

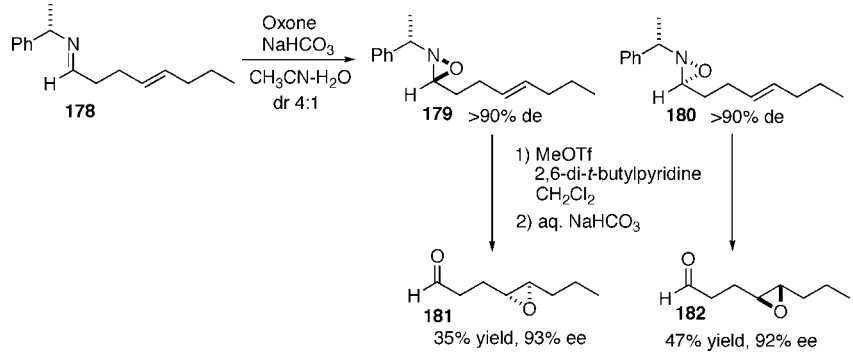
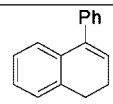
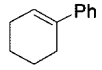
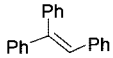
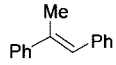


Table 37. Asymmetric Epoxidation with Iminium Salts 175[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**175a**	95	38 (1S,2R)
2		**175b**	90	41 (1S,2R)
3		**175a**	100	29 (1R,2R)
4		**175b**	100	60 (1S,2S)
5		**175c**	50[b]	63 (R,R)
6		**175a**	100	17 (S)
7		**175b**	90	59 (S)
8		**175c**	63[b]	26 (R)
9		**175a**	93	14 (R,R)
10		**175b**	95	37 (S,S)
11		**175c**	61[b]	50 (R,R)

[a] Conditions: 0.05 equiv of catalyst, Oxone (2.0 equiv), Na_2CO_3 (4 equiv), H_2O/MeCN (1:1), 0 °C. [b] Isolated yield (%).

epoxidation conditions since the reaction can be carried out at lower temperature in organic solvent (Table 38).[139,134]

In 2002 and 2005, Lacour and co-workers reported catalysts **176** which are structurally similar to **175** but with the counterion being replaced as TRISPHAT (Figure 51).[143,141] The lipophilicity of TRISPHAT keeps the iminium salt in the organic solvent, which can be beneficial to enantioselectivities.[143a] Up to 80% ee was obtained for the epoxidation of 4-phenyl-1,2-dihydronaphthalene with **176b** (Table 39, entry 6).

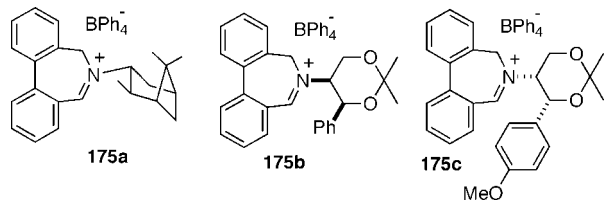
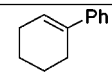
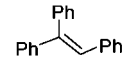
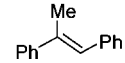


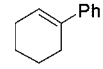
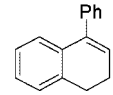
Figure 50.

Table 38. Asymmetric Epoxidation with Iminium Salt 175b under Nonaqueous Conditions[a]

Entry	Substrate	Conv. (%)	ee (%)
1		100	67 (S,S)
2		78	60 (S)
3		50	40 (S,S)

[a] Catalyst (0.1 equiv), TPPP (2.0 equiv) in CH_3CN at –40 °C.

Table 39. Asymmetric Epoxidation with Iminium Salts 176[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**176a**	100	69 (S,S)
2		**176b**	100	65 (S,S)
3		**176a**	85	76 (1R,2S)
4		**176b**	72	70 (1R,2S)
5[b]		**176a**	91	79
6[b]		**176b**	100	80 (1R,2S)

[a] 0.05 equiv of catalyst at 20 °C. [b] 0 °C.

3.3. Chiral Acyclic Iminium Salts

Most iminium salts used in asymmetric epoxidations are cyclic; however, several acyclic iminium salts have also been investigated. In 1997 and 1999, Armstrong and co-workers reported epoxidation of olefins catalyzed by acyclic iminium salts derived from intermolecular condensation between an amine and a carbonyl compound.[144] It was found that

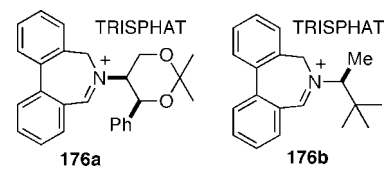
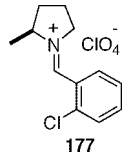
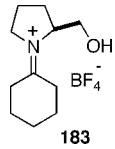


Figure 51.



177

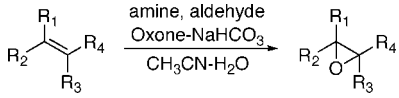
Figure 52.



183

Figure 53.

Scheme 34. Asymmetric Epoxidation with *in situ* Generated Iminium Salt



iminium salts derived from pyrrolidine and aromatic aldehydes with *para*- or *ortho*-electron-withdrawing substituents are effective catalysts for the epoxidation. Ketone-derived iminium salts can also promote the epoxidation. However, the chiral versions of these iminium salts were generally difficult to synthesize and purify possibly due to their facile hydrolysis. Iminium salt **177** (Figure 52) was successfully prepared and gave 100% conversion and 22% ee for 1-phenylcyclohexene with stoichiometric amount of **177**.

In 1999, Armstrong and co-workers also reported a highly stereoselective intramolecular epoxidation with oxaziridinium salts generated from unsaturated oxaziridines such as **179** and **180** by methylation with MeOTf (Scheme 33).[145,146] Oxaziridines **179** and **180** were formed by the oxidation of imine **178** with Oxone. The resulting diastereomeric mixture (4:1) could be separated and purified to >20:1. The purified **179** and **180** were individually treated with MeOTf to form the corresponding oxaziridinium salts, which underwent a stereoselective intramolecular epoxidation to give epoxide **181** and **182** in 93% ee and 92% ee, respectively, upon hydrolysis of the imine epoxide (Scheme 33).

In 2000, Komatsu and co-workers reported that ketiminium salts derived from pyrrolidine and cyclohexanone were good epoxidation catalysts for a variety of olefins.[147] Treating cinnamyl alcohol with 10 mol % chiral L-prolinol derived ketiminium salt **183** (Figure 53) and Oxone−$NaHCO_3$ in CH_3CN-H_2O at 25 °C for 16 h gave the epoxide in 70% yield and 39% ee.

In 2001, Yang and co-workers developed an epoxidation system using catalytic iminium salts generated *in situ* from chiral amines and aldehydes (Scheme 34).[148] Up to 59% ee was obtained with amine **184** and aldehyde **186** (Figure 54) (Table 40, entry 2). When amine **185** (1.0 equiv) and aldehyde **186** (1.0 equiv) were used, *trans*-stilbene epoxide was obtained in 80% conversion and 65% ee.

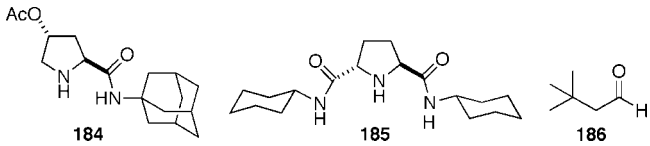
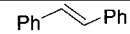
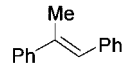
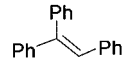
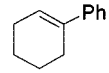
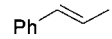
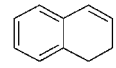
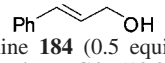


Figure 54.

Table 40. Asymmetric Epoxidation of Olefins with Amine 184 and Aldehyde 186[a]

Entry	Substrate	Reaction time (h)	Conv. (%)	ee (%)
1		5	81	46 (S,S)
2[b]		1.3	100	59 (S,S)
3[c]		2.5	81	52 (S)
4		1.5	85	46 (S,S)
5		8	97	25 (S)
6		8	81	26
7		8	94	17 (S,S)

[a] Amine **184** (0.5 equiv), aldehyde **186** (0.5 equiv), Oxone (4.0 equiv), and $NaHCO_3$ (10.0 equiv) in CH_3CN-H_2O at rt. [b] 0 °C. [c] Amine **184** (0.2 equiv) and aldehyde **186** (0.2 equiv).

4. Conclusion

Asymmetric epoxidation of olefins catalyzed by chiral ketones and iminum salts has been intensively studied over the past two decades. However, discovering highly enantioselective chiral catalysts has proven to be challenging. A variety of chiral ketones and iminum salts have been investigated in various laboratories, and significant progress has been made in the area. Chiral ketones have been shown to be effective catalysts for asymmetric epoxidation of olefins with a broad substrate scope. High enantioselectivity has been obtained for a wide variety of trans-, trisubstituted olefins, and a number of cis-olefins as well as certain terminal and tetrasubstituted olefins. The epoxidation transition state model has been extensively studied, allowing rationalization and prediction of the stereochemical outcome with a reasonable level of confidence. The ketone-catalyzed asymmetric epoxidation provides a viable synthetic method and has already been found to be practical and useful in organic synthesis. The development of new ketone catalysts and additional optimization of the reaction conditions will further expand the substrate scope and improve the reaction process. Chiral iminum salts have also been shown to be very active catalysts for the epoxidation of olefins. In some cases, the catalyst loading can be very low. High enantioselectivity has also been achieved in a number of cases. The presence of nitrogen substituents should provide additional diversities for catalyst design. Further understanding of the reaction transition states and factors for stereochemical control will certainly facilitate the development of more effective catalysts.

5. References

(1) For leading reviews, see: (a) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885. (b) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981.

(2) For a leading review on chiral ylide-based asymmetric epoxidation, see: Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.

(3) For leading reviews, see: (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis;* Ojima, I. Ed.; VCH: New York, 2000; Chapter 6A.

(4) For leading references on vanadium-catalyzed asymmetric epoxidation of allylic alcohols, see: (a) Murase, N.; Hoshino, Y.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1999**, *64*, 338. (b) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452. (c) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389. (d) Bourhani, Z.; Malkov, A. V. *Chem. Commun.* **2005**, 4592. (e) Malkov, A. V.; Bourhani, Z.; Koèovský, P. *Org. Biomol. Chem.* **2005**, *3*, 3194.

(5) For leading references on vanadium-catalyzed asymmetric epoxidation of homoallylic alcohols, see: (a) Makita, N.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 941. (b) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.

(6) For leading reviews on metal-catalyzed unfunctionalized olefins, see: (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH: New York, 1993; Chapter 4.2. (b) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404. (c) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59. (d) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH: New York, 2000; Chapter 6B. (e) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (f) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603.

(7) For leading references on titanium-catalyzed asymmetric epoxidation of unfunctionalized olefins with H_2O_2, see: (a) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4935. (b) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478. (c) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Synlett* **2006**, 3545. (d) Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4559.

(8) For a recent report on chiral molybdenum-catalyzed asymmetric epoxidation of unfunctionalized olefins, see: Barlan, A. U.; Basak, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5849.

(9) For leading reviews, see: (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Lauret, C.; Roberts, S. M. *Aldrichimica Acta* **2002**, *35*, 47. (c) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94. (d) Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006**, *84*, 74. (e) Shibasaki, M.; Kanai, M.; Matsunaga, S. *Aldrichimica Acta* **2006**, *39*, 31.

(10) For general leading references on dioxiranes, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (d) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581. (e) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. (f) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219.

(11) For a leading review, see: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(12) For leading reviews on asymmetric epoxidation by chiral ketones, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 342. (d) Shi, Y. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; Chapter 3. (e) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (f) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (g) Shi, Y. In *Handbook of Chiral Chemicals*; Ager, D., Ed.; CRC Press, Taylor & Francis Group: Boca Raton, 2006; Chapter 10.

(13) For examples of *in situ* generation of dioxiranes see: (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (c) Gallopo, A. R.; Edwards, J. O. *J. Org. Chem.* **1981**, *46*, 1684. (d) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. (e) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925. (f) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227. (g) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577. (h) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (i) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887. (j) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964. (k) Boehlow, T. R.; Buxton, P. C.; Grocock, E. L.; Marples, B. A.; Waddington, V. L. *Tetrahedron Lett.* **1998**, *39*, 1839. (l) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (m) Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem.* **1998**, *63*, 8952. (n) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, *63*, 9888.

(14) For information on the stability of dioxiranes, see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Baumstark, A. L.; Beeson, M.; Vasquez, P. C. *Tetrahedron Lett.* **1989**, *30*, 5567. (c) Camporeale, M.; Fiorani, T.; Troisi, L.; Adam, W.; Curci, R.; Edwards, J. O. *J. Org. Chem.* **1990**, *55*, 93. (d) Adam, W.; Curci, R.; Elena, M.; Nuñez, M. E. G.; Mello, R. *J. Am. Chem. Soc.* **1991**, *113*, 7654. (e) Murray, R. W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* **1992**, *114*, 1346. (f) Singh, M.; Murray, R. W. *J. Org. Chem.* **1992**, *57*, 4263. (g) Hull, L. A.; Budhai, L. *Tetrahedron Lett.* **1993**, *34*, 5039. (h) Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* **1994**, *35*, 2981.

(15) Curci, R.; Fiorentino, M.; Serio, M. R. *Chem. Commun.* **1984**, 155.

(16) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.

(17) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587.

(18) For a calculation study on stereoelectronics of the transition state for fluorinated dioxirane mediated epoxidation, see: Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297.

(19) (a) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (c) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943.

(20) For a related iminium-catalyzed epoxidation under homogenous conditions (CH_3CN-H_2O) with Oxone−$NaHCO_3$, see: Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271.

(21) (a) Furutani, T.; Hatsuda, M.; Imashiro, R.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4763. (b) Seki, M.; Furutani, T.; Hatsuda, M.; Imashiro, R. *Tetrahedron Lett.* **2000**, *41*, 2149. (c) Kuroda, T.; Imashiro, R.; Seki, M. *J. Org. Chem.* **2000**, *65*, 4213. (d) Seki, M.; Yamada, S.-i.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677. (e) Hatsuda, M.; Hiramatsu, H.; Yamada, S.-i.; Shimizu, T.; Seki, M. *J. Org. Chem.* **2001**, *66*, 4437. (f) Furutani, T.; Hatsuda, M.; Shimizu, T.; Seki, M. *Biosci., Biotechnol., Biochem.* **2001**, *65*, 180.

(22) (a) Seki, M.; Furutani, T.; Imashiro, R.; Kuroda, T.; Yamanaka, T.; Harada, N.; Arakawa, H.; Musama, M.; Hashiyama, T. *Tetrahedron Lett.* **2001**, *42*, 8201. (b) Furutani, T.; Imashiro, R.; Hatsuda, M.; Seki, M. *J. Org. Chem.* **2002**, *67*, 4599. (c) Imashiro, R.; Seki, M. *J. Org. Chem.* **2004**, *69*, 4216.

(23) (a) Song, E. C.; Kim, Y. H.; Lee, K. C.; Lee, S.-g.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (b) Kim, Y. H.; Lee, K. C.; Chi, D. Y.; Lee, S.-g.; Song, C. E. *Bull. Korean Chem. Soc.* **1999**, *20*, 831.

(24) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995.

(25) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479.

(26) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943.

(27) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett.* **1999**, *40*, 8029.

(28) (a) Matsumoto, K.; Tomioka, K. *Heterocycles* **2001**, *54*, 615. (b) Matsumoto, K.; Tomioka, K. *Chem. Pharm. Bull.* **2001**, *49*, 1653. (c) Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631.

(29) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288.

(30) (a) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (b) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610.

(31) Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* **2003**, *68*, 3232.

(32) (a) Armstrong, A.; Hayter, B. R.; Moss, W. O.; Reeves, J. R.; Wailes, J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057. (b) Armstrong, A.; Moss, W. O.; Reeves, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779.

(33) Armstrong, A.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 257.

(34) Armstrong, A.; Dominguez-Fernandez, B.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 6614.

(35) Klein, S.; Roberts, S. M. *J. Chem. Soc., Perkins Trans. 1* **2002**, 2686.

(36) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

(37) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(38) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.

(39) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1.

(40) (a) Chen, C.-C.; Whistler, R. L. *Carbohydr. Res.* **1988**, *175*, 265. (b) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377.

(41) (a) Ball, D. L.; Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1125. (b) Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820.

(42) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

(43) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425.

(44) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807.

(45) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675.

(46) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.

(47) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.

(48) (a) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (b) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

(49) (a) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (b) Zhu, Y.; Manske, K. J.; Shi, Y. *J. Am. Chem. Soc.* **1999**,

121, 4080. (c) Feng, X.; Shu, L.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11002. (d) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.
(50) Adam, W.; Fell, R. T.; Saha-Möller, C. R.; Zhao, C.-G. *Tetraherdon: Asymmetry* **1998**, *9*, 397.
(51) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475.
(52) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521.
(53) Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715.
(54) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.
(55) For a synthesis of ketone **53**, also see: Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.
(56) As close analogues of $KHSO_5$, arenesulfonic peracids generated from (arenesulfonyl)imidazole$-H_2O_2-$NaOH have also been shown to react with simple ketones to generate dioxiranes as illustrated by ^{18}O-labeling experiments, see: Schulz, M.; Liebsch, S.; Kluge, R.; Adam, W. *J. Org. Chem.* **1997**, *62*, 188.
(57) It has been reported that dioxiranes can also be generated when a ketone reacts with oxidants such as (a) HOF, Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169. (b) $ONOO^-$, 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.
(58) For a general reference on H_2O_2, see: Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer Academic Publishers: Dordrecht, 1992.
(59) For leading reviews on epoxidation of olefins with H_2O_2, see: (a) Grigoropoulou, G.; Clark, J. H.; Elings, J. A. *Green Chem.* **2003**, *5*, 1. (b) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977. (c) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457. (d) Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006**, *84*, 74. (e) Matsumoto, K. *Yuki Gosei Kagaku Kyokaishi* **2006**, *64*, 869. (f) Arends, I.W.C. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6250.
(60) (a) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721. (b) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5231.
(61) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9.
(62) For leading references on epoxidation using $RCN-H_2O_2$, see: (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Payne, G. B. *Tetrahedron* **1962**, *18*, 763. (c) McIssac, J. E., Jr; Ball, R. E.; Behrman, E. J. *J. Org. Chem.* **1971**, *36*, 3048. (d) Bach, R. D.; Knight, J. W. *Org. Synth.* **1981**, *60*, 63. (e) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.
(63) Li, W.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853.
(64) (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437.
(65) (a) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (b) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (c) Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 12982. (d) Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 3790.
(66) For a related transition state calculation, see: Singleton, D. A.; Wang, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6679.
(67) Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718.
(68) Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904.
(69) Marshall, J. A.; Mikowski, A. M. *Org. Lett.* **2006**, *8*, 4375.
(70) Wiseman, J. M.; McDonald, F. E.; Liotta, D. C. *Org. Lett.* **2005**, *7*, 3155.
(71) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711.
(72) Morimoto, Y.; Nishikawa, Y.; Takashi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806.
(73) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. *J. Org. Chem.* **2005**, *70*, 5922.
(74) Bian, J.; Van Wingerden, M.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 7428.
(75) Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050.
(76) (a) Corey, E. J.; Xiong, Z. *J. Am. Chem. Soc.* **2000**, *122*, 4831. (b) Corey, E. J.; Xiong, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9328.
(77) Adams, C. M.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4723.
(78) (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123. (d) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.
(79) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056.
(80) For $SiMe_3$-based strategy for polyether synthesis, see: Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339.
(81) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.
(82) (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Van Duyne, F.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. (c) Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144. (d) Nakanishi, K. *Toxicon* **1985**, *23*, 473.
(83) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588.
(84) For other synthetic applications of ketone **41**, see: (a) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335. (b) Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M. *Angew, Chem. Int. Ed.* **2000**, *39*, 2552. (c) Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 221. (d) Morimoto, Y.; Iwai, T.; Kinoshita, T. *Tetrahedron Lett.* **2001**, *42*, 6307. (e) Shen, K.-H.; Lush, S.-F.; Chen, T.-L.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 8106. (f) Guz, N. R.; Lorenz, P.; Stermitz, F. R. *Tetrahedron Lett.* **2001**, *42*, 6491. (g) Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813. (h) Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Flörsheimer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, 4086. (i) Morimoto, Y.; Takaishi, M.; Iwai, T.; Kinoshita, T.; Jacobs, H. *Tetrahedron Lett.* **2002**, *43*, 5849. (j) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574. (k) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593. (l) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2489. (m) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514. (n) Madushaw, R. J.; Li, C.-L.; Su, H.-L.; Hu, C.-C.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 1872. (o) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477. (p) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36. (q) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659. (r) Cachoux, F.; Isarno, T.; Wartmann, M.; Altmann, K.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7469. (s) Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, *128*, 9561. (t) Morimoto, Y.; Takishi, M.; Adachi, N.; Okita, T.; Yata, H. *Org. Biomol. Chem.* **2006**, *4*, 3220. (u) Ager, D. J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J. *Org. Process Res. Dev.* **2007**, *11*, 44.
(85) (a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435.
(86) For an improved synthesis of ketone **104**, see: Shu, L.; Shen, Y.-M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963.
(87) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.
(88) Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409.
(89) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293.
(90) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715.
(91) For large-scale synthesis of ketones **111**, see: Zhao, M.-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.
(92) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115.
(93) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973.
(94) (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.
(95) Wang, B.; Shen, Y.-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519.
(96) For a synthesis of chiral 4-aryl-γ-butyrolactones using ketone **41**, see: (a) Yoshida, M.; Ismail, M.A.-H.; Nemoto, H.; Ihara, M. *Heterocycles* **1999**, *50*, 673. (b) Yoshida, M.; Ismail, M.A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629.
(97) Burke, C. P.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4475.
(98) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093.
(99) Burke, C. P.; Shu, L.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 6320.
(100) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545.
(101) Shing, T. K. M.; Leung, Y. C.; Yeung, K. W. *Tetrahedron* **2003**, *59*, 2159.
(102) (a) Shing, T. K. M.; Leung, G. Y. C.; Yeung, K. W. *Tetrahedron Lett.* **2003**, *44*, 9225. (b) Shing, T. K. M.; Leung, G. Y. C.; Luk, T. *J. Org. Chem.* **2005**, *70*, 7279.
(103) Shing, T. K. M.; Luk, T.; Lee, C. M. *Tetrahedron* **2006**, *62*, 6621.
(104) Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403.
(105) (a) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (b) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.
(106) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521.
(107) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749.

(108) (a) Armstrong, A.; Hayter, B. R. *Tetrahedron: Asymmetry* **1997**, *8*, 1677. (b) Armstrong, A.; Hayter, B. R. *Tetrahedron* **1999**, *55*, 11119.
(109) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.
(110) For the synthesis of ketones **137**, see: Solladié-Cavallo, A.; Bouérat, L. *Tetrahedron: Asymmetry* **2000**, *11*, 935.
(111) Solladié-Cavallo, A.; Bouérat, L. *Org. Lett.* **2000**, *2*, 3531.
(112) Solladié-Cavallo, A.; Jierry, L.; Norouzi-Arasi, H.; Tahmassebi, D. *J. Fluorine Chem.* **2004**, *125*, 1371.
(113) In an earlier study on the epoxidation with 2-fluoro-4-*t*-butylcyclohexanones, Demark and coworkers observed that the ketone with an equatorial F is a much more active catalyst than the ketone with an axial F (ref 29).
(114) For the synthesis of ketones **138** and **139**, see: Solladié-Cavallo, A.; Jierry, L.; Bouérat, L.; Taillasson, P. *Tetrahedron: Asymmetry* **2001**, *12*, 883.
(115) For the determination of configuration of ketone **139**, see: Freedman, T. B.; Cao, X.; Nafie, L. A.; Solladié-Cavallo, A.; Jierry, L.; Bouérat, L. *Chirality* **2004**, *16*, 467.
(116) Solladié-Cavallo, A.; Jierry, L.; Lupattelli, P.; Bovicelli, P.; Antonioletti, R. *Tetrahedron* **2004**, *60*, 11375.
(117) (a) Solladié-Cavallo, A.; Bouérat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557. (b) Solladié-Cavallo, A.; Jierry, L.; Klein, A. *C. R. Chimie* **2003**, *6*, 603.
(118) Solladié-Cavallo, A.; Jierry, L.; Klein, A.; Schmitt, M.; Welter, R. *Tetrahedron: Asymmetry* **2004**, *15*, 3891.
(119) (a) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113. (b) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Forlani, R.; Maietti, S.; Pedrini, P. *J. Org. Chem.* **2002**, *67*, 5802.
(120) (a) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Mari, L. *Tetrahedron: Asymmetry* **2004**, *15*, 3831. (b) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Mari, L. *Tetrahedron* **2006**, *62*, 4482.
(121) For the determination of absolute configuration of the epoxides obtained from asymmetric epoxidation using keto bile acid, see: Devlin, F. J.; Stephens, P. J.; Bortolini, O. *Tetrahedron: Asymmetry* **2005**, *16*, 2653.
(122) Chan, W.-K.; Yu, W.-Y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* **2003**, *68*, 6576.
(123) Rousseau, C.; Christensen, B.; Petersen, T. E.; Bols, M. *Org. Biomol. Chem.* **2004**, *2*, 3476.
(124) (a) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573. (b) Picot, A.; Milliet, P.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1577. (c) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron* **1981**, *37*, 4201.
(125) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061.
(126) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *49*, 423.
(127) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941.
(128) (a) Hanquet, G.; Lusinchi, X.; Milliet, P. *C. R. Acad. Sci., Ser. II* **1991**, *313*, 625. (b) Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727.
(129) For additional study on related 3,4-dihydroisoquinolinium salt-catalyzed epoxidation, see: (a) Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2002**, *43*, 803. (b) Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2004**, *45*, 747. (c) Page, P. C. B.; Buckley, B. R.; Appleby, L. F.; Alsters, P. A. *Synlett* **2005**, 3405.
(130) (a) Ref 20. (b) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.
(131) (a) Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774. (b) Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3325. (c) Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926.
(132) For NMR studies on the formation of oxaziridinium salt from iminium **162c** under non-aqueous conditions, see: Page, P. C. B.; Barros, D.; Buckley, B. R.; Marples, B. A. *Tetrahedron: Asymmetry* **2005**, *16*, 3488.
(133) Page, P. C. B.; Buckley, B. R.; Rassias, G. A.; Blacker, A. J. *Eur. J. Org. Chem.* **2006**, 803.
(134) Page, P. C. B.; Barros, D.; Buckley, B. R.; Ardakani, A.; Marples, B. A. *J. Org. Chem.* **2004**, *69*, 3595.
(135) (a) Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375. (b) Page, P. C. B.; Buckley, B. R.; Barros, D.; Blacker, A. J.; Heaney, H.; Marples, B. A. *Tetrahedron* **2006**, *62*, 6607.
(136) (a) Brózda, D.; Koroniak, Ł.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017. (b) Głuzyńska, A.; MaŚkowska, I.; Rozwadowska, M. D.; Sienniak, W. *Tetrahedron: Asymmetry* **2004**, *15*, 2499.
(137) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191.
(138) (a) Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543. (b) Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2006**, *8*, 4669.
(139) Page, P. C. B.; Buckley, B. R.; Barros, D.; Blacker, A. J.; Marples, B. A.; Elsegood, M. R. J. *Tetrahedron* **2007**, *63*, 5386.
(140) Page, P. C. B.; Farah, M. M.; Buckley, B. R.; Blacker, A. J. *J. Org. Chem.* **2007**, *72*, 4424.
(141) (a) Gonçalves, M.-H.; Martinez, A.; Grass, S.; Page, P. C. B.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297. (b) Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334.
(142) Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580.
(143) (a) Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8527. (b) Vachon, J.; Pérollier, C.; Monchaud, D.; Marsol, C.; Ditrich, K.; Lacour, J. *J. Org. Chem.* **2005**, *70*, 5903.
(144) (a) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K. *Synlett* **1997**, 1075. (b) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341.
(145) Armstrong, A.; Draffan, A. G. *Tetrahedron Lett.* **1999**, *40*, 4453.
(146) For calculational studies on transition states for this system and for epoxidations by oxaziridinium salts, see: Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 2948.
(147) Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810.
(148) Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587.

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