

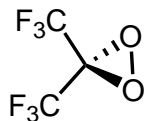
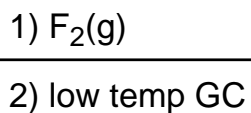
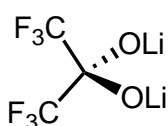
The Development of Dioxirane Mediated Enantioselective Epoxidation Reactions

- Introduction to Dioxiranes
- Early Epoxidations
- Initial Asymmetric Epoxidations
- Recent Advances, focusing on the Shi Group

Brian Connell
Evans Group Seminar
9/24/99

Dioxiranes: Cyclic Peroxides

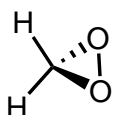
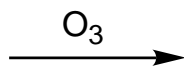
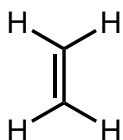
The First Synthesis (Talbot & Thompson, 1972):



Characterized by:

UV
IR
¹⁹F NMR
mass spec

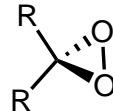
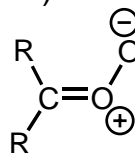
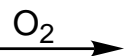
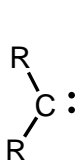
Martiney (1977), Chapman and Hess (1984):



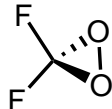
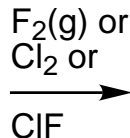
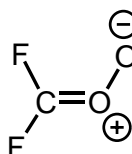
Microwave spectroscopy:

C-H 1.090 Å
C-O 1.387 Å
O-O 1.515 Å

Duncan and Shields (1986):

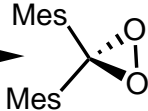
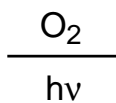
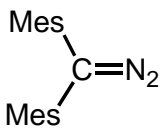


Burger et al (1994):



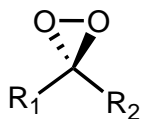
stable in the gas phase

Kirschfield et al (1994):



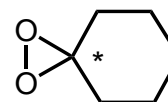
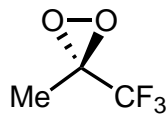
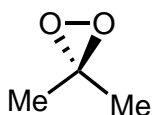
stable for several days

Known Dioxiranes
(Characterized)



R ₁	R ₂
Me	Me
Me	CF ₃
CF ₃	CF ₃
CF ₃	CF ₂ Cl
H	H
Ph	Ph
CF ₃	Ph
Cl	Ph
F	F
Mes	Mes

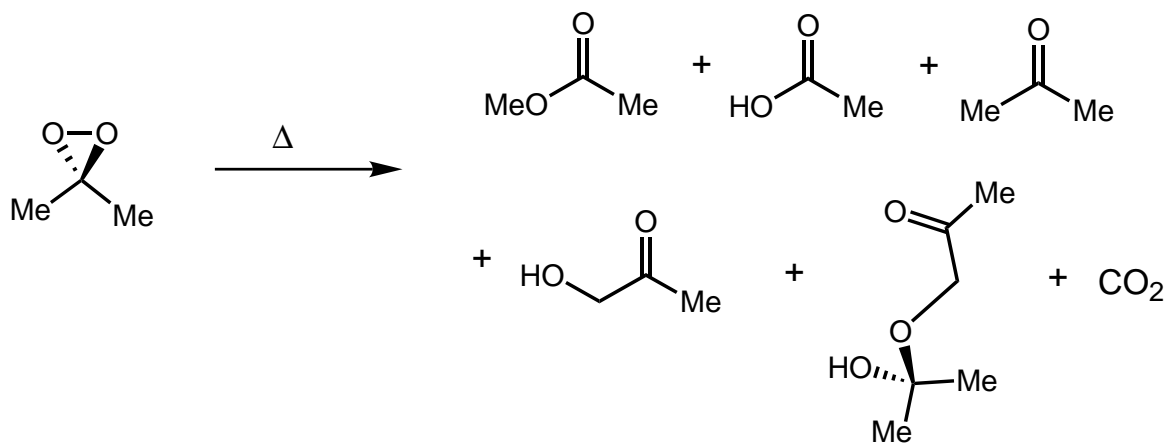
Dioxirane NMR Chemical Shift Data



Nucleus

^1H	1.65	1.97	
^{13}C	22.73, 22.69, 102.3	14.51, 97.32, 122.2 (CF ₃)	104.51
^{17}O	302	297	
^{19}F		-81.5	

Thermal Stability

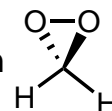


- $t_{1/2} = \sim 7$ h (disputed)

- stabilized by the presence of O_2

- 24.9 kcal/mol ΔG^\ddagger

- compare to 15.5 kcal/mol ΔG^\ddagger for O–O bond cleavage in

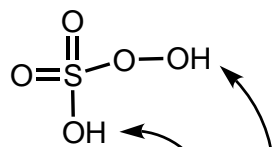


- first order kinetics at low concentration (10^{-2} M); complex kinetics at higher concentrations

- radical pathways confirmed by ESR, spin trapping reagents, oxygen trapping, etc.

Oxone: Background

Caro's Acid
 H_2SO_5

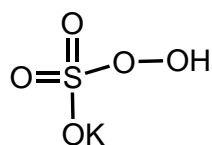


explosive

$\text{pK}_a(1): < 0$

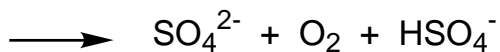
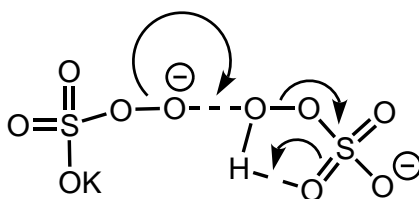
$\text{pK}_a(2): 9.4$

Oxone; Caroate
 KHSO_5



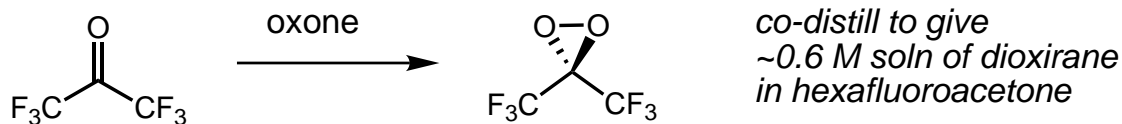
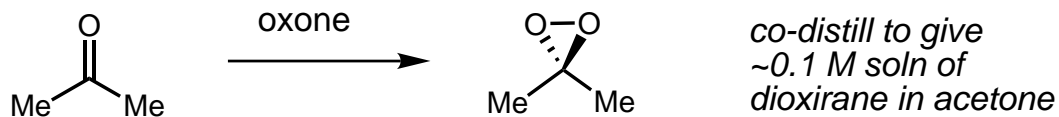
Available commercially as
 $\text{K}_2\text{SO}_4 \cdot \text{KHSO}_4 \cdot 2 \text{KHSO}_5$
 25 kg/\$180 from Aldrich

Decomposition pathway:



pK_a data: *JACS*, **1956**, 78, 1125.
 decomp pathway: *Inorg. Chem.* **1964**, 1331;
Inorg. Chim Acta, Rev, **1968**, v2, 53.

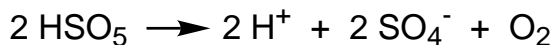
Synthetically Useful Dioxirane Synthesis



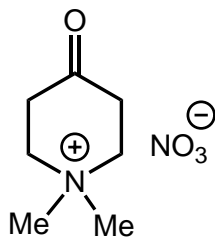
Curci, *JOC*, **1980**, 4758 & **1988**, 3890;
JACS **1991**, 7654.

convenient preparation:
W. Adam *Chem. Ber.* **1991**, 124, 2377.

Montgomery had reported that ketones catalyze the decomp of oxone (*JACS*, 1974, 7820).

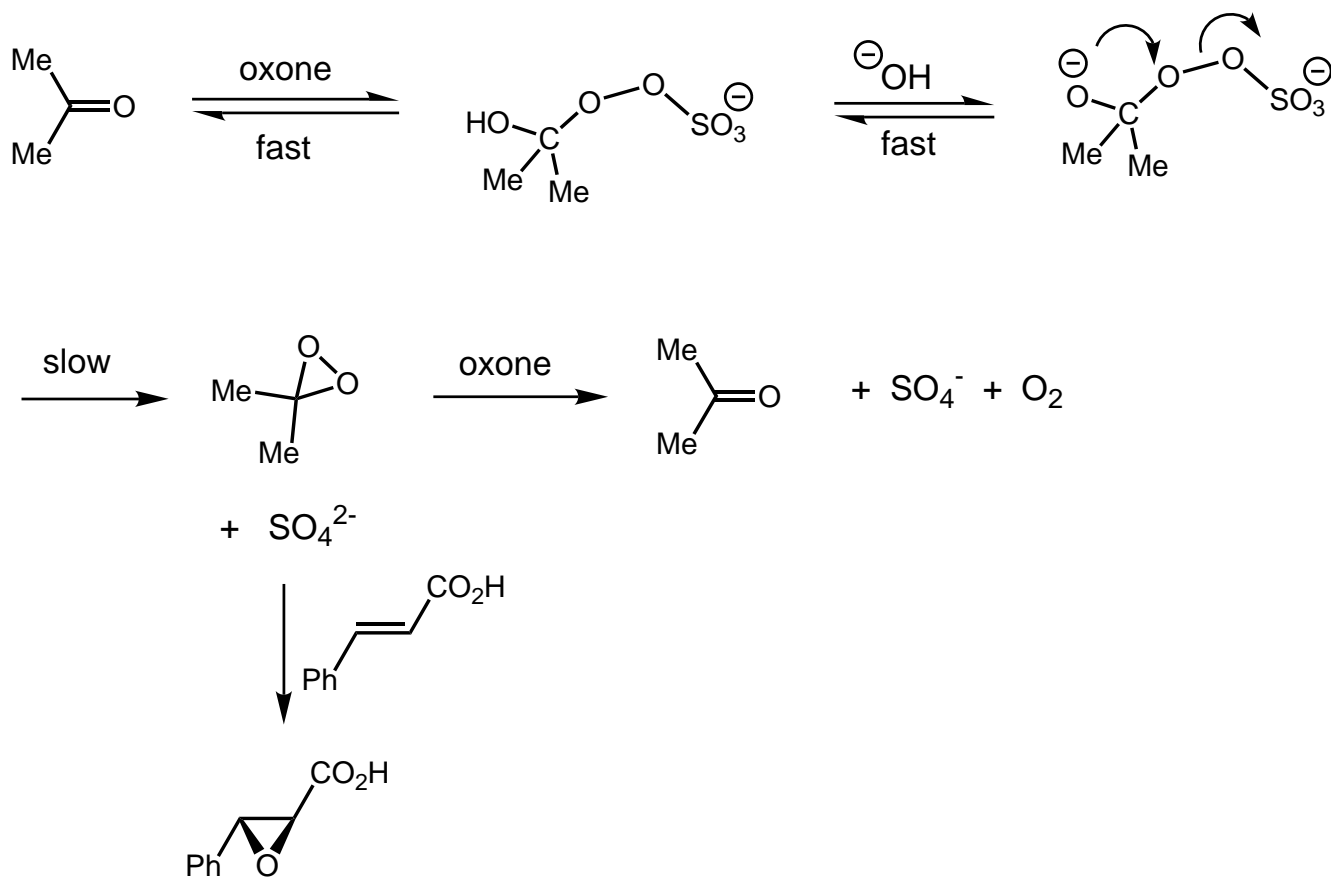


<u>Ketone present</u>	<u>Relative rate</u>
none	1
acetone	10
cyclohexanone	94
	14,000



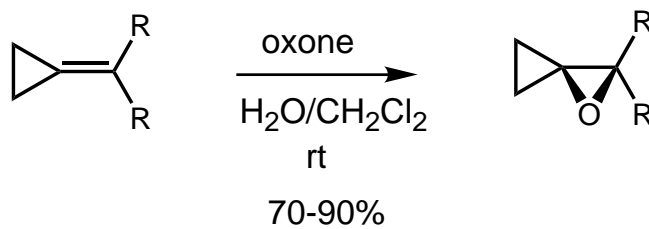
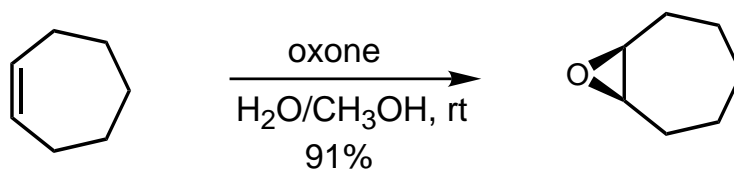
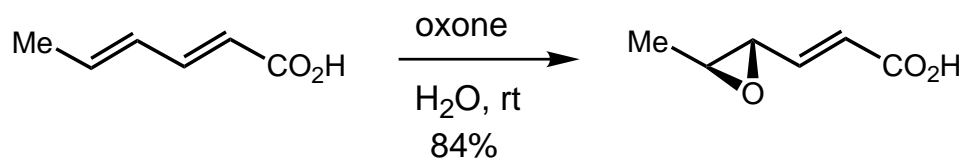
*Only catalytic amounts of
ketone were required.*

Mechanism of Dioxirane Formation with Oxone



Formation of an O–O bond seems a bit strange, but all data is consistent with the mechanism shown, including independent ^{18}O labeling of the oxone and ketone.

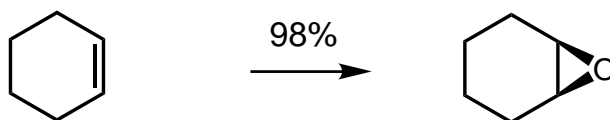
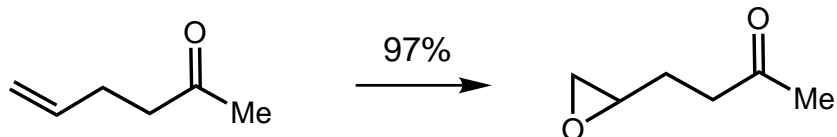
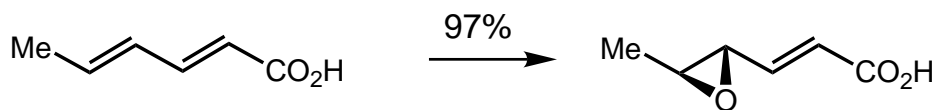
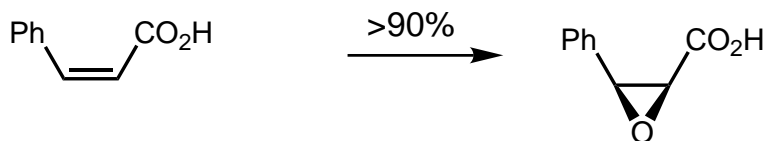
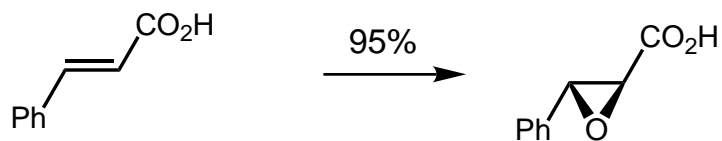
Oxone Mediated Epoxidations



JOC, **1985**, 1544.

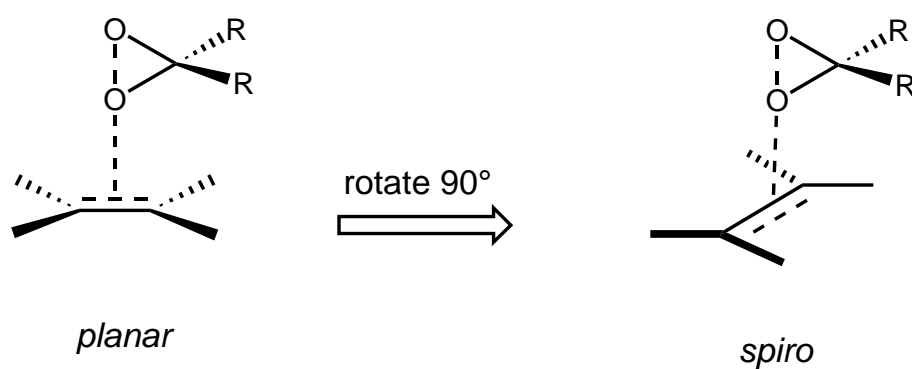
Recl. Trav. Chim. Pays-Bas. **1985**, 350.

Synthetic Epoxidations with Oxone/Acetone



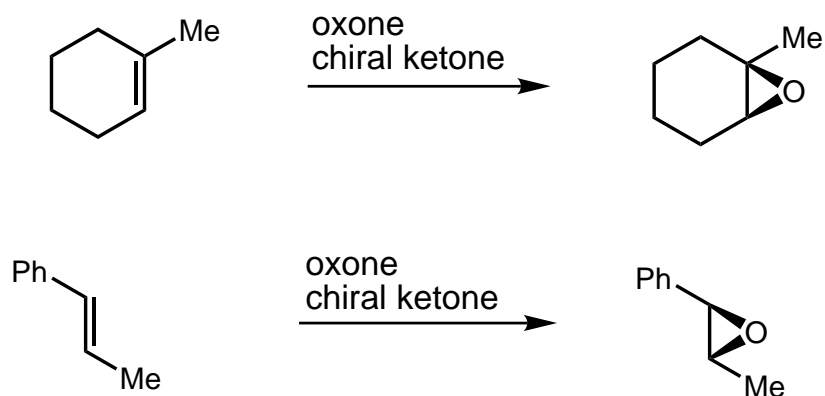
Standard Reaction Conditions:
excess oxone in acetone/water (pH
7.5 phosphate buffer) at $\sim 0^\circ\text{C}$ for 2 h.

Transition State for the Dioxirane Mediated Olefin Epoxidation

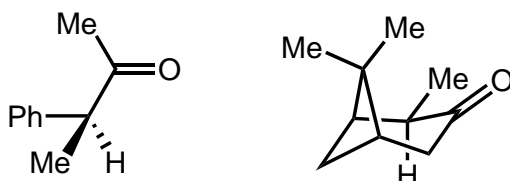


stabilizing $O_{lp} \rightarrow \pi^* C=C$
cis olefins react ~10 times faster than *trans*

First "Enantioselective" Version



2 chiral ketones explored:



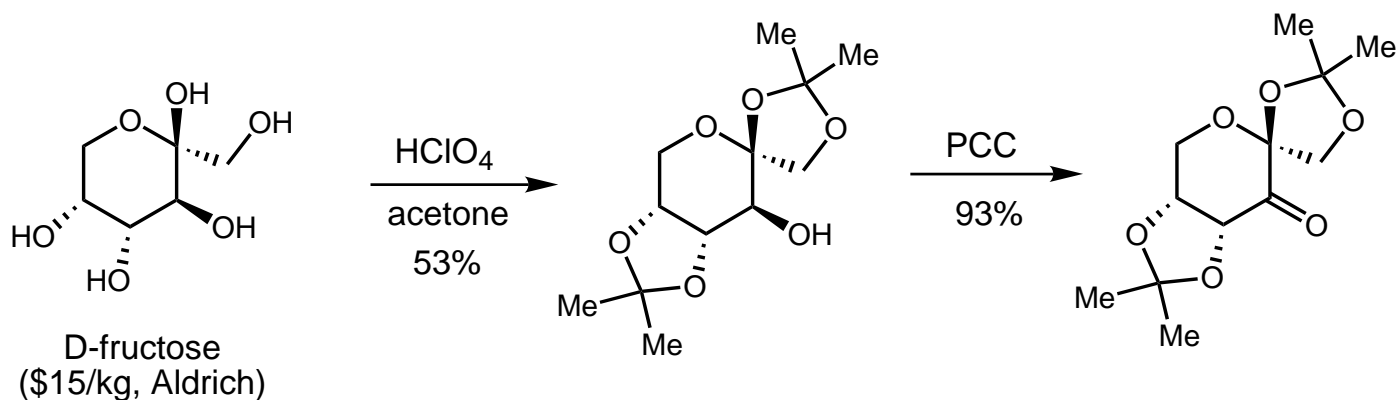
20-300% ketone used
yields 68-92%
ee's 4.2 - 12.5%

ee's determined using $\text{Eu}(\text{tfc})_3$ doped ^1H NMR.

Curci, *JCS Chem Comm*, **1984**, 155.

"...the use of ketones in substoichiometric amounts with no appreciable loss in selectivity is significant and suggests that further research in this area is certainly well justified." Eric Jacobsen in *Catalytic Asymmetric Synthesis*, 1993, chap 4.2, Wiley-VCH.

Shi's First Stoichiometric Dioxirane Mediated Epoxidation



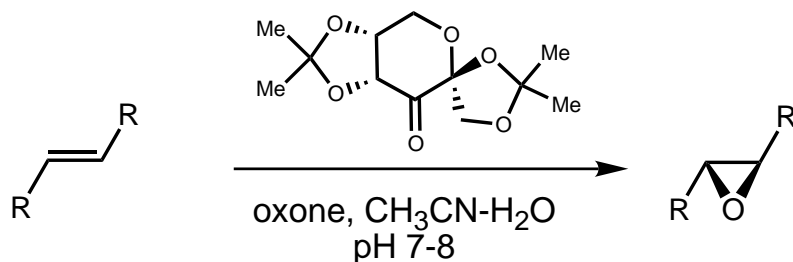
enantiomer can be readily prepared from L-sorbose in 3 steps (51%)

Rational design features:

- Stereocenters are close to the reacting center
- Fused ring and quaternary center minimize possibility of ketone epimerization
- Steric discrimination between faces of carbonyl

JACS, **1996**, 9806.

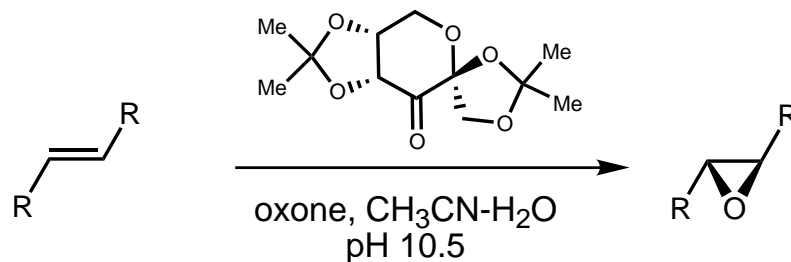
Initial Results



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

^a All reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (3 equiv), Oxone (5 equiv), and NaHCO₃ (15.5 equiv) in CH₃CN–aqueous EDTA (4 × 10⁻⁴ M) (~1.5:1) (refs 7b and 10); the reactions were stopped after 2 h (for detail see supporting information). ^b The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^c Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide products directly with Eu(hfc)₃. ^d Enantioselectivity remained unchanged (95% ee) when 0.5 and 0.25 equivs of chiral ketone were used except that the yields were lowered. ^e Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^f After recrystallization. ^g Enantioselectivity was determined by ¹H NMR shift analysis of the derived acetate with Eu(hfc)₃. ^h The epoxide was opened (NaOMe–MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ¹H NMR shift analysis of the resulting acetate with Eu(hfc)₃. ⁱ The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ^j The absolute configuration was not determined.

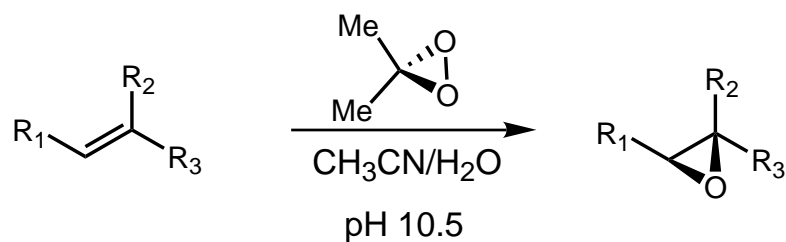
Dramatic pH Effect Observed



Entry	Substrate	Ketone/ Substrate	Yield ^b (%)	ee (%)	Config. ^h
1 ^c		0.3	75	97 ^d	(+)-(R,R) ^{10a}
2		0.3	93	92 ^e (91.7 ^s)	(+)-(R,R) ^{10a}
3		0.3	70	90 ^e	(+)-(R,R) ^{10a}
4		0.3	87	94 ^e	(+)-(R,R) ^{10a}
5		0.2	70	91 ^f	(+)-(R,R) ^{10b}
6		0.2	88	93 ^f	(+)-(R,R) ⁱ
7		0.3	76	91 ^e	(+)-(R,R) ^{10c}
8 ^c		0.3	66	93.5 ^d	(+)-(R) ^{10d}

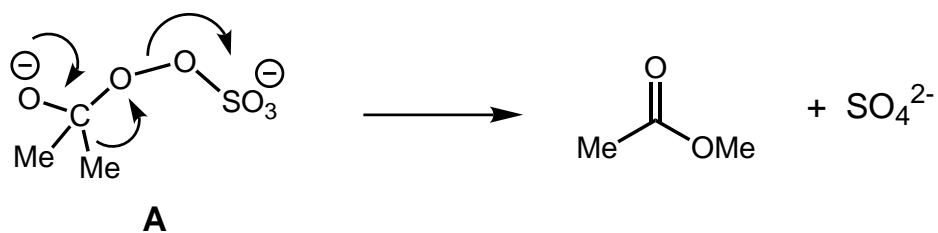
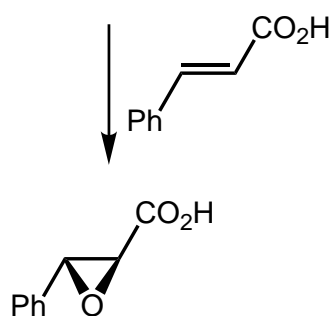
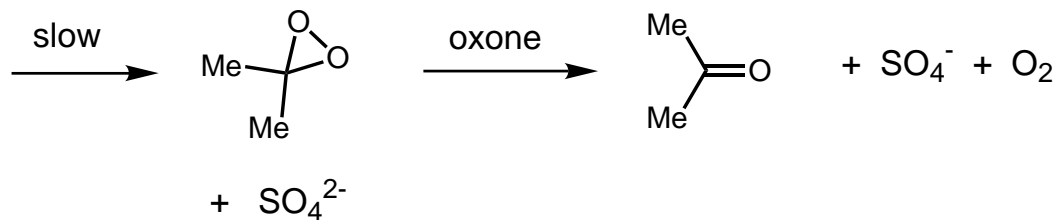
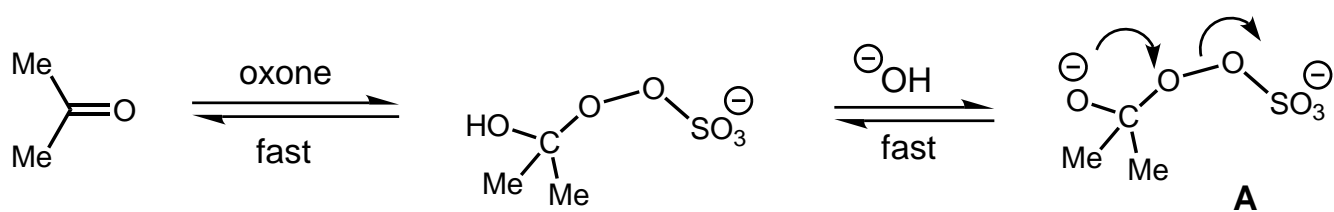
^a All reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (0.2–0.3), Oxone (1.38 equiv), and K₂CO₃ (5.8 equiv) in (1.5:1) CH₃CN–0.05 M Na₂B₄O₇·10H₂O in 4 × 10⁻⁴ M aqueous EDTA; the reactions were stopped after 1.5 h (see text). ^b The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^c Carried out in 2.5:1 CH₃CN–0.05 M Na₂B₄O₇·10H₂O in 4 × 10⁻⁴ M aqueous EDTA. ^d Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^e Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide products directly with Eu(hfc)₃. ^f The epoxide was opened (NaOMe–MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ¹H NMR shift analysis of the resulting acetate with Eu(hfc)₃. ^g Enantioselectivity was determined by chiral GC (Chiraldex γ-TA column). ^h The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ⁱ Absolute configuration (R,R) assumed by analogy with entry 5.

High pH Epoxidations



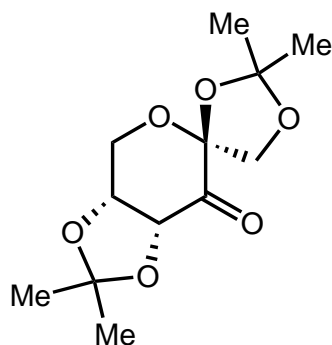
Entry	Substrate	Reaction time (h)	Yield ^b (Conv.) (%)
1		4	67 (79) ^{6c}
2		4	77 (89) ^{6c}
3		4	91 (>95) ^{6c}
4		2	72 (>95) ^{6c}
5		2	67 (>95) ^{6c}
6		2	79 (>95) ^{6c}
7		2	80 (>95) ^{6c}
8		1.5	92 (>95) ^{6c}
9		2	77 (>95) ^{6c}
10		2	85 (94) ^{6c}
11		4	84 (>95) ^{6c}
12		4	86 (>95) ^{6c}
13		4	90 (>95) ⁸
14		4	66 (>95) ^{6c}
15		4	50 (>95) ⁹
16		2	98 (>95) ^{6c}
17		2	84 (>95) ^{6c}
18		1.5	88 (>95) ¹⁰
19		4	72 (>95) ^{6c}
20		4	75 (>95) ^{6c}

What Causes the pH Effect?

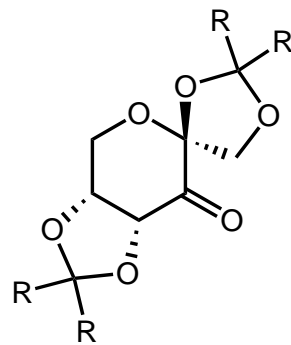


Proposal:
Baeyer-Villiger Competition leads to decomposition of chiral catalyst

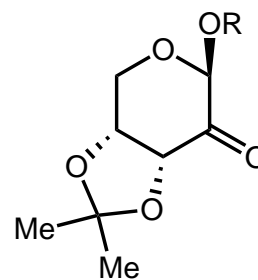
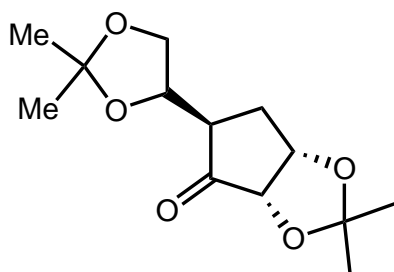
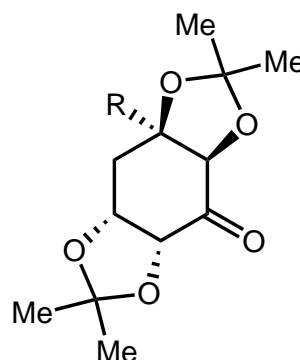
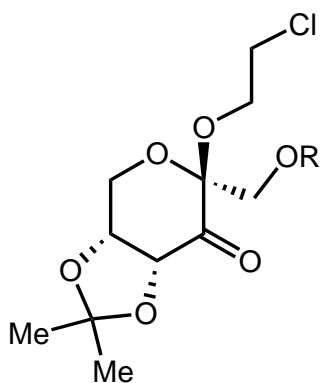
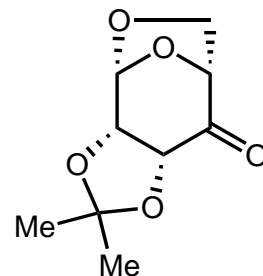
Structural Modification of the Ketone



Original Ketone



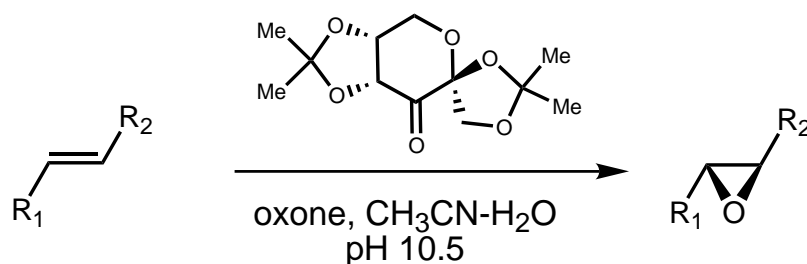
R = Et, $-(CH_2)_4$, $-(CH_2)_5$, $-(CH_2)_6$



None are better than the original

JOC, 1998, 8475.
JOC, 1999, 6443.

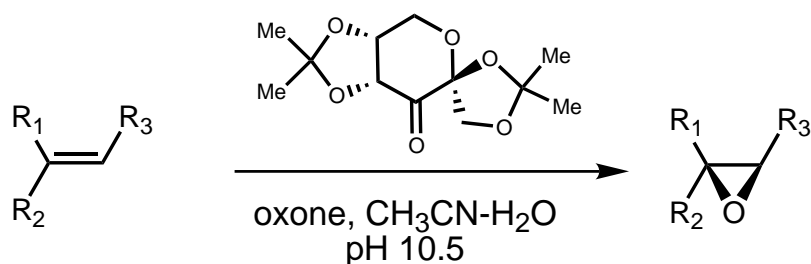
Representative Disubstituted Olefins



Entry	Substrate	Method ^a	T (°C)	Yield ^c (%)	ee (%)	Config ^g
1		A	0	73	95.2 ^c	(+)-(R,R) ^{23a}
		B	0	75	97 ^c	
		C	0	78	98.9 ^c	
		C	0	85	97.9 ^c	
		C (ent-1)	0	81	98.3 ^c	
2		A	0	81	88 ^b	(+)-(R,R) ^{23b}
		B	0	93	91.7 ^f	
		C	-10	94	95.5 ^f	
		C (ent-1)	-10	94	95.7 ^f	
3		A	0	74	93 ^g	(+)-(R,R) ^{23c}
		B	0	87	94 ^g	
		C	0	71	95.2 ^c	
4		C	0	55	94.0 ^c	(+)-(R,R) ^k
5		A	0	61	93 ^g	(+)-(2S,3R) ^{23c}
		C	0	49	96.2 ^f	
6		A	0	41	93 ^g	(+)-(2S,3R) ^k
7		C	-10	91 ^d	93.3 ^f	(+)-(R,R) ^k
8		C	-10	78 ^d	95.7 ^f	(-)-(R,R) ^k
9		A	0	80	93 ^h	(+)-(R,R) ^{23c}
		C	-10	83	94.5 ^h	
10		A	0	84	87 ^h	(+)-(R,R) ^{23c}
		C	-10	85	93 ^h	
11		A	0	81	90 ⁱ	(+)-(R,R) ^{23d}
		B ^b	0	88	93 ⁱ	
		C	-10	89	95 ⁱ	
12		B ^b	0	70	91 ⁱ	(+)-(R,R) ^{23e}
13		C	-10	92	92 ^g	(+)-(R,R) ^{23f}
14		B	0	76	91 ^g	(+)-(R,R) ^{23d}
		C	0	68	92 ^g	

^a Method A: all reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (3 equiv), Oxone (5 equiv), and NaHCO₃ (15.5 equiv) in CH₃CN–aqueous Na₂(EDTA) (4 × 10⁻⁴ M) solution (1.5:1, v/v). The reactions were stopped after 2 h (ref 10). Method B: all reactions were carried out with substrate (1 equiv), ketone (0.3 equiv), Oxone (1.38 equiv), and K₂CO₃ (5.8 equiv) in CH₃CN–0.05 M Na₂B₄O₇·10H₂O of aqueous Na₂(EDTA) (4 × 10⁻⁴ M) solution (1.5:1 v/v). The reactions were stopped after 1.5 h (ref 11). Method C: all reactions were carried out with substrate (1 equiv), ketone (0.3 equiv), Oxone (1.38 equiv), and K₂CO₃ (5.8 equiv) in CH₃CN–DMM–0.05 M Na₂B₄O₇·10H₂O of aqueous Na₂(EDTA) (4 × 10⁻⁴ M) solution (1:2:2, v/v). The reactions were stopped after 30 min for 20 °C, 1.5 h for 0 °C, and 2 h for -10 °C. ^b 0.2 equiv of ketone was used. ^c The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^d The yield is for the mixture of *trans*- and *cis*-epoxides. In entry 7, 29.3% ee (GC) was obtained for the *cis*-epoxide; in entry 8, 25.7% ee (GC) was obtained for the *cis*-epoxide. ^e Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^f Enantioselectivity was determined by chiral GC (Chiraldex γ-TA column). ^g Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide products directly with Eu(hfc)₃. ^h Enantioselectivity was determined by ¹H NMR shift analysis of the derived acetate with Eu(hfc)₃. ⁱ The epoxide was opened (NaOMe–MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ¹H NMR shift analysis of the resulting acetate with Eu(hfc)₃. ^j The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ^k The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode.

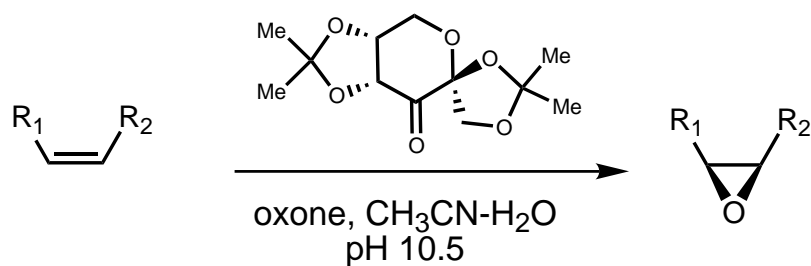
Representative Trisubstituted Olefins



Entry	Substrate	Method ^a	T (°C)	Yield ^b (%)	ee (%)	Config. ^h
1		A	0	73	92 ^e	(+)-(R,R) ^{24a}
		C	0	89	95.5 ^c	
2		A	0	65	92.2 ^e	(-)-(R) ^{24a}
		C	0	54	96.7 ^c	
3		A	0	69	91 ^f	(-)-(R,R) ^{24b}
		C	-10	94	98 ^f	
4		A	0	74	94 ^e	(-)-(1S,2R) ⁱ
		C	-10	98	95.2 ^c	
5		B	0	66	93.5 ^e	(+)-(R) ^{24c}
		C	0	92	97.0 ^e	
6		C	-10	89 ^c	96.8 ^f	(R,R) ⁱ
7		C	-10	93	76.4 ^f	(+)-(R) ⁱ
8		C	-10	97	86.5 ^g	(+)-(R) ^{24c}
9		C	-10	35 (100 ^d)	91 ^f	(-)-(R) ⁱ
10		C	-10	94	83.5 ^g	(+)-(R) ⁱ
11		C	-10	91	83.5 ^g	(+)-(R,R) ⁱ
12		C	-10	89	94 ^g	(+)-(R,R) ⁱ
13		C	-10	77 (100 ^d)	81 ^f	(+)-(1S,2R) ^{24d,e}
14		C (ent-1)	-10	41	97.2 ^f	(-)-(R,R) ⁱ

^a Methods are the same as in Table 4. ^b The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^c The yield is for the mixture of *trans*- and *cis*-epoxides. 83% ee (GC) was obtained for the *cis*-epoxide. ^d The conversion was determined by GC (HP-17 column). ^e Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^f Enantioselectivity was determined by chiral GC (Chiraldex γ -TA column). ^g Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide products directly with Eu(hfc)₃. ^h The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ⁱ The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode.

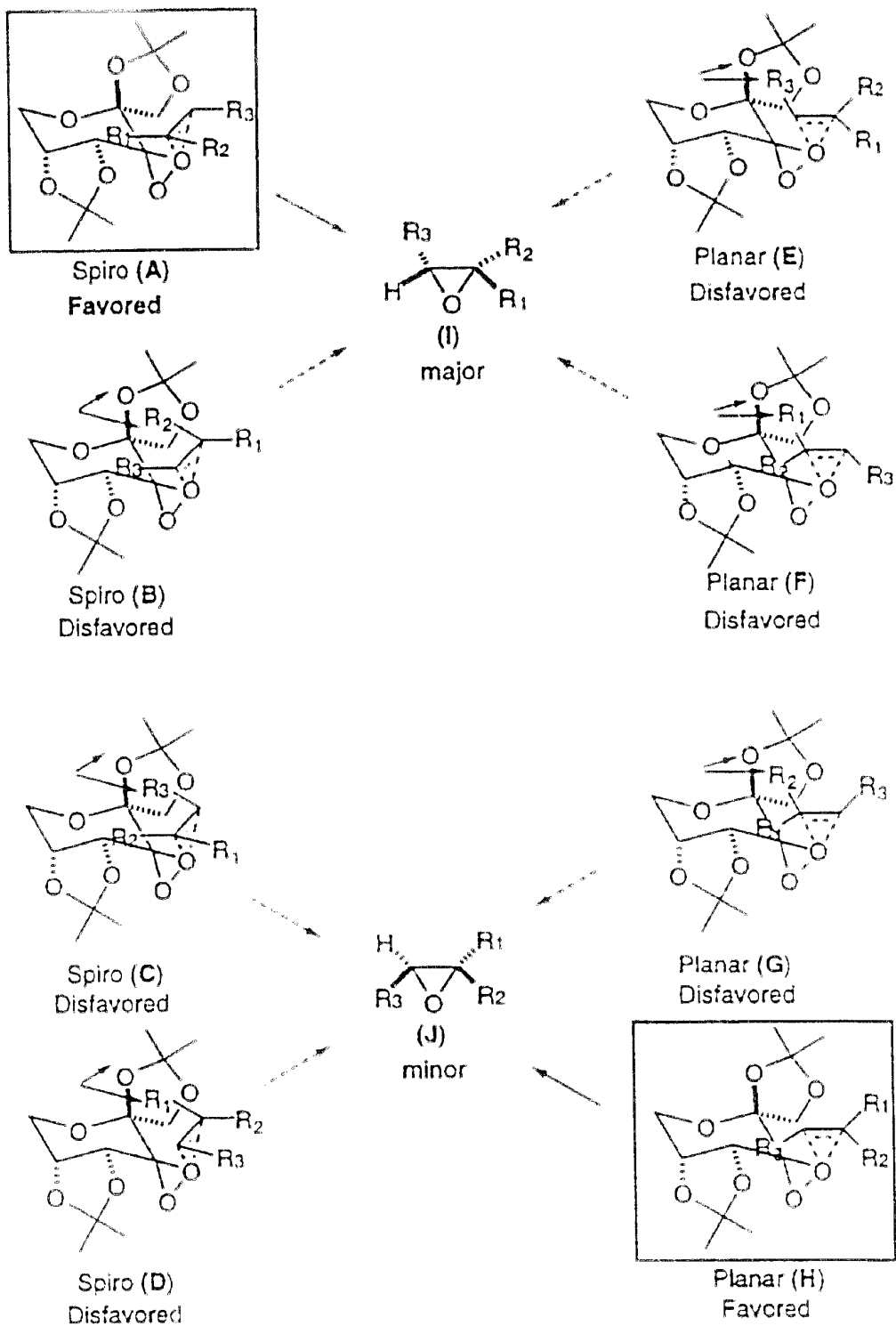
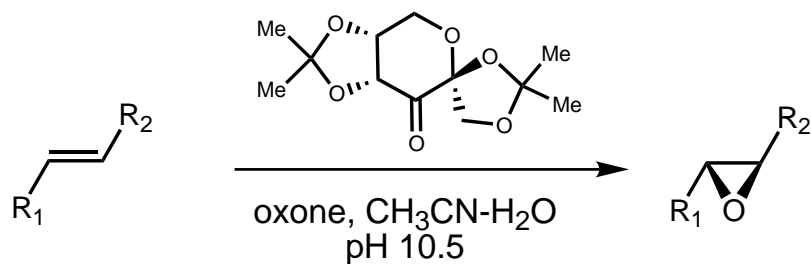
Representative Terminal and *Cis* Olefins



Entry	Substrate	Method ^a	T (°C)	Yield ^b (%)	ee (%)	Config. ^f
1		B	-10	64	13.6 ^c	(+)-(R) ^{25a}
		C	-10	90	24.3 ^c	
2		B	-10	80	27 ^e	(+)-(R) ^{25b}
		C	-10	92	17 ^e	
3		B	-10	92.2	35 ^e	(-) ^g
		C	-10	99	31 ^e	
4		B	-10	81.3	27.6 ^d	(-)-(S) ^{25c}
		C	-10	95	19.6 ^d	
5		B	-10	85.2	32 ^e	(-)-(1S,2R) ^{24c,25d}
		C	-10	92	12 ^e	
6		B	-10	50	56.2 ^c	(+)-(R,R) ^{24e,25e}
		C	-10	43	61.4 ^c	

^a Methods are the same as in Table 4. All reactions were stopped after 2 h. ^b The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^c Enantioselectivity was determined by chiral GC (Chiraldex γ -TA column). ^d Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^e Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide products directly with Eu(hfc)₃. ^f The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ^g The absolute configuration is not ascertained.

Origin of Enantioselectivity



Evidence of Mechanism

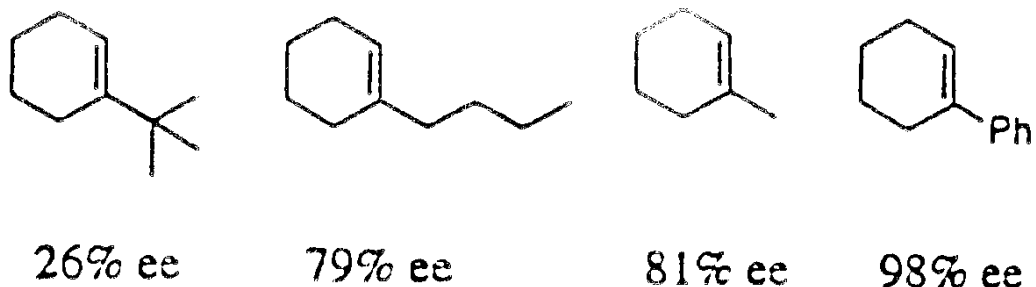
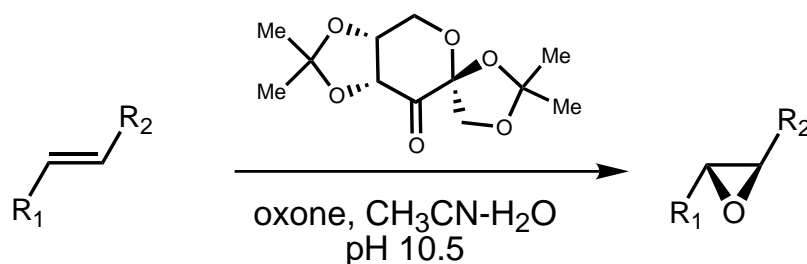


Figure 8. Effect of the size of R_1 on enantioselectivities (decreasing the size of R_1 results in a higher ee).

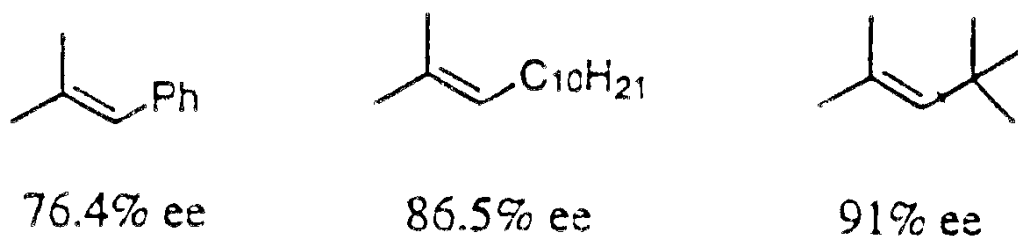


Figure 9. Effect of the size of R_3 on enantioselectivities (increasing the size of R_3 results in a higher ee).

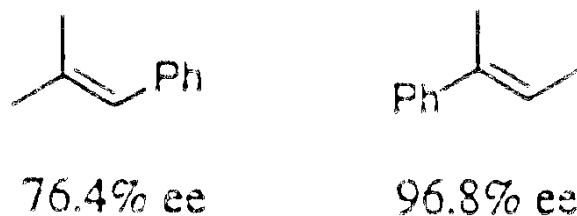
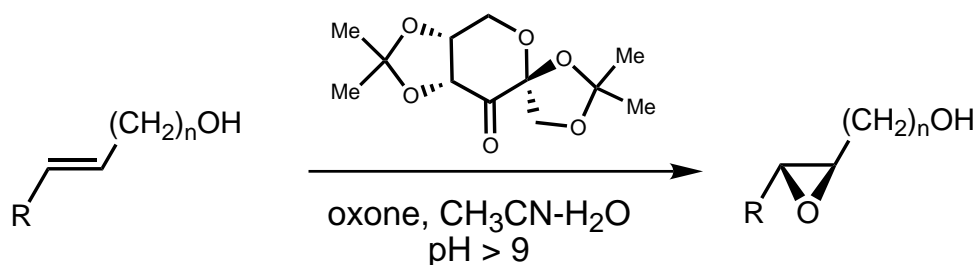


Figure 10. Effect of the size of R_1 and R_3 on enantioselectivities (decreasing the size of R_1 and increasing the size of R_3 enhance the ee).

Alcohol Substrates



Entry	Olefins	T (°C)	t (h)	Yield ^c (%)	ee (%)	Config. ^h
1		-10	3	85	94 (98g) ^d	(R,R) ¹⁰
		-10	3	82	94 ^d	(S,S) ¹⁰
2		-10	2	45	91 ^d	(R,R) ¹¹
		-15 ^b	7	43	92 ^d	
3		-10	3	68	91 ^e	(R,R) ¹⁰
4		0	2	87	94 ^d	(R) ⁱ
5		-10	3	92	92 ^f	(R,R) ^{10,12}
		-15 ^b	5	93	94 ^f	
6		-10	3	83	91 ^f	(R,R) ¹³
		-15 ^b	5	85	92 ^f	
7		-15 ^b	5	75	74 ^d	(R,R) ¹⁰
8		-10	3	82	90 ^e	(R,R) ¹⁴
9		0	2	90	91 ^d	(R,R) ⁱ
10		-10	2	86	90 ^e	(R,R) ⁱ
		-15 ^b	5	83	91 ^e	
11		0	2	87	91 ^d	(R,R) ⁱ
		0	2	88	91 ^d	(S,S) ⁱ

^a All reactions were carried out with substrate (1 eq), ketone **1** (0.3 eq), Oxone (1.38 eq), and K₂CO₃ (5.8 eq) in DMM-CH₃CN-aqueous K₂CO₃/AcOH (prepared by adding 0.5 mL of AcOH to 100 mL of 0.1 M aqueous K₂CO₃, pH 9.3) (2:1:2 v/v) unless otherwise noted. ^b DME was used instead of DMM-CH₃CN as solvent. ^c Isolated yield. ^d Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). ^e Enantioselectivity was determined by the ¹H NMR shift analysis of derived acetate with Eu(hfc)₃. ^f Enantioselectivity was determined by chiral GC (Chiraldex B-TA column). ^g After recrystallization. ^h The absolute configuration was determined by comparing the measured optical rotations with the reported ones. ⁱ The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode.

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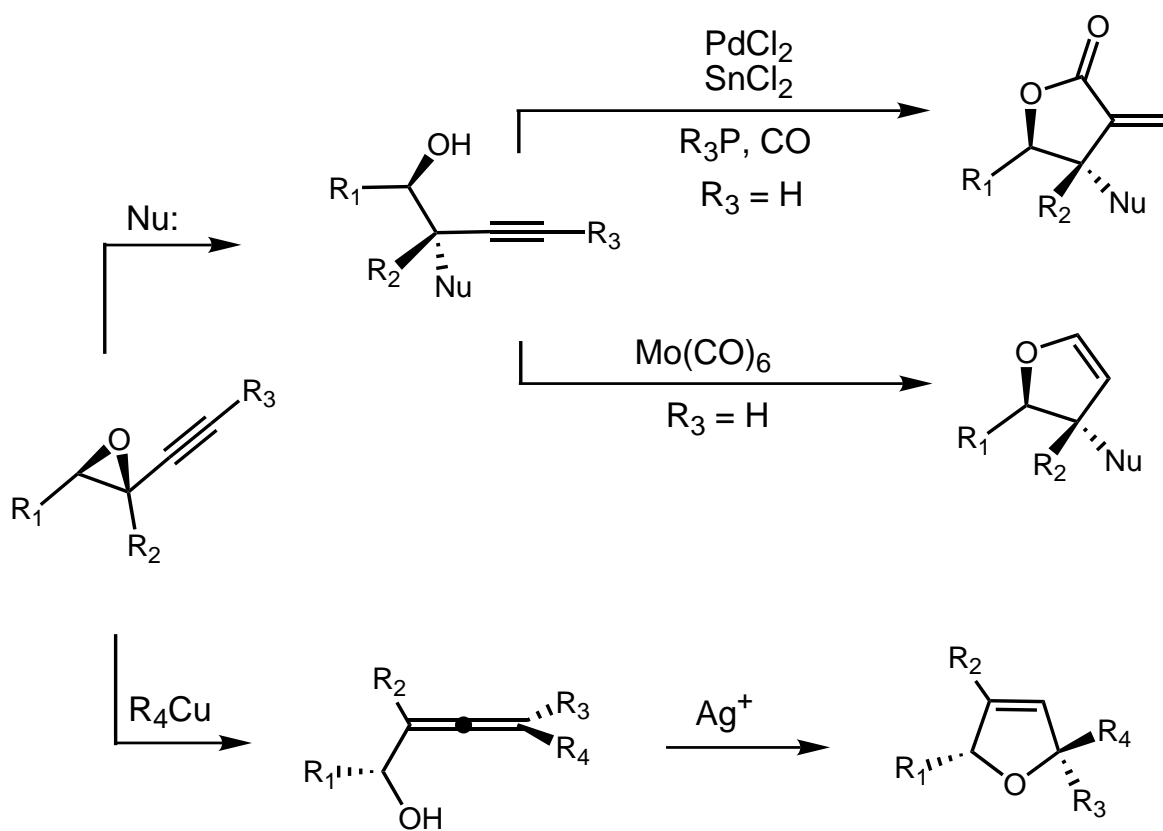
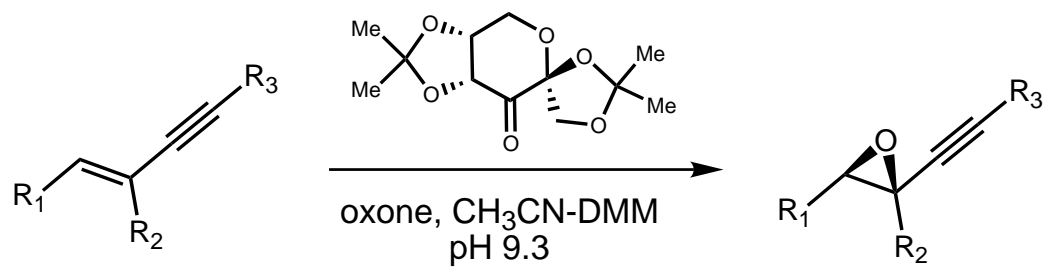
Epoxidation of Dienes

The chiral dioxirane is more regioselective than MCPBA, and complementary to the Sharpless epoxidation.

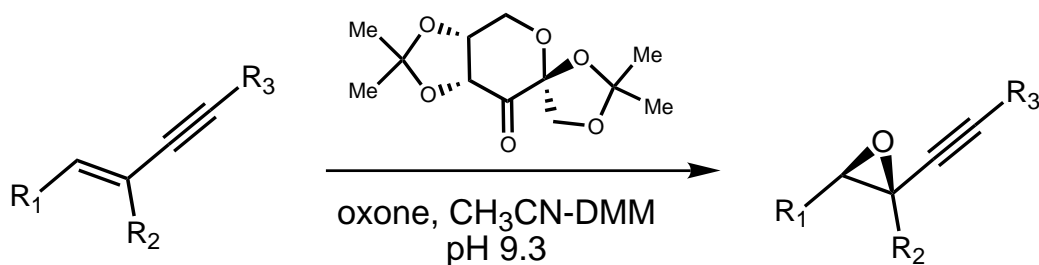
Entry	Dienes	Epoxides	Conv ^b (%)	Ratio ^c	Yield ^d (%)	ee ^p (%)
1			94 ^f	22:1	77	97 ^k
2			87 ^e	26:1	65	97 ^k
3			100 ^e	12:1	54	95 ^k
4			69 ^{g,h}	7:1	41	96 ^k
5			100 ^f	4.6:1	68(13)	96(91) ^l
6			100 ^e		65	89 ^k
7			100 ^f		68 ⁱ	90 ^m
8			100 ^f		81 ⁱ	96 ⁿ
9			76 ^g		68	95 ^k
10			88 ^g		82	95 ^k
11			72 ^g		61	94 ^k
12			100 ^f		89 ⁱ	94 ^m
13			77 ^g	1:1	31 ^{i,j}	95 ^{o,q}
14			92 ^g	14:1	77 ⁱ	94 ^{o,q}
15			100 ^g		81 ⁱ	95 ^o
16			100 ^e		60 ⁱ	92 ^o
17			100 ^g		79 ⁱ	95 ^o

^a All reactions were carried out at 0 °C with diene (1 equiv), ketone (0.2–0.3 equiv), Oxone (1.12–1.38 equiv), and K₂CO₃ (5.0–6.2 equiv) in CH₃CN–DMM–0.05 M Na₂B₄O₇·10H₂O of aqueous EDTA (4 × 10⁻⁴ M) solution (1:2:2, v/v). Oxone was added over 1.5 h unless otherwise stated, and the reactions were stopped immediately. ^b The conversions were determined by the ¹H NMR of the crude reaction mixtures. ^c The ratios were determined by the ¹H NMR of the crude reaction mixtures. For symmetric dienes the ratio refers to the monoepoxide/bisepoxide ratio (the precise stereochemistry of the bisepoxides has not been determined yet). For unsymmetric dienes it refers to the ratio of the two monoepoxides. For entries 6–12 and 15–17, the other monoepoxide regioisomers were barely detectable by ¹H NMR if there was any. ^d The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. The number in parentheses refers to the yield of the minor epoxide. It should be noted that the vinyl epoxides are not very stable, and portions are lost during the column isolation. ^e 0.20 equiv of catalyst used. ^f 0.25 equiv of catalyst used. ^g 0.30 equiv of catalyst used. ^h Oxone was added over 4 h, and the reaction was stopped immediately. ⁱ Trace amounts of bisepoxide were detected in the crude reaction mixtures by ¹H NMR. ^j The epoxide distal to the SiMe₃ group was isolated, and the epoxide proximal to the SiMe₃ group was detected in the crude reaction mixtures by ¹H NMR but decomposed during column isolation. ^k Enantioselectivities were determined by chiral HPLC (Chiralcel OD). ^l The TBS ether was converted to the corresponding alcohol with TBAF, and enantioselectivities were determined by chiral GC (Chiraldex γ-TA column). The number in parentheses refers to the ee of the minor epoxide. ^m Enantioselectivities were determined by chiral HPLC (Chiralcel OB). ⁿ The TBS ether was converted to the corresponding alcohol with TBAF, and enantioselectivities were determined by chiral HPLC (Chiralcel OB). ^o Enantioselectivities were determined by chiral shift NMR with Eu(hfc)₃. ^p The absolute configurations of the epoxides for entries 1 and 10 were determined by comparing to the authentic samples prepared by different routes, and the configurations for the remaining epoxides were tentatively assumed by analogy based on the spiro reaction mode. ^q The number refers to the ee of the epoxide distal to the SiMe₃ group.

Enyne Epoxidation



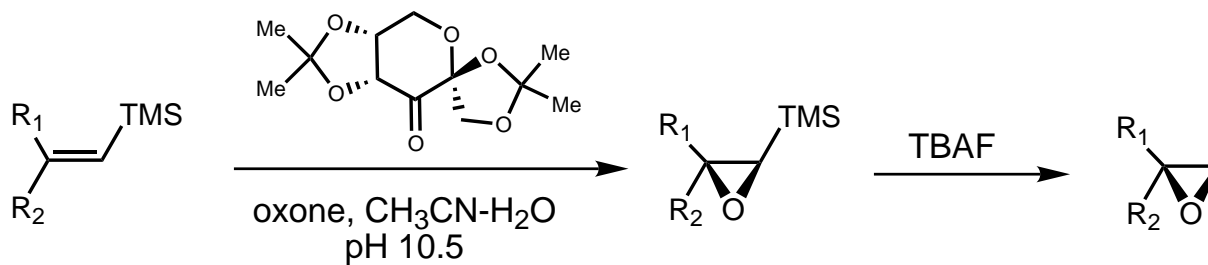
Enyne Results



entry	substrate	T (°C)	t (h)	yield (%) ^c	ee (%)	config.
1		-10	3	78	93 ^d	(R,R) ⁱ
2	R = H (<i>ent</i> -1)	-10	3	75	94 ^d	(S,S) ⁱ
3	R = CH ₃	-10	3	88	90 ^d	(R,R) ^j
4	R = TMS	-10	3	86	93 ^e	(R,R) ⁱ
5	R = CO ₂ Et	0	2	71	93 ^f	(R,R) ^j
6		-10	3	97	77 ^g	(R,R) ^j
7		-10	3	98	96 ^g	(R,R) ^j
8		-10	3	99	86 ^g	(R,R) ^j
9 ^b		0	4	59	96 ^g	(R,R) ⁱ
10 ^b	R = TBS	0	4	60	96 ^g	(R,R) ⁱ
11 ^b	R = Me	0	3	35	94 ^h	(R,R) ^j
12		-10	4	71	89 ^g	(R,R) ⁱ
13	R = TBS	-10	4	69	89 ^g	(R,R) ⁱ
14	R = CH ₂ OMe	-10	4	35	89 ^g	(R,R) ^j
15		-10	3	84	95 ^g	(R,R) ⁱ
16		0	2	64	94 ^g	(R,R) ⁱ
17		-10	3	60	93 ^f	(R,R) ^j
18	R = TMS	-10	3	83	97 ^g	(R,R) ^j
19	R = TBS	-10	2	93	97 ^g	(R,R) ^j

^a All reactions except entries 9–11 were carried out with substrate (1 equiv), ketone (0.3 equiv), Oxone (1.38 equiv), and K₂CO₃ (5.8 equiv) in CH₃CN–DMM–aqueous K₂CO₃/AcOH solution (prepared by adding 0.5 mL of AcOH to 100 mL of 0.1 M aqueous K₂CO₃, pH 9.3) (1:2:2, v/v). ^b The reaction was run with substrate (1 equiv), ketone (0.5 equiv), Oxone (2.07 equiv), and K₂CO₃ (8.7 equiv) in CH₃CN–DMM–aqueous K₂CO₃/AcOH solution (1:2:2, v/v). ^c The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. ^d Enantioselectivity was determined by chiral GC (Chiraldex B-TA column) after desilylation. ^e Enantioselectivity was determined directly with Eu(hfc)₃. ^f Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^g Enantioselectivity was determined by chiral GC (Chiraldex G-TA column). ^h The absolute configuration was determined by a correlation of the epoxide with a prepared authentic sample (see text). ⁱ The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode.

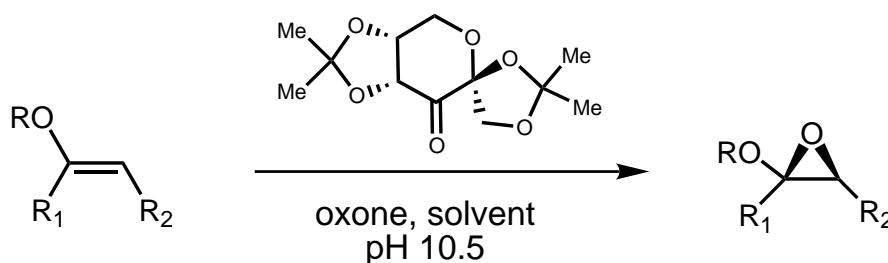
Vinyl Silane Epoxidations



entry	substrate	yield (%) ^b	ee (%)	config.
1		74	94 ^c	(<i>R,R</i>) ^{g,9}
2		82	92 ^c	(<i>R,R</i>) ^h
3		66	93 ^d	(<i>R,R</i>) ^h
4		51	90 ^e	(<i>R,R</i>) ^h
5		67	84 ^e	(<i>R,R</i>) ^h
6		67	92 ^f	(<i>R,R</i>) ^h
7		80 71 ⁱ	90 ^e 93 ^e	(<i>R,R</i>) ^h (<i>R,R</i>) ^h
8		75	91 ^e	(<i>R,R</i>) ^h

^a All epoxidations were carried out at 0 °C (bath temperature) with substrate (1 equiv), ketone (0.65 equiv), Oxone (1.38 equiv), and K₂CO₃ (5.8 equiv) in CH₃CN–dimethoxymethane–0.05 M Na₂B₄O₇·10H₂O aqueous Na₂(EDTA) (4 × 10⁻⁴) solution (1:2:2 v/v); the reactions were stopped after 3 h. ^b The epoxides were purified via flash chromatography and gave satisfactory spectroscopic characterization. ^c Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation. ^d Enantioselectivity was determined by chiral HPLC (Chiralpak AD) after desilylation. ^e Enantioselectivity was determined by ¹H NMR shift analysis of the epoxide directly with Eu(hfc)₃. ^f Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^g The absolute configurations were determined by comparing the measured optical rotations with the reported ones after desilylation. ^h The absolute configuration was tentatively assigned by analogy based on the spiro reaction mode. ⁱ 0.3 equiv of ketone used.

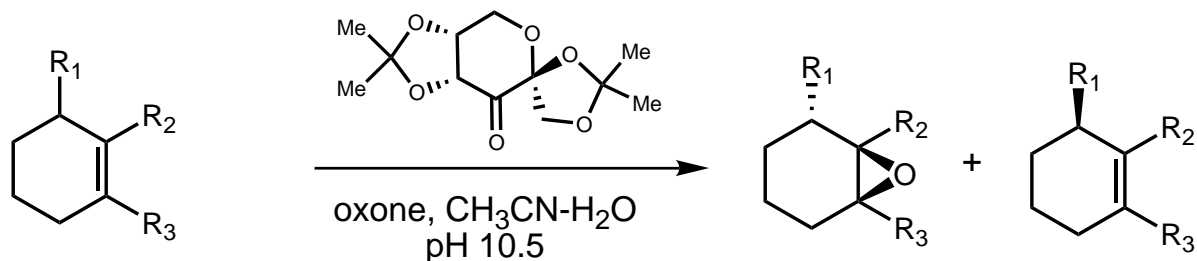
Epoxidation of Enol Ethers and Esters



Entry	Substrate	Product	t (h)	Yield (%) ^b	ee (%)
1			2.0	80	90 ^{c,f}
2			1.0	70	83 ^{c,f}
3			2.0	59	74 ^{d,g}
4			1.5	82	93 ^{e,g}
5			1.5	79	80 ^{c,g}
6			1.5	87	91 ^{c,g}
7			1.5	82	95 ^{c,g}
8			1.5	92	88 ^{e,h}
9			2.0	66	91 ^{d,h}
10			3.0	46	91 ^{d,h}

^a All reactions were carried out at 0 °C (bath temperature) with substrate (1 eq.), ketone (0.3 eq.), Oxone (1.38 eq.) and K₂CO₃ (5.8 eq.) in organic solvent (15 mL) and aqueous buffer solution (10 mL) except that for entry 2 where the reaction was carried out at -5 °C. The organic solvent used was either CH₃CN (entries 1, 2, 5, 7 and 9) or CH₃CN-DMM (1/2, v/v) (entries 3, 4, 6, 8 and 10). For entries 1, 2, 4, 5, 7, 8 and 9, 0.05 M Na₂B₄O₇·10 H₂O of EDTA (4 × 10⁻⁴ M) was used as buffer; for others, AcOH-0.1M K₂CO₃ (4/1000, v/v) was used as buffer (for a representative procedure see: ref. 10). ^b The α-hydroxy ketones and epoxides were purified on silica gel column (for epoxides, silica gel was pretreated with Et₃N) by flash chromatography and gave satisfactory spectroscopic characterization. ^c Enantioselectivity was determined by chiral HPLC (chiracel OB) (for details see ref. 11). ^d Enantioselectivity was determined by ¹H NMR shift analysis of epoxide products directly with Eu(hfc)₃. ^e Enantioselectivity was determined by chiral HPLC (chiracel OD) (for details see ref. 11). ^f The absolute configuration was determined by comparing the measured optical rotations with the reported ones (see: refs. 12, 4, and 13). ^g The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode. ^h The epoxides were hydrolyzed to α-hydroxy ketones and the absolute configurations were determined by comparing the measured optical rotations of the α-hydroxy ketones with the reported ones (see: refs. 13, 12, and 4).

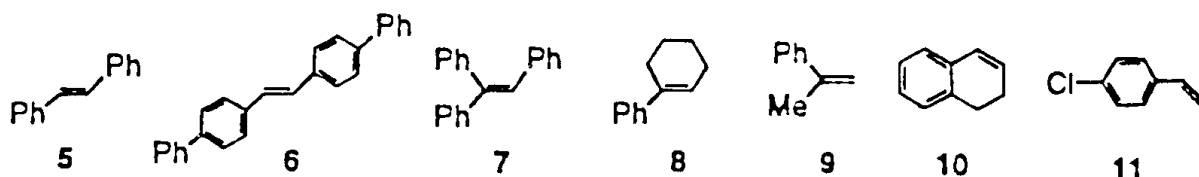
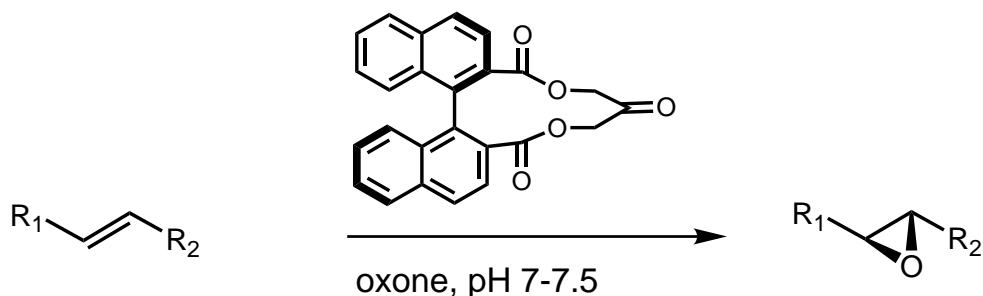
Kinetic Resolutions



entry	substrate	temp (°C)	con. (%) ^b	recov'd SM ee (%) ^c	trans epoxide ee (%)	epoxide (trans/cis) ^d	<i>k_{rel}</i> ^e (<i>k_t/k_c</i>)
1 ^f	R = TMS	-10	49	96 ^g (S) ^h	95 ^g	>20	>100
2 ^f	R = Me	-10	65	99 ^g (S)	85 ^g	6	16
3 ^f	R = COMe	0	54	96 ^g (S)	88 ^g	12	39
4 ^{h,o}	R = COOEt	-10	51	94 ^g (S)	97 ^g	>20	70
5 ^p	R = TBS	-10	70	99 ^g (R)	81 ^g	4	11
6 ^r	R = Me	-10	61	95 ^g (R)	nd	6	14
7 ^r		0	72	81 ^m (R)	nd	1.7	4
8 ^r	R = TBS	-10	49	75 ^r (R)	nd	13	18
9 ^r	R = TBS	20	66	96 ^r (R)	nd	8	11
10 ^q	R = OTMS	-10	61	91 ^m (R)	76 ^t	4	11
11 ^r	R = ⁱ Pr	-10	59	93 ^m (S)	85 ^t	8	15
12 ⁱ	R = ^t Bu	-10	54	99 ^m (R) ^u	84 ^t	>20	61

^a All reactions were carried out with substrate (1 equiv), ketone (0.25–0.75 equiv), Oxone (2.3 equiv), and K₂CO₃ (9.5 equiv) in CH₃CN-DMM-0.05 M Na₂B₄O₇·10H₂O in aqueous EDTA (4 × 10⁻⁴ M) solution (1:2:2, v/v/v). Oxone was added over 2.5 h except for entry 5 and entry 6 (1.5 h). ^b Conversion was determined by ¹H NMR of the crude reaction mixture after workup. In cases where the ee of the epoxide was determined and one diastereomer of the epoxide was formed predominately (entries 1, 4, and 12), the conversion could be cross-checked applying the ee's of the olefin and epoxide to the following equation: ee(olefin)/ee(epoxide) = C/(1 - C). In these cases the measured conversion was consistent with the calculated conversion. ^c The absolute configuration was tentatively assumed on the basis of the spiro reaction mode unless otherwise noted. ^d The ratio of trans and cis epoxides was determined by ¹H NMR. ^e The relative rate was calculated using the equation $k_{rel} = k_t/k_c = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$, where C is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref 12). ^f 0.35 equiv of ketone used. ^g Enantioselectivity was determined by chiral HPLC (Chiralcel OD). ^h The configuration was determined by comparing the measured optical rotation with the known alcohol after desilylation (ref 11). ⁱ 0.45 equiv of ketone used. ^j Enantioselectivity was determined by chiral HPLC (Chiralcel AD). ^k Enantioselectivity was determined by ¹H NMR shift analysis using Eu(hfc)₃. ^l 0.50 equiv of ketone used. ^m Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). ⁿ 0.60 equiv of ketone used. ^o 2.8 equiv of Oxone used. ^p 0.40 equiv of ketone used. ^q Enantioselectivity was determined by chiral HPLC (Chiralcel AD) of the corresponding benzoate. ^r 0.25 equiv of ketone used. ^s Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. ^t 0.75 equiv of ketone used. ^u The configuration was determined by comparing the measured optical rotation with the known ketone after hydrolysis (ref 9).

Yang System



entry	catalyst	substrate	time (min)	epoxide yield (%) ^b	epoxide config	ee (%) ^c
1	(<i>R</i>)-4	5	20	99	(-)-(<i>S,S</i>) ^d	47
2 ^e	(<i>R</i>)-4	6	480	82	(-)-(<i>S,S</i>) ^d	87
3 ^e	(<i>S</i>)-4	6	480	80	(+)-(<i>R,R</i>) ^d	87
4	(<i>R</i>)-4	7	60	98	(+)-(<i>S</i>) ^f	50
5 ^g	(<i>R</i>)-4	8	90	83	(-)-(<i>S,S</i>) ^f	33
6 ^h	(<i>R</i>)-4	9	210	70	nd ⁱ	18
7 ^j	(<i>R</i>)-4	10	80	85	nd ⁱ	<5
8 ^j	(<i>R</i>)-4	11	60	83	(-)-(<i>S</i>) ^k	18

^a Unless otherwise indicated, all the epoxidation reactions were carried out at room temperature with 0.1 mmol of substrate and 0.1 mmol of ketone **4**, 0.5 mmol of Oxone, 1.55 mmol of NaHCO₃, 2 mL of CH₃CN, and 1.7 mL of aqueous Na₂•EDTA solution (4 × 10⁻⁴ M). ^b Isolated yield after flash column chromatography. ^c Determined by ¹H NMR using chiral shift reagent Eu(hfc)₃ (Aldrich Cat. No. 16,474-7). ^d Determined by circular dichroism spectroscopy (see supporting information). ^e 0.01 mmol of ketone **4**, 2.5 mL of CH₃CN, and 2 mL of aqueous Na₂•EDTA solution (4 × 10⁻⁴ M). ^f Reference 11a. ^g 0.2 mmol of the substrate. ^h 0.5 mmol of the substrate. ⁱ Not determined. ^j 0.2 mmol of the substrate, 0.01 mmol of ketone **4**. ^k Reference 18.

Conclusions

- Recent advances in asymmetric epoxidation have developed around chiral dioxirane mediated reactions.
- Trans and tri-substituted unfunctionalized olefins can now be epoxidized in good ee.
- Future goals include tetrasubstituted and terminal olefin epoxidation.
- Other goals include higher enantioselectivity & convenient reaction protocol.
- Catalyst stability is a liability.