DISSERTATION

ASYMMETRIC EPOXIDATION OF VARIOUS OLEFINS CATALYZED BY FRUCTOSE- AND GLUCOSE-DERIVED KETONES

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ON LO ANDREA WONG ENTITLED ASYMMETRIC EPOXIDATION OF VARIOUS OLEFINS CATALYZED BY FRUCTOSE- AND GLUCOSE-DERIVED KETONES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

ASYMMETRIC EPOXIDATION OF VARIOUS OLEFINS CATALYZED BY FRUCTOSE- AND GLUCOSE-DERIVED KETONES

Numerous laboratories have studied dioxirane- and oxaziridinium-mediated epoxidations during the past two decades. Many chiral ketone and iminium salt catalysts, bearing a wide variety of structural features, have been investigated. Out of the systems studied a fructose-derived ketone has been proven to be one of the most general and practical catalysts. This catalyst epoxidizes trans- and trisubstituted olefins in good yield and enantioselectivity, and it has been employed in the syntheses of many complex molecules.

In efforts to expand the substrate scope a series of glucose-derived, oxazinolidine-bearing ketones were reported to be excellent catalysts for the epoxidation of conjugated cis-olefins. The stereodifferentiation in the epoxidation transition state originates from the attraction between the *N*-substituent of the oxazolidinone and the R_π substituent on the olefin. The existence of this interaction was supported by the observation that 6-substituted chromenes were epoxidized with higher enantioselectivities than 8-substituted chromenes. Using this glucose-derived ketone system, substituted chiral styrene oxides could be obtained in 80-92% ee.

Fluoroolefins were investigated as epoxidation substrates with several fructose- and glucose-derived ketone catalysts. A fluorine substituent was found to improve enantioselectivity in some cases but was detrimental to enantioselectivity in others.

The substrate scope of a diacetate-containing ketone was expanded. High enantioselectivities were obtained for the epoxidation of trans- and trisubstituted olefins, and cis-olefins bearing a bulky substituent. The optical rotations of the resulting cis-epoxides were opposite to those obtained using glucose-derived ketones.

1,1-Disubstituted terminal olefins were epoxidized in good enantioselectivities with a glucose-derived morpholinone ketone. From the absolute configuration of the resulting epoxides, the major transition state appears to be a planar-like transition state. Also studied was a glucose-derived dimethylmorpholinone ketone that has the combined features of several of the previously studied ketones. This catalyst epoxidizes trans- and trisubstituted olefins in high enantoselectivities, but compared to the oxazolidinone-containing ketones gives slightly lower enantioselectivities with cis- and 1,1-disubstituted olefin substrates. Lastly, the epoxidation transition state model was studied using ^{18}O-labeled ketone catalysts, and the results support the currently accepted transition state model.

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TABLE OF CONTENTS

CHAPTER ONE: ASYMMETRIC EPOXIDATION OF OLEFINS CATALYZED BY CHIRAL KETONES AND IMINIUM SALTS

1.1. INTRODUCTION 1

1.2. CHIRAL KETONE-CATALYZED EPOXIDATION 3

1.2.1. Introduction 3

1.2.2. Early Ketones 4

1.2.3. C_2-Symmetric Binaphthyl-Based and Related Ketones 6

1.2.4. Ammonium Ketones 14

1.2.5. Bicyclo[3.2.1]octan-3-ones and Related Ketones 15

1.2.6. Carbohydrate-Based and Related Ketones 18

1.2.6.1. Catalyst Development 18

1.2.6.2. Synthetic Applications for Ketone **1-41** 38

1.2.6.3. Developing Catalyst for *cis*-Olefins, Styrenes, and Other Olefins 49

1.2.6.4. Other Carbohydrate-Based Catalysts 68

1.2.7. Carbocyclic Ketones 70

1.2.8. Ketones with an Attached Chiral Moiety 78

1.3. CHIRAL IMINIUM SALT-CATALYZED EPOXIDATION 79

1.3.1. Introduction 79

1.3.2. Chiral Cyclic Iminium Salts 81

1.3.2.1. Dihydroisoquinoline-Based Iminium Salts 81

1.3.2.2. Binaphthylazepinium-Based Iminium Salts 86

1.3.2.3. Biphenylazepinium-Based Iminium Salts 90

1.3.3. Chiral Acyclic Iminium Salts 93

1.4. CONCLUSION 96

CHAPTER TWO: ASYMMETRIC EPOXIDATION OF STYRENES AND STUDIES OF SUBSTITUENT EFFECT ON EPOXIDATION OF CHROMENES

2.1. INTRODUCTION 98

2.2. RESULTS AND DISCUSSION 101

2.2.1. Asymmetric Epoxidation of Styrenes 101

2.2.2. Substituent Effect on Asymmetric Epoxidation of Chromenes 105

2.3. CONCLUSIONS 112

2.4. EXPERIMENTAL 112

CHAPTER THREE: ASYMMETRIC EPOXIDATION OF FLUOROOLEFINS — FLUORINE EFFECT ON ENANTIOSELECTIVITY

3.1. INTRODUCTION 132

3.2. RESULTS AND DISCUSSION 135

3.3. CONCLUSIONS 143

3.4. EXPERIMENTAL 144

3.5. VCD SPECTRA BY BIOTOOLS 160

CHAPTER FOUR: SUBSTRATE SCOPE EXPANSION FOR DIACETATE-CONTAINING KETONE **1-53**

4.1. INTRODUCTION 172

4.2. RESULTS AND DISCUSSION 174

4.3. CONCLUSIONS 179

4.4. EXPERIMENTAL 179

CHAPTER FIVE: ASYMMETRIC EPOXIDATION OF TRANS-, CIS- AND 1,1-DISUBSTITUTED OLEFINS BY MORPHOLINONE KETONES

5.1. ASYMMETRIC EPOXIDATION OF 1,1-DISUBSTITUTED OLEFINS BY MORPHOLINONE KETONE 189

5.1.1. Introduction 189

5.1.2. Results and Discussion 193

5.2. ASYMMETRIC EPOXIDATION OF 1,1-DISUBSTITUTED OLEFINS BY 2,2-DIMETHYLMORPHOLIN-3-ONE KETONE 199

5.2.1. Introduction 199

5.2.2. Results and Discussion 202

5.3. CONCLUSIONS 209

5.4. EXPERIMENTAL 210

CHAPTER SIX: ^{18}O-LABELING STUDIES OF ASYMMETRIC EPOXIDATION CATALYZED BY DIOXIRANE

6.1. INTRODUCTION 217

6.2. RESULTS AND DISCUSSION 218

6.3. CONCLUSIONS 228

6.4. EXPERIMENTAL 229

CHAPTER ONE

ASYMMETRIC EPOXIDATION OF OLEFINS CATALYZED BY CHIRAL KETONES AND IMINIUM SALTS

1.1. 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

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[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.; Kočovský, P *Org. Biomol. Chem.* **2005**, *3*, 3194.

vanadium catalysts, metal-catalyzed epoxidation of unfunctionalized olefins,[6,7,8] 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] have received much attention. Significant progress has been made toward the epoxidation of various types of olefins,

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[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, SM. *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: 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.

particularly unfunctionalized *trans*- and trisubstituted olefins, which has been a long-standing challenge. This review describes progress in this area.

1.2. CHIRAL KETONE-CATALYZED EPOXIDATION

1.2.1. Introduction

Dioxiranes can be generated *in situ*[10,13] from ketones and Oxone (potassium $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (Scheme 1.1).[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.

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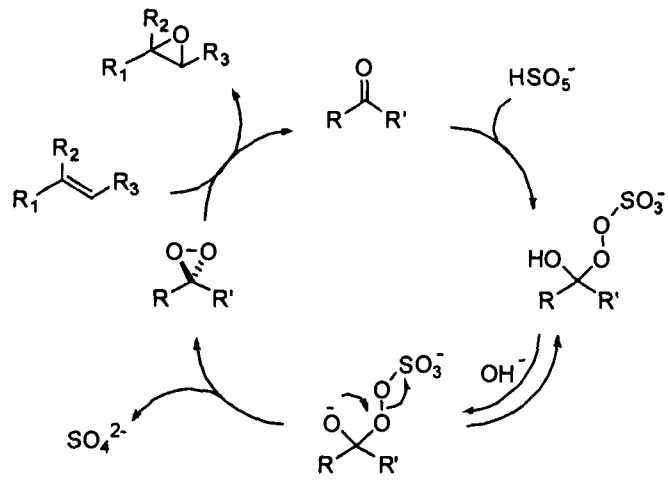
[13] For examples of *in situ* generation of dioxiranes, see: (a) Edwards, J.O.; Pater, R.H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino M.; Troisi, L.; Edwards, J.O.; Pater, R.H. *J. Org. Chem.* **1980**, *45*, 4758. (c) Gallopo, A.R.; Edwards, J.O. *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.

Scheme 1.1 Ketone-Catalyzed Epoxidation of Olefins



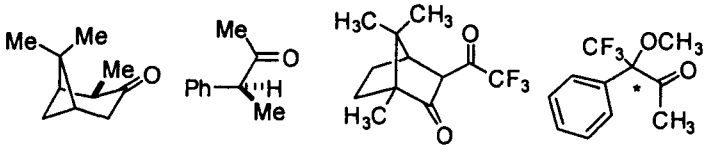
1.2.2. Early Ketones

In 1984, Curci and coworkers reported the asymmetric epoxidation of 1-methylcyclohexene and *trans*-β-methylstyrene with (+)-isopinocamphone (**1-1**) and (*S*)-(+)-3-phenylbutan-2-one (**1-2**) as catalyst in a biphasic mixture of CH_2Cl_2 - H_2O (pH 7-8) (Figure 1.1).[15] These ketones provided good yields and up to 12.5% ee was obtained (Table 1.1, entries 1-3, 6-7). Then in 1995, two ketone catalysts containing electron-withdrawing trifluoromethyl groups (**1-3** and **1-4**) (Figure 1.1) were reported by Curci and coworkers.[16] These ketones were much more active than **1-1** and **1-2**. High conversions were achieved with 0.8 – 1.2 equivalents of ketone at 2-5 ^{o}C within 17-48 hours (Table 1.1), and the ketones could be recovered from the reaction. Up to 20% ee was obtained for *trans*-2-octene (Table 1.1, entry 8) using this method. Also in 1995, Marples and coworkers reported the epoxidation using chiral 1-tetralones and 1-

[15] Curci, R.; Fiorentino, M.; Serio, M.R. *Chem. Commun.* **1984**, 155.

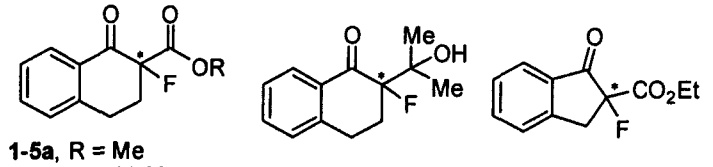
[16] Curci, R.; D'Accolti, L.; Fiorentino, M; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.

indanones bearing fluorines at α-positions (Figure 1.2).[17,18] The dioxiranes generated from these ketones were reactive towards olefins but provided no enantioselectivity.



1-1 1-2 1-3 1-4

Figure 1.1

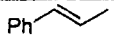
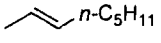


1-5a, R = Me
1-5b, R = (-)-Menthyl

1-6 1-7

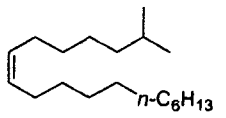
Figure 1.2

Table 1.1 Asymmetric Epoxidation with Chiral Ketones 1-1 – 1-4

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

[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.

9[c]		(*S*)-1-**4**	80	16 (7*R*,8*S*)

[a] 1.0 equiv. ketone used. [b] 0.2 equiv. ketone used. [c] 0.8-1.2 equiv. ketone used. [d] 0.5 equiv. ketone used.

1.2.3. C_2-Symmetric Binaphthyl-Based and Related Ketones

In 1996, Yang and coworkers reported a series of elegant binaphthylene-derived chiral ketones **1-8** (Figure 1.3).[19] C_2 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 **1-8** very active catalysts. High conversion for epoxidation can be obtained with as low 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 **1-8a** 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 **1-8a** can be recovered in >80% yield.

The X-ray structure of ketone **1-8a** showed the hydrogens on carbons 3 and 3' to be closest to the reacting center among all the atoms on the binaphthylene unit, and likely to be the steric sensors for the epoxidation.[19b,c] Various substituents were subsequently

[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.

introduced in place of hydrogens at the 3 and 3' positions (selected examples are shown in Figure 1.3). As the substituents became larger going from H (47% ee) to Cl (76% ee) to Br (75% ee) to I (32% ee), the enantioselectivity towards *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, **1-8d** was found to be the most reactive. Apparently the electron-withdrawing ketal groups provide further activation to the carbonyl. As shown in Table 1.2, *para*-substituted *trans*-stilbenes proved to be very effective substrates for the epoxidation with ketones **1-8**, and the ee's increased as the size of the substituents on the phenyl groups of the olefins increased (Table 1.2, entries 1-9). On the other hand, increasing the size of the *meta*-substituent of stilbene had little effect on enantioselectivity.[19c] Seki and coworkers made extensive efforts to improve the synthesis of ketone **1-8**,[21] and also extended the epoxidation to cinnamates (Table 1.2, entries 15-19).[22] Epoxide **1-9** (Figure 1.4), a key intermediate for calcium antagonist diltiazem hydrochloride (**1-10**), could be obtained in up to 85% ee using ketone **1-8b** (Table 1.2, entry 18).

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[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.

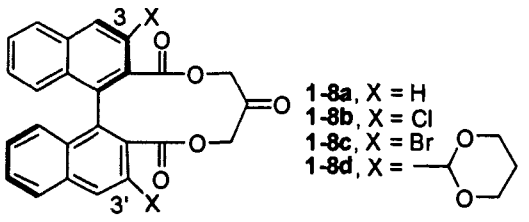
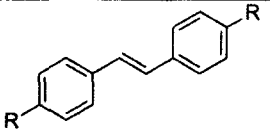
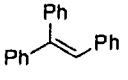
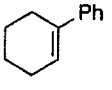
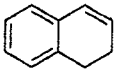
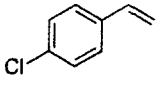
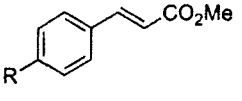


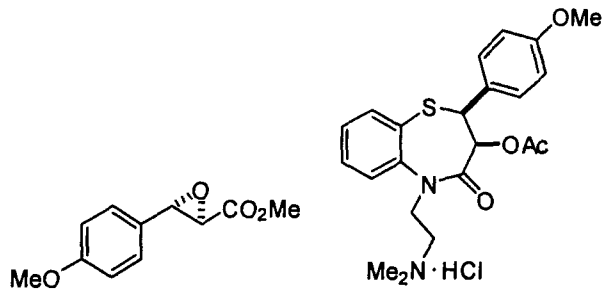
Figure 1.3

Table 1.2 Asymmetric Epoxidation with Ketones 1-1 – 1-8

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

15[b]	R = H	**1-8a**	75	74 (2*R*,3*S*)
16[b]	R = Me	**1-8a**	95	72 (2*R*,3*S*)
17[b]	R = OMe	**1-8a**	92	80
18[c]		**1-8b**	74	85
19[b]	R = *t*-Bu	**1-8a**	81	92 (2*R*,3*S*)

[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.



1-9 **1-10**

Figure 1.4

In 1997, Song and coworkers reported the use of ether-linked C_2-symmetric ketones **1-11** and **1-12** (Figure 1.5).[23] Up to 59% ee was obtained for *trans*-olefins (Table 1.3, entries 1-4). These ketones showed both lower reactivity and enantioselectivity when compared to ketones **1-8**, possibly due to the weaker electron-withdrawing ability of the ether as compared to the ester. In the same year, Adam and coworkers also reported the synthesis of two ether-linked C_2-symmetric ketones **1-13** and **1-14**, which are derived from mannitol and (+)-tartaric acid, respectively (Figure 1.5).[24] Up to 81% ee was obtained with these ketones (Table 1.3, entries 5-9).

[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.

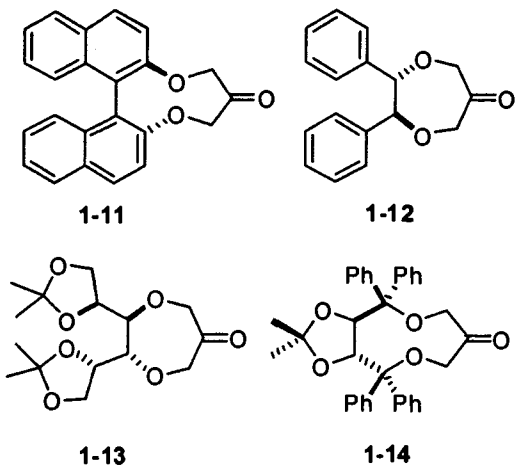
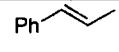
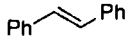
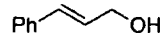
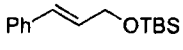
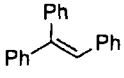


Figure 1.5

Table 1.3 Asymmetric Epoxidation with Ketones 1-11 – 1-14

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

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

In 1999 and 2002, Denmark and coworkers reported asymmetric epoxidations using 7-membered C_2-symmetric carbocyclic biaryl ketones **1-15** (Figure 1.6).[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 **1-8**. While non-fluorinated ketone **1-15a** displayed low reactivity, the epoxidation efficiency was greatly enhanced by fluorine substitution at the α-carbon. Difluoroketones **1-15c** and **1-15d** were found to be highly active, and a variety of trans-olefins can be epoxidized with good to high enantioselectivity (Table 1.4, entries 3-4, 10-12). In 2002, Behar reported structurally related fluorinated binaphthyl ketones **1-16** (Figure 1.7).[26] Ketones **1-16c** and **1-16d** were found to be most reactive and enantioselective for the epoxidation of *trans*-ß-methylstyrene (Table 1.4, entries 7-8).

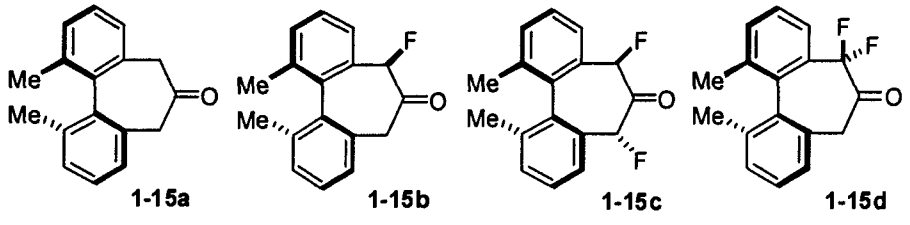


Figure 1.6

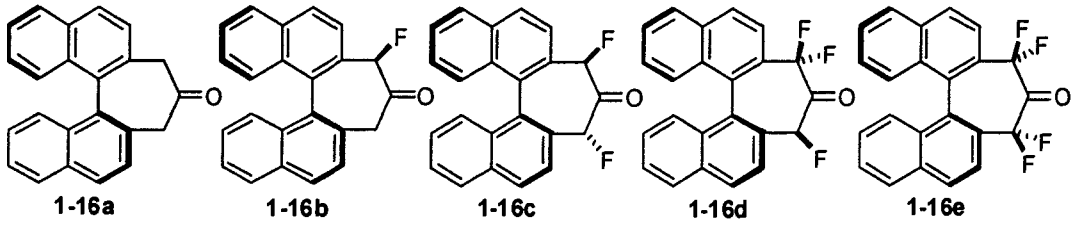
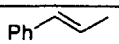
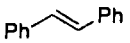
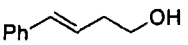
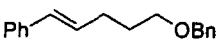
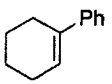
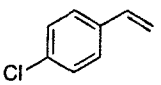
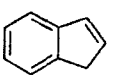


Figure 1.7

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

[26] Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943.

Table 1.4 Asymmetric Epoxidation Using Ketones 1-15 – 1-16

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

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

In 1999, Cranell and coworkers reported that *N,N*-dialkylalloxans such as **1-17a** were very robust catalysts for epoxidation and can be recovered without decomposition (Figure 1.8).[27] No enantioselectivity was obtained for the epoxidation of *trans*-stilbene with chiral ketone **1-17b**. It appears that the chiral center was not close enough to the reacting carbonyl.

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

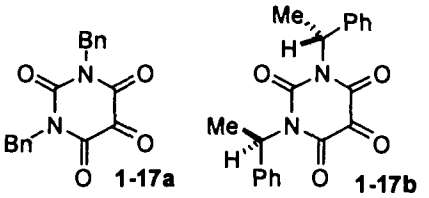
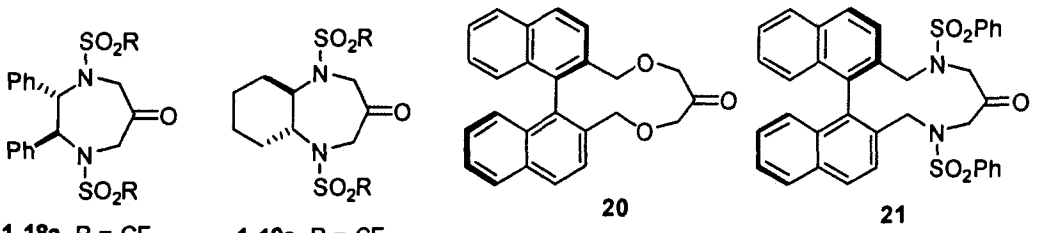


Figure 1.8

In 2001, Tomioka and coworkers reported several seven-membered cycloalkanones bearing 1,2-diphenylethane-1,2-diamine and cyclohexane-1,2-diamine backbones such as ketones **1-18** and **1-19** (Figure 1.9). Up to 30% ee was obtained for the epoxidation of *trans*-stilbene with ketone **1-18b**.[28a,b] Ketones **1-20** and **1-21** bearing the 11-membered ether and sulfonylamide (Figure 1.9) were also investigated by Tomioka and coworkers. While almost no enantioselectivity was observed, relatively high yields were obtained for *trans*-stilbene oxide.[28b] Subsequently, they reported that higher ee's were obtained with tricyclic ketone **1-22** and bicyclic ketone **1-23** (Figure 1.10).[28c] For example, stoichiometric amount of ketones **1-22** and **1-23** 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 **1-22**.



1-18a, R = CF_3
1-18b, R = Ph
1-18c, R = C_6H_5
1-18d, R = 3,5-$(CF_3)_2C_6H_3$

1-19a, R = CF_3
1-19b, R = Ph

Figure 1.9

[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.

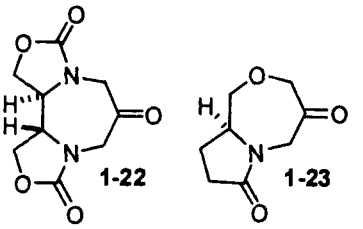


Figure 1.10

1.2.4. Ammonium Ketones

In 1995, Denmark and coworkers reported that 4-oxopiperidinium salt **1-24** (Figure 1.11) 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 1.11).[12a,13h,j,l,25,29] Sterically congested ammonium ketones **1-25** and **1-26** displayed low reactivity for the epoxidation. 1-Cyclohexene oxide and *trans*-ß-methylstyrene oxide could be obtained in 58% and 34% ee, respectively, using ammonium salt **1-26** as the epoxidation catalyst.[12a] Tropinone-based rigid ammonium ketone **1-27** with fluorine as an additional activating group was found to be highly reactive. The epoxidation of *trans*-stilbene with 10 mol% of ketone **1-27** provided the epoxide in 79% yield and 58% ee.[25,29] Bis(ammonium) ketones **1-28, 1-30 – 1-32** were also found to be active catalysts. For example, >95% conversion was obtained with 10 mol% of **1-31** and **1-32** for the epoxidation of *trans*-β-methylstyrene. Up to 40% ee was obtained for *trans*-β-methylstyrene with ketone **1-30**.

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

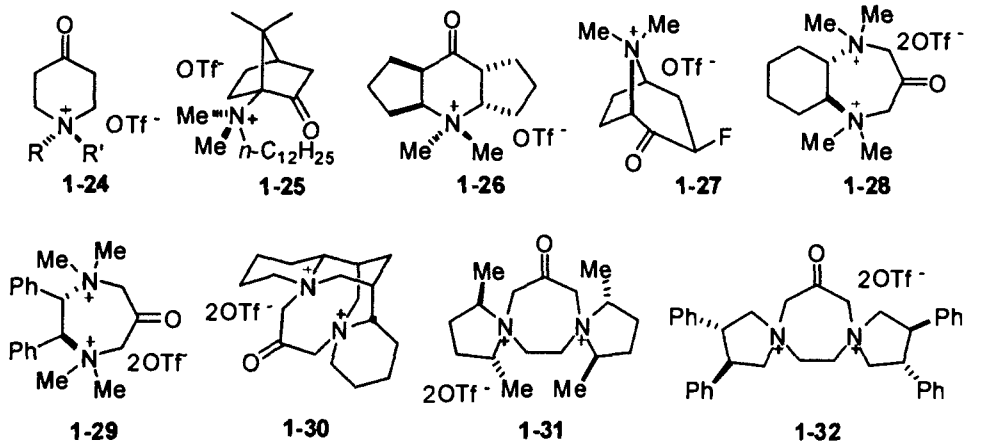

Figure 1.11

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

In 1998, Armstrong and coworkers reported tropinone-based ketone **1-33a**, which contains a bridgehead nitrogen at the α position and a fluorine atom at the α position, was a highly active catalyst for epoxidation (Figure 1.12).[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 1.5, entry 16). Similar enantioselectivities were observed with α-fluorotropinone immobilized on silica compared to the non-supported catalyst.[31] Further studies showed that replacing the fluorine of **1-33a** with an acetate and/or replacing the bridgehead nitrogen with an oxygen increased the enantioselectivity for epoxidation (Figure 1.12).[30b,32] Up to 98% ee_{max} was obtained for phenylstilbene with ketone **1-34b**.

---

[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.

Recently, Armstrong and coworkers investigated chiral tetrahydropyran-4-ones **1-35** for asymmetric epoxidation reactions to test the role of the two-carbon bridge contained in bicyclic ketones **1-33** and **1-34**.[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 1.5, entries 5-7, 18, 22). These results for ketones **1-35** suggested the α ester group seems to play an important role in reactivity and selectivity in this reaction. Armstrong and coworkers also investigated bicyclo[3.2.1]octanones **1-36** and **1-37** bearing two electronegative substituents at the α positions.[34] Studies showed that these α-disubstitutions in ketones **1-36** and **1-37** proved to be non-beneficial for enantioselectivity in asymmetric epoxidations (Table 1.5, entries 8-11). Epoxidation with 2-substituted-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones **1-38** was also reported by Klein and coworkers (Figure 1.12).[35] Ketone **1-38c** bearing a fluorine atom was found to be most reactive, and up to 68% ee was obtained for stilbene (Table 1.5, entries 12 and 19).

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[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.

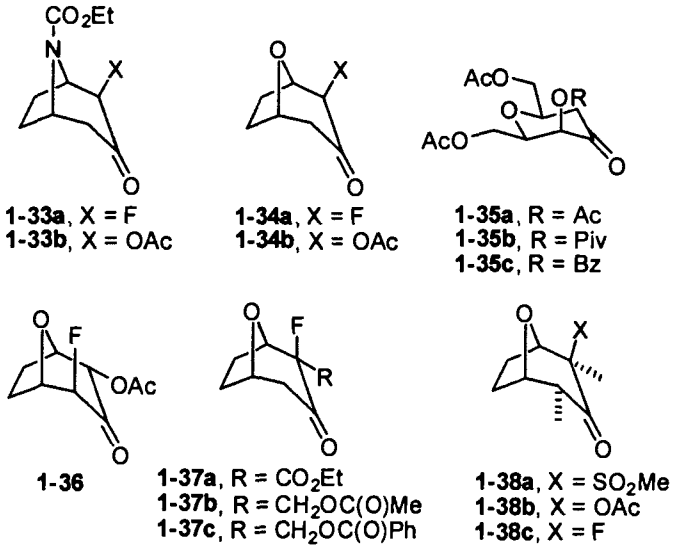
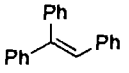
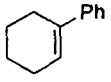


Figure 1.12

Table 1.5. Catalytic Asymmetric Epoxidation with Ketones 1-33 – 1-38

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1[a]		**1-33a**	100	76 (*R*,*R*)
2[b]		**1-33b**	100	86[d]
3[b]		**1-34a**	100	83[d]
4[b]		**1-34b**	85	93[d] (*R*,*R*)
5[a]		**1-35a**	100	81 (*S*,*S*)
6[a]		**1-35b**	52	43 (*S*,*S*)
7[a]		**1-35c**	100	83 (*S*,*S*)
8[b]		**1-36**	100	64 (*S*,*S*)
9[b]		**1-37a**	92	77[d] (*R*,*R*)
10[b]		**1-37b**	84	68[d] (*R*,*R*)
11[b]		**1-37c**	80	63[d] (*R*,*R*)
12[c]		**1-38c**	67	68
13[a]		**1-33a**	100	29 (*R*)
14[b]		**1-34b**	100	48[d] (*R*)
15[a]		1-33a	100	73 (*R*,*R*)

16[a]		**1-33a**	100	83 (*R*)
17[b]		**1-34b**	71	98[d] (*R*)
18[a]		**1-35c**	60	82 (*S*)
19[c]		**1-38c**	47	66 (*R*)
20[a]		**1-33a**	100	69 (*R*)
21[b]		**1-34b**	89	82[d] (*R*,*R*)
22[a]		**1-35c**	100	74 (*S*,*S*)

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

1.2.6. Carbohydrate-Based and Related Ketones

1.2.6.1. Catalyst Development

In 1996, a fructose-derived ketone (**1-41**) was reported to be a highly reactive and enantioselective asymmetric epoxidation catalyst for *trans*- and trisubstituted olefins.[36] This ketone can be readily obtained from a two-step synthesis (ketalization then oxidation) from D-fructose (Scheme 1.2)[37,38,39] The enantiomer of this ketone (*ent*-**1-41**) can also be easily obtained from L-fructose, which can be synthesized from L-sorbose.[40]

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

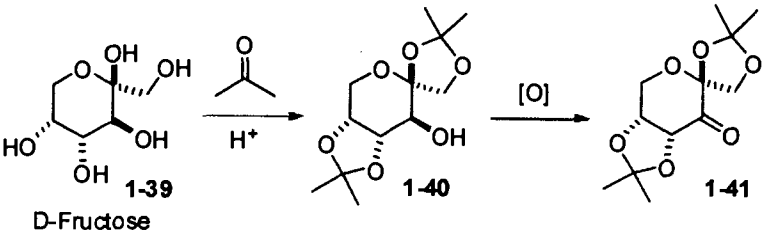
[37] Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

[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.

Scheme 1.2 Synthesis of Ketone 1-41



Ketone **1-41** belongs to a class of ketones designed on the basis of the following general considerations (Figure 1.13): (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]

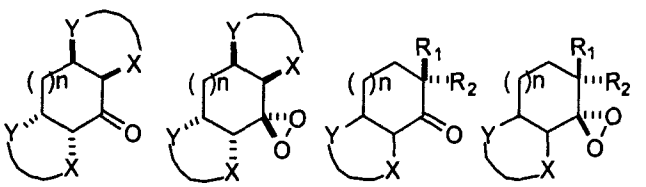


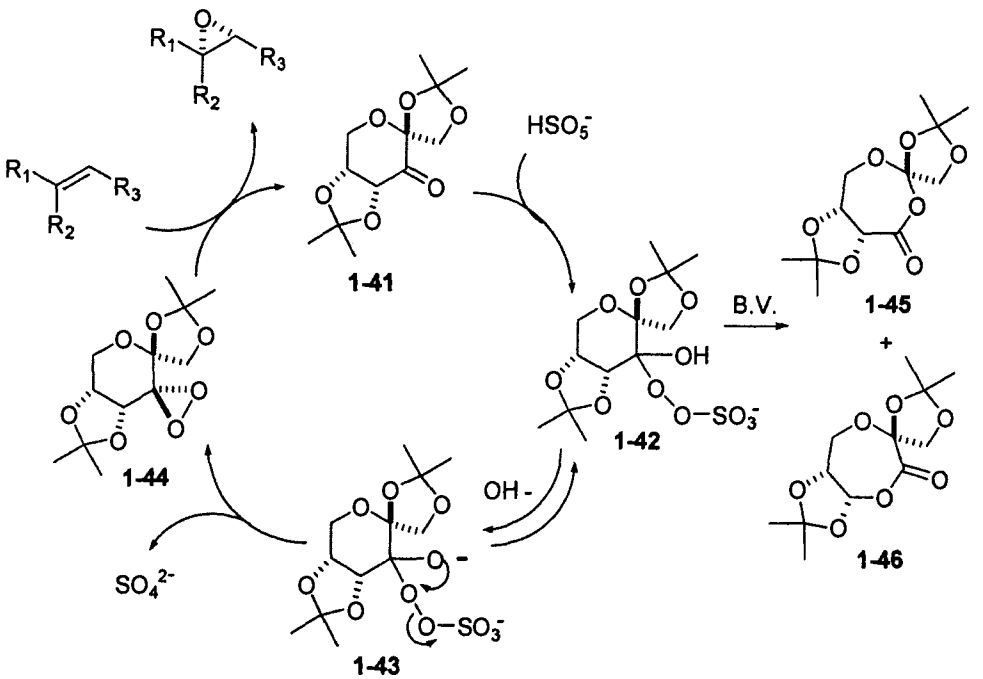
Figure 1.13

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 **1-**

[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.

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 **1-41** readily decomposes at this pH, and Baeyer-Villiger oxidation was assumed to be one of the possible decomposition pathways although the corresponding lactones **1-45** and **1-46** had not been isolated as they might be rapidly hydrolyzed under the reaction conditions (Scheme 1.3). The reaction pH was then raised with the hope that at higher reaction pH, the formation of anion **1-43** and subsequent formation of the desired dioxirane **1-44** could further be favored over the undesired Baeyer-Villiger oxidation from **1-42**. It was also hoped that ketone **1-41** could react with Oxone fast enough before its autodecomposition at high pH.

Scheme 1.3 Catalytic Cycle of Ketone 1-41-Mediated Epoxidation



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 a result, a catalytic asymmetric epoxidation process became feasible for ketone **1-41**. 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 **1-41** was explored with a variety of olefins using a catalytic amount of ketone (Table 1.6 –Table 1.11). High enantioselectivities can be obtained for a wide range of unfunctionalized *trans*- and trisubstituted olefins (Table 1.6).[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 1.6, entry 6). A variety of 2,2-disubstituted vinyl silanes can be epoxidized in

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[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.

high ee's (Table 1.7).[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 1.8).[46] The epoxidation of conjugated dienes[47] and enynes[48] can be accomplished with high ee's to obtain vinyl epoxides and propargyl epoxides (Table 1.9 and 1.10). 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 epoxidized in high enantioselectivities. Optically active α-hydroxyl or α-acyloxy ketones can be obtained by hydrolysis or stereoselective rearrangement of the resulting chiral enol ester epoxides (Scheme 1.4). 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

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[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.

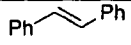
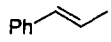
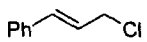
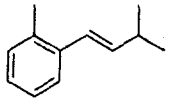
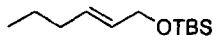
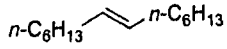
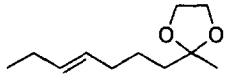
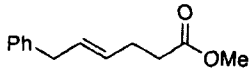
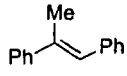
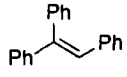
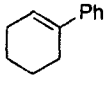
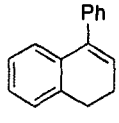
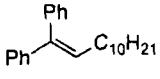
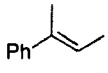
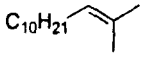
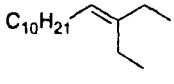
[48] (a) Cao, G-A.; Wang, Z-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (b) Wang, Z-X.; Cao, G-A; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

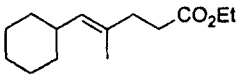
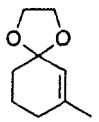
[49] (a) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (b) Zhu, Y.; Manske, K.J.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4080. (c) Feng, X.; Shu, L.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11002. (d) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

[50] Adam, W.; Fell, R.T.; Saha-Möller, C.R.; Zhao, C-G. *Tetraherdon: Asymmetry* **1998**, *9*, 397.

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 1.5).[49c]

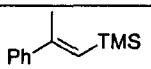
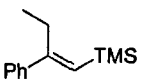
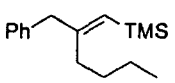
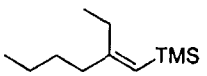
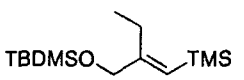
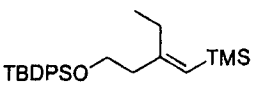
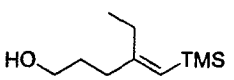
Table 1.6 Asymmetric Epoxidation of *trans*- and Trisubstituted Olefin with Ketone 1-41[a]

Entry	Substrate	Yield (%)	ee (%)
1		85	98 (*R*,*R*)
2		94	96 (*R*,*R*)
3		49	96 (2*S*,3*R*)
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 (1*S*,2*R*)
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*-**1-41**)	97 (*R*,*R*)

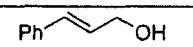
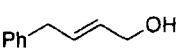
[a] Conditions: Ketone (0.3 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), MeCN-DMM-0.05 M $Na_2B_4O_7{\cdot}10H_2O$ of aq Na_2EDTA (1:2:2 v/v).

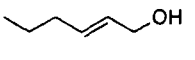
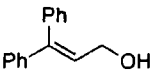
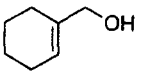
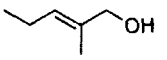
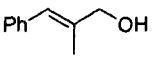
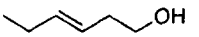
Table 1.7 Asymmetric Epoxidation of 2,2-Disubstituted Vinylsilanes with Ketone 1-41[a]

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. ketone used.

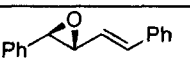
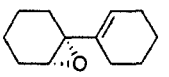
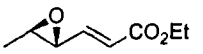
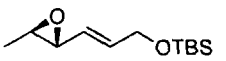
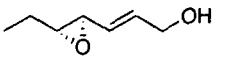
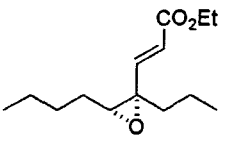
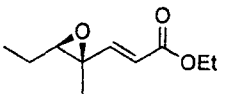
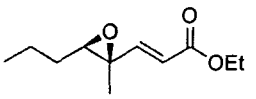
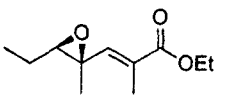
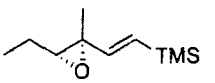
Table 1.8 Asymmetric Epoxidation of Hydroxyalkenes with Ketone 1-41[a]

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*)

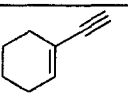
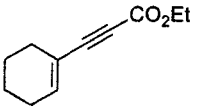
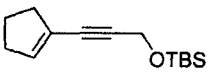
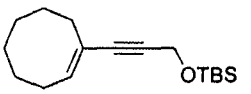
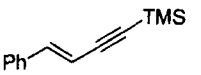
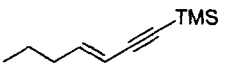
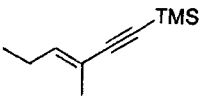
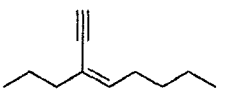
[a] Conditions: Ketone (0.3 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), MeCN-DMM-aq K_2CO_3/AcOH (2:1:2 v/v).

Table 1.9 Asymmetric Epoxidation of Conjugated Dienes with Ketone 1-41[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

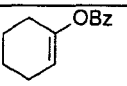
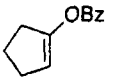
[a] Conditions: Ketone (0.2-0.3 equiv.), Oxone (1.12-1.38 equiv.), K_2CO_3 (5.0-6.2 equiv.), MeCN-DMM-0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq Na_2EDTA (1:2:2 v/v).

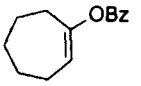
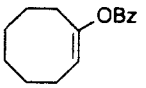
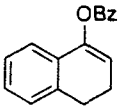
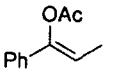
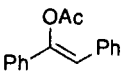
Table 1.10 Asymmetric Epoxidation of Conjugated Enynes with Ketone 1-41[a]

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).

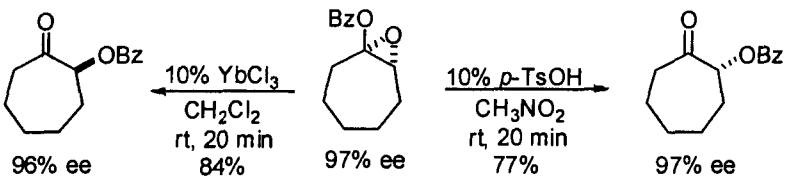
Table 1.11 Asymmetric Epoxidation of Silyl Enol Ethers and Esters with Ketone 1-41[a]

Entry	Substrate	Yield (%)	ee (%)
1		82	93 (R,R)
2		79	80 (R,R)

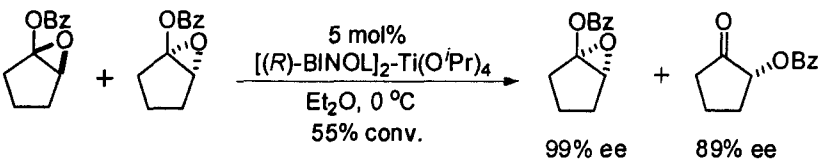
3		87	91 (R,R)
4		82	95 (R,R)
5		92	88 (R,R)
6		66	91 (2S,3R)
7		46	91 (2S,3R)

[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

Scheme 1.4 Rearrangement of Enol Ester Epoxide to α-Acyloxy Ketones



Scheme 1.5 Kinetic Resolution of Racemic Enol Ester Epoxide



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

[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.

Figure 1.14 and Table 1.12, the spiro 5-membered ketal group of **1-41** appears to be better than both the six-membered ketal and the acyclic groups (**1-41** vs. **1-48**, **1-49** and **1-50**). Methyl ketals also seem to give better epoxidation reactivity and enantioselectivity compared to ethyl ketals (**1-41** vs. **1-47**). The epoxidation results also indicated that the pyranose oxygen is beneficial to catalysis since ketone **1-41** gave better epoxidation results compared to its carbocylic counterpart (**1-51**).[52]

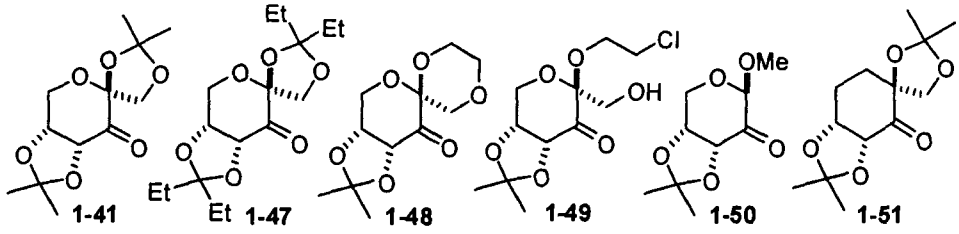
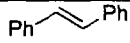
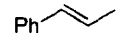


Figure 1.14

Table 1.12 Asymmetric Epoxidation with Ketones 1-41, 1-47 – 1-51[a]

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

10	**1-49**	8	65 (*R*,*R*)
11	**1-50**	15	59 (*R*,*R*)
12	**1-51**	61	87 (*R*,*R*)

[a] Conditions: Ketone (0.3 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), MeCN/0.05M $Na_2B_4O_7{\cdot}10H_2O$ of aq EDTA ($4x10^{-4}$ M) solution (1.5:1, v/v), 1.5 h.

Baeyer-Villiger oxidation is believed to be one of the major decomposition pathways for ketone **1-41** under the epoxidation conditions (Scheme 1.3); therefore, a high catalyst loading is required (typically 20-30 mol%). During the search for a more robust catalyst, ketone **1-52** (Figure 1.15) was synthesized with the hope that the replacement of the fused ketal of **1-41** by a more electron-withdrawing oxazolidinone would reduce the decomposition of this catalyst *via* Baeyer-Villiger oxidation (Scheme 1.3).[53] Indeed, only 5 mol% (1 mol% in some cases) of ketone **1-52** is needed to get comparable epoxidation results with 20-30 mol% of ketone **1-41** (Table 1.13). Besides using oxazolidinone to suppress the undesired Baeyer-Villiger oxidation of the catalysts, acetate groups were also tested for this purpose. Ketone **1-41** epoxidizes electron-deficient α-ß-unsaturated esters sluggishly since dioxiranes are electrophilic reagents. Ketone **1-53**, readily available from ketone **1-41**, was found to be an effective catalyst toward these esters (Figure 1.15).[54,55] High ee's and good yields can be obtained for a number of α,ß-unsaturated esters (Table 1.14). High reactivity and enantioselectivity should make

[53] Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715.

[54] (a) Wu, X-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (b) Wang, B.; Wu, X-Y.; Wong, O.A.; Nettles, B.; Zhao, M-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986.

[55] For a synthesis of ketone **1-53**, also see: Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.

ketone **1-53** useful for other olefins as well. The information obtained with ketones **1-52** and **1-53** should be useful for the design of more effective catalysts in the future.

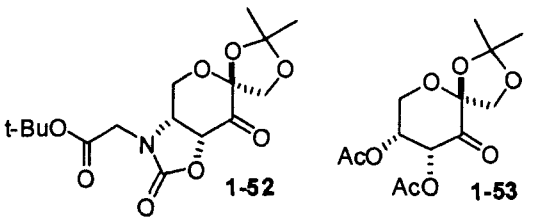
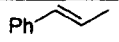
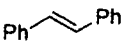
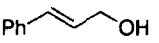
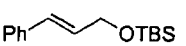
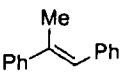
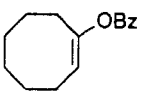
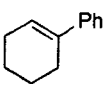
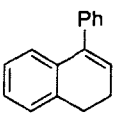


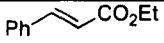
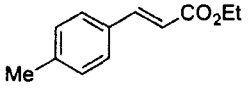
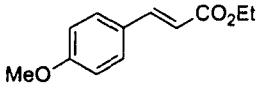
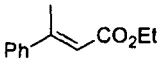
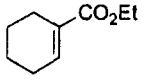
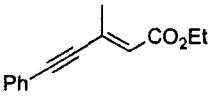
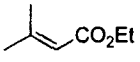
Figure 1.15

Table 1.13 Asymmetric Epoxidation with Ketone 1-52[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 1.14 Asymmetric Epoxidation with Ketone 1-53[a]

Entry	Substrate	Yield (%)	ee (%)
1[b]		73	96 (2*S*,3*R*)
2[c]		91	97
3[d]		57	90 (2*S*,3*R*)
4[c]		93	96 (2*S*,3*R*)
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. ketone used. [c] 0.25 equiv. ketone used. [d] 0.2 equiv. ketone used.

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 1.3).[56,57] Hydrogen peroxide (H_2O_2) is an attractive substitute for Oxone because it has a high active oxygen content

[56] As close analogues of $KHSO_5$, areneslfonic 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.

and its reduction product is water.[58,59] Studies with ketone **1-41** showed that a combination of RCN and H_2O_2 can be used as oxidant (Scheme 1.6).[60,61,62] Peroxyimidic acid **1-54** 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 1.15). A mixed solvent such as CH_3CN-EtOH-CH_2Cl_2 can be used for olefins with poor solubility.[60b] In addition to ketone **1-41**, the RCN-H_2O_2 system can be extended to other ketones, such as trifluoroacetone.[44,63]

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[58] For a general reference on H_2O_2, see: Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant,* Kluwer Academic Publishers, **1992.**

[59] For leading reviews on epoxidation of olefins with H_2O_2, see: (a) Grigoropoulou, G.; Clark, J.H.; Elings, J.A. *Green Chemistry* **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, Jr., J.E.; 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.

Scheme 1.6 Catalytic Cycle of Ketone 1-41 Catalyzed Epoxidation Using H_2O_2

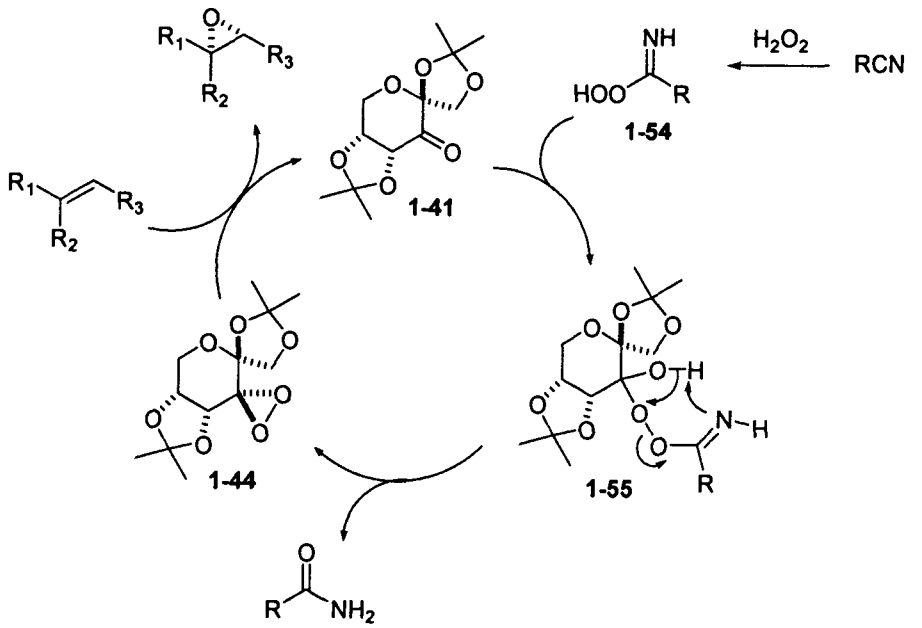
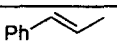
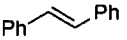
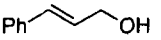
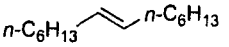
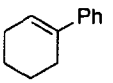
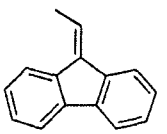
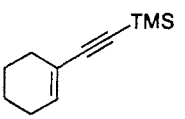
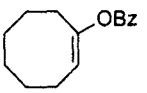
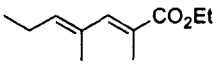


Table 1.15 Asymmetric Epoxidation with Ketone 1-41 and H_2O_2 as Oxidant

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.

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 1.16.[10c,d,18,19b,c,36,37,64,65,66] Based on the observation that the epoxidation of *cis*-hexene with dimethydioxirane was 7-9 times faster than that of *trans*-hexene, Baumstark and coworkers 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 non-bonding orbital and the olefin π^* orbital, which is not feasible geometrically in the planar transition state.[65]

[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.

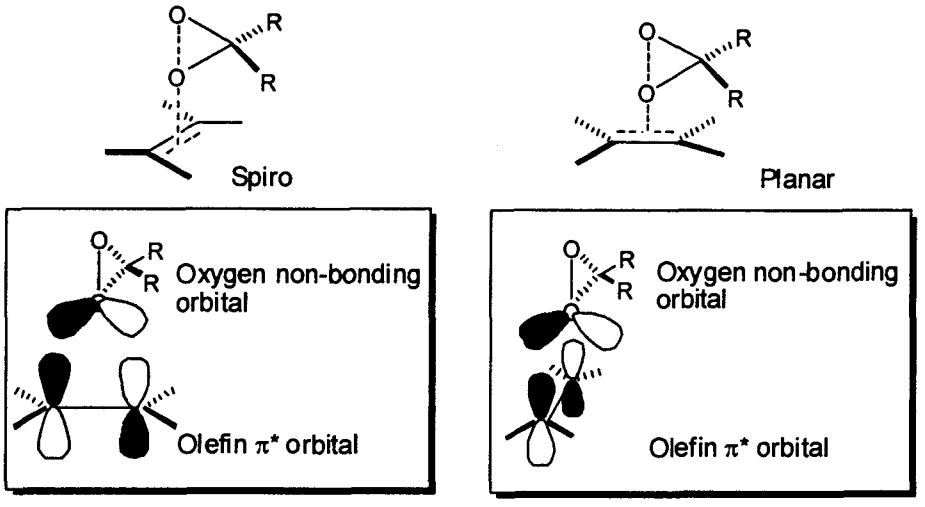


Figure 1.16

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 **1-41**, the sterically more accessible equatorial oxygen is likely to be transferred onto the olefin being epoxidized. Figure 1.17 lists a few possible transition states for the epoxidation with ketone **1-41**. 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 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 substituents. 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]

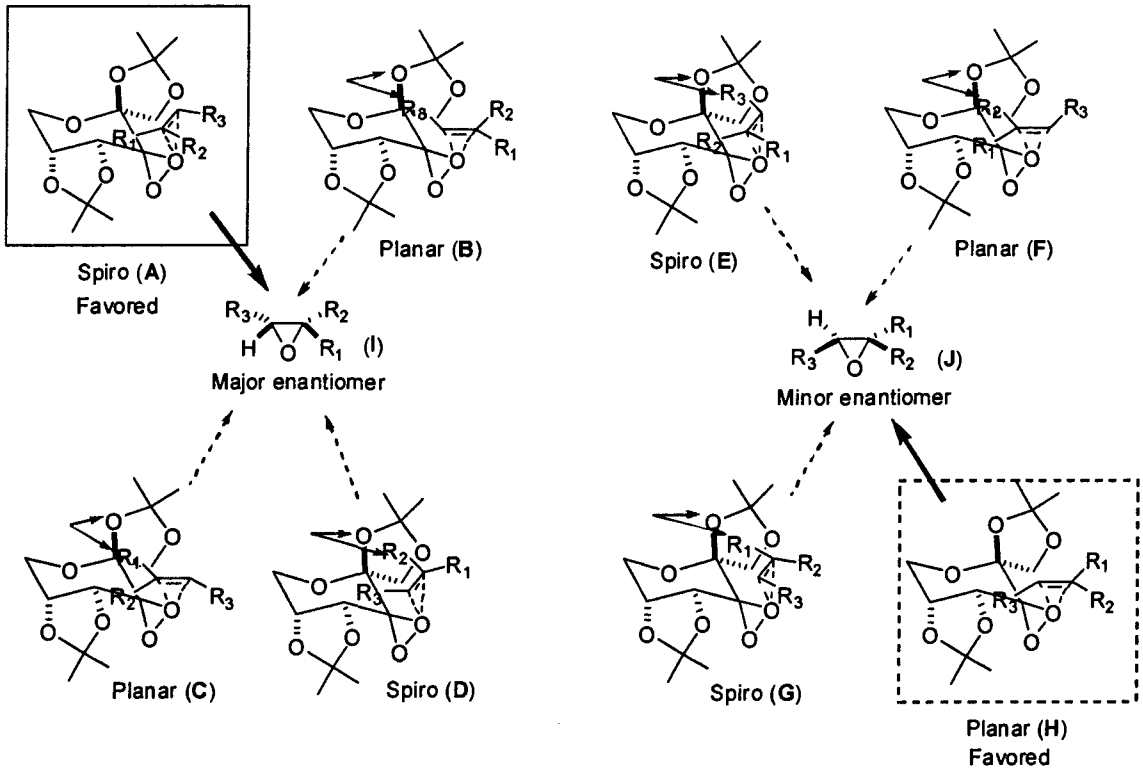


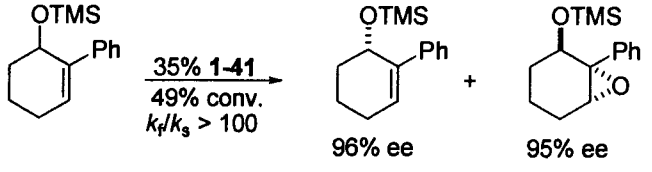
Figure 1.17

The aforementioned transition state model for the epoxidation with **1-41** 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 **1-41** (Scheme 1.7).[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 1.18). The unfavorable

[67] Frohn, M.; Zhou, X.; Zhang, J-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718.

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 **1-41** 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 1.8).[68] The observed reaction outcome can be effectively rationalized by the above transition state analysis.

Scheme 1.7 Kinetic Resolution of 1,3-Disubstituted Cyclohexene



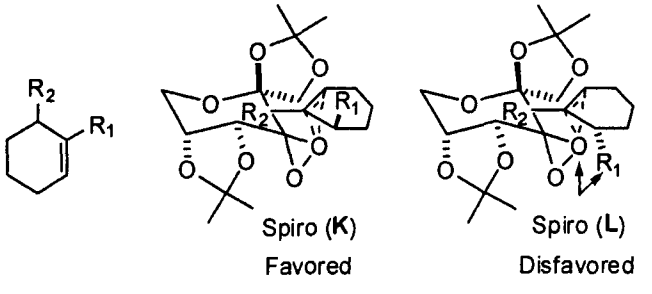
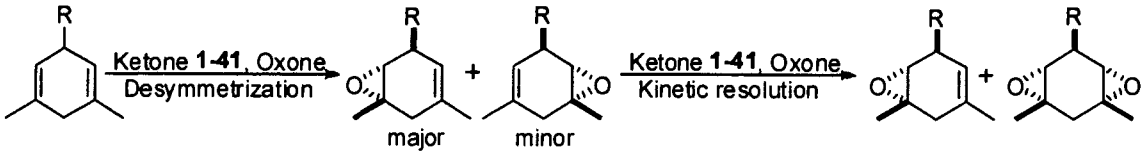


Figure 1.18

[68] Lorenz, J.C.; Frohn, M.; Zhou, X.; Zhang, J-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904.

Scheme 1.8 Desymmetrization and Kinetic Resolution of Substituted 1,4-Cyclohexadiene

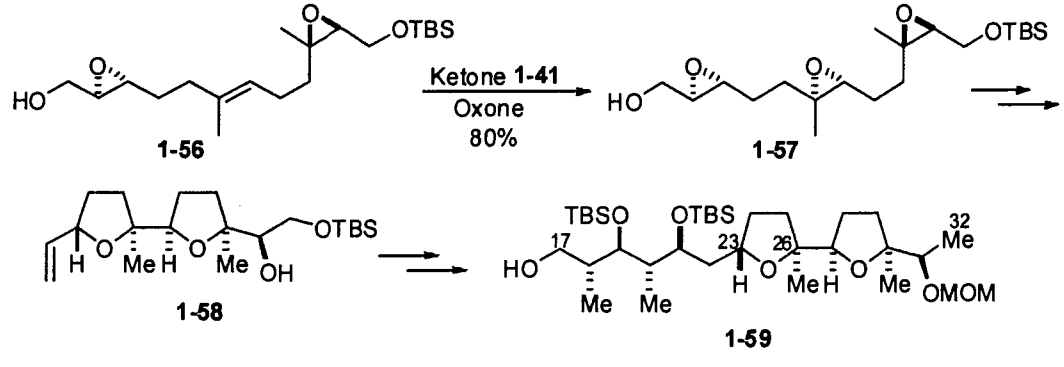


1.2.6.2. Synthetic Applications of Ketone 1-41

Fructose-derived ketone **1-41** is readily available and is effective for a wide variety of trans- and trisubstituted olefins. The epoxidation with ketone **1-41** has been used to synthesize optically active molecules by other researchers. Some of these syntheses will be highlighted in this section.

In 2006, Marshall and coworkers employed ketone **1-41** in the synthesis of the bistetrahydrofuran C17-C32 segment of antibiotic ionomycin.[69] Epoxide **1-56** was obtained by Sharpless epoxidation of allylic alcohols, and the internal trisubstituted olefin was epoxidized with ketone **1-41** and Oxone to give epoxide **1-57** in 80% yield (Scheme 1.9).

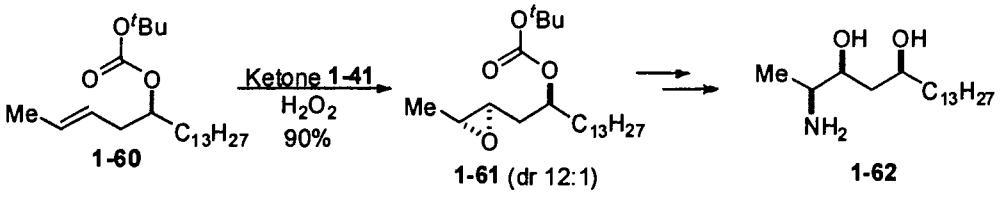
Scheme 1.9 Synthesis of Bistetrahydrofuran C17-C32 Fragment (1-59)



[69] (a) Marshall, J.A.; Mikowski, A.M. *Org. Lett.* **2006**, *8*, 4375. (b) Marshall, J.A.; Hann, R.K. *J. Org. Chem.* **2008**, *73*, 6753.

In 2005, McDonald and coworkers reported that the epoxidation of **1-60** with ketone **1-41** gave epoxide **1-61** in 90% yield with high diastereoselectivity (dr 12:1) (Scheme 1.10).[70] Epoxide **1-61** was subsequently converted into 1-deoxy-5-hydroxy-sphingolipid analogue **1-62** 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.

Scheme 1.10 Synthesis of Aminodiol 1-62

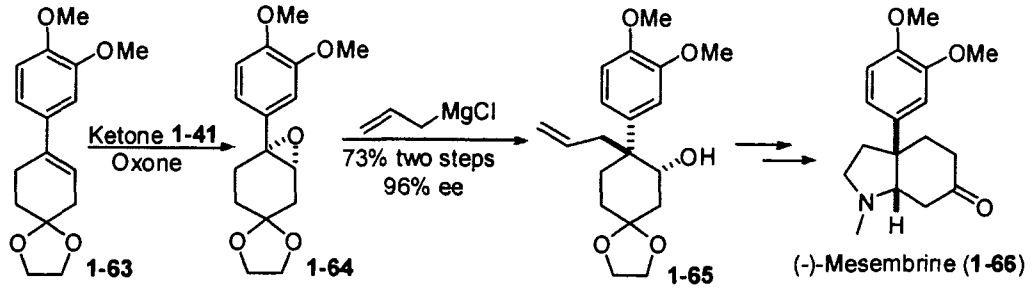


In 2005, Taber and coworkers reported that the epoxidation of **1-63** with **1-41** followed by regioselective ring opening of crude epoxide **1-64** with allylmagnesium chloride gave alcohol **1-65** in overall 73% yield and 96% ee. Alcohol **1-65** was subsequently converted into (-)-mesembrine (**1-66**) (a natural product with anxiolytic properties) in five steps (Scheme 1.11).[71]

[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.

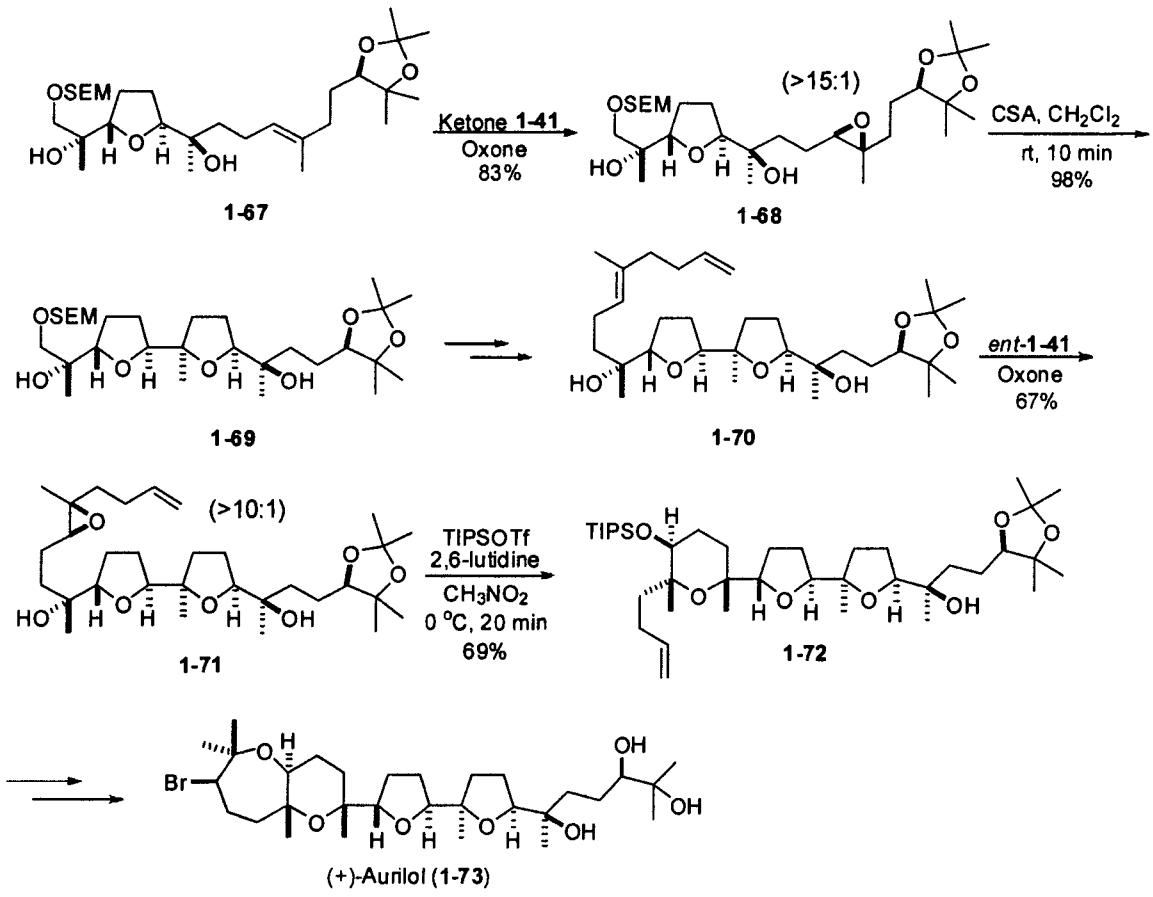
Scheme 1.11 Synthesis of (-)-Mesembrine (1-66)



In 2005, Morimoto and coworkers accomplished the first total synthesis of cytotoxic bromotriterpene polyether (+)-aurilol (**1-73**) *via* biogenetic-like regioselective ether ring formation to establish the complete stereochemistry assignment (Scheme 1.12).[72] Epoxidation of **1-67** with **1-41** gave epoxide **1-68** with high diastereoselectivity. Epoxide **1-68** underwent acid-catalyzed 5-exo-tet cyclization to produce tetrahydrofuran with the desired stereochemistry. Subsequently, diene **1-70** was selectively epoxidized only at the trisubstituted olefin with *ent*-**1-41** to give epoxide **1-71** which underwent an unusal silyl triflate-promoted 6-endo-tet cyclization to form the corresponding tetrahydropyran with the desired stereochemistry. Epoxides **1-68** and **1-71** play important roles in setting stereocenters in the final product.

[72] Morimoto, Y.; Nishikawa, Y.; Takashi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806.

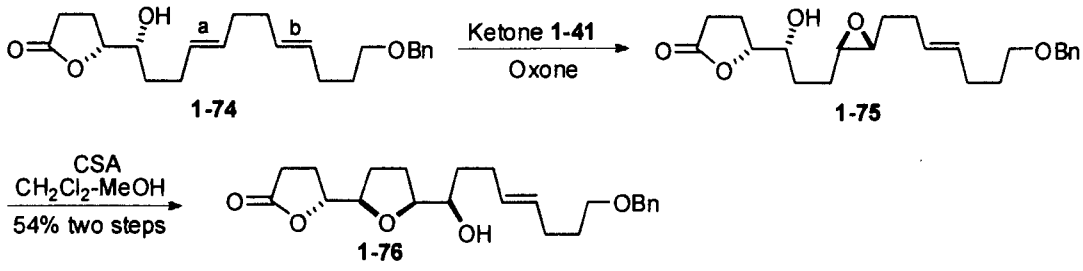
Scheme 1.12 Synthesis of (+)-Aurilol (1-73)



In 2005, Sinha and coworkers 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 **1-41** and *ent*-**1-41**.[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 **1-74**, that contains two *trans*-double bonds, can be selectively epoxidized at olefin **a** using **1-41**, giving mono-THF lactone **1-76** in 54% overall yield after cyclization with CSA (Scheme 1.13).

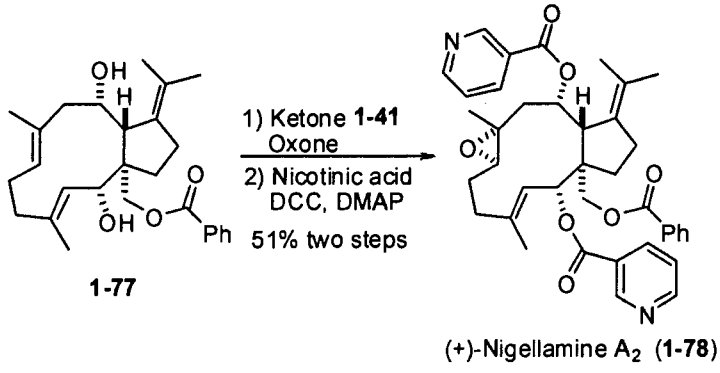
[73] Das, S.; Li, L-S.; Abraham, S.; Chen, Z.; Sinha, S.C. *J. Org. Chem.* **2005**, *70*, 5922.

Scheme 1.13 Synthesis Tetrahydrofuran Lactone 1-76



In 2006, Ready and coworkers reported that compound **1-77**, 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 (**1-78**) in 51% yield over two steps (Scheme 1.14).[74]

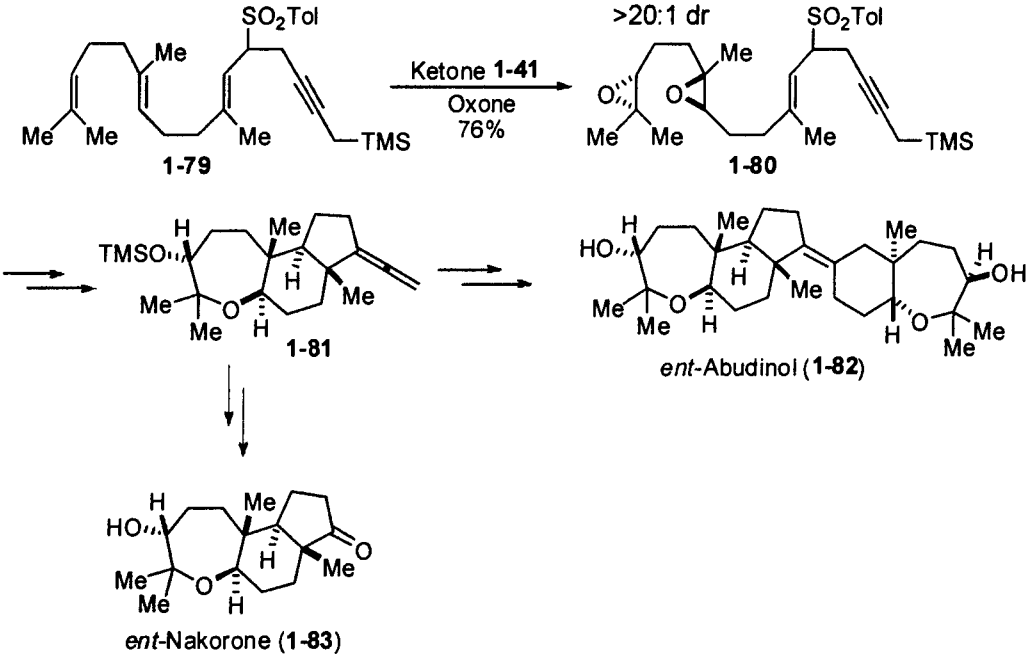
Scheme 1.14 Synthesis of (+)-Nigellamine A_2 (1-78)



[74] Bian, J.; Van Wingerden, M.; Ready, J.M. *J. Am. Chem. Soc.* **2006**, *128*, 7428.

Ketone **1-41** was also employed in McDonald and coworkers' total synthesis of nakorone, and abudinol B.[75] Triene-yne **1-79** was selectively epoxidized on the two more electron-rich double bonds, leaving the olefin next to the electron-withdrawing sulfone group unreacted (Scheme 1.15). Bis-epoxide **1-80** was transformed into both *ent*-nakorone (**1-83**) and *ent*-abdinol B (**1-82**).

Scheme 1.15 Synthesis of *ent*-Abudinol (1-82) and *ent*-Nakorone (1-83)

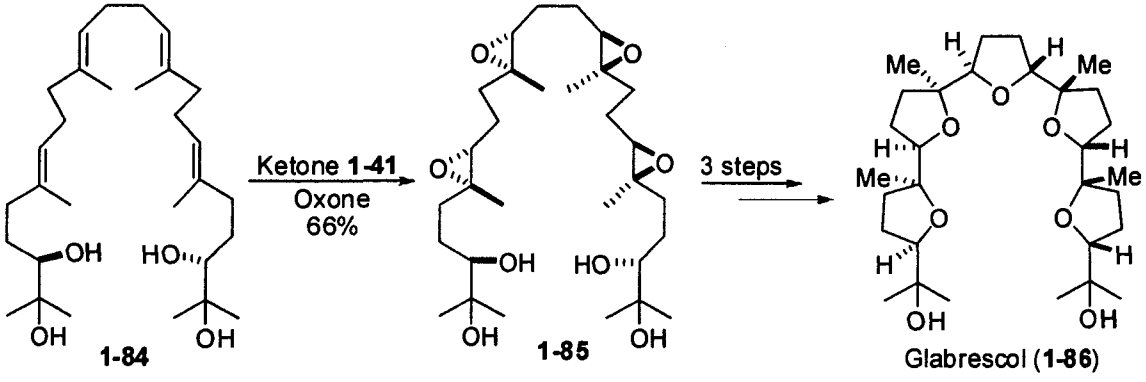


In 2000, in efforts to verify the structure of glabrescol, a chiral C_2 symmetric pentacyclic oxasqualenoid, Corey and coworkers reported the tetraepoxidation of tetraene

[75] Tong, R.; Valentine, J.C.; McDonald, F.E.; Cao, R.; Fang, X.; Hardcastle, K.I. *J. Am. Chem. Soc.* **2007**, *129*, 1050.

1-84 to form epoxide **1-85**, which was transformed into glabrescol (**1-86**) in three steps (Scheme 1.16).[76]

Scheme 1.16 Synthesis of Glabrescol (1-86)

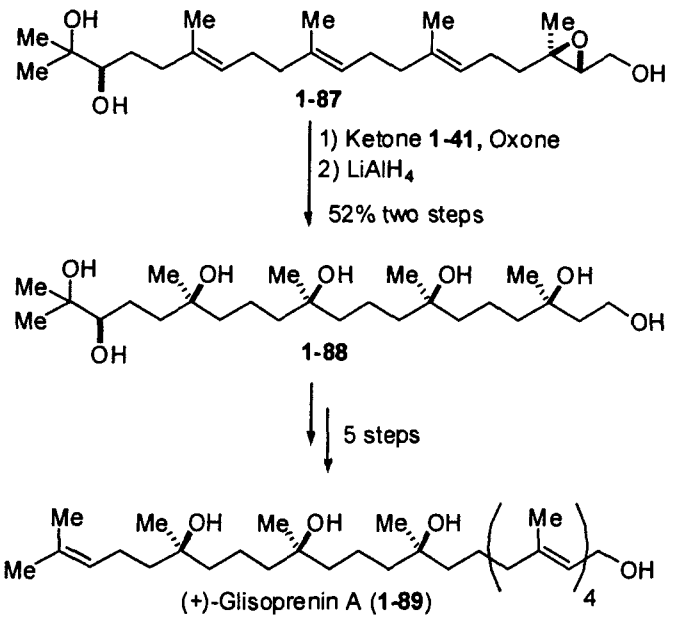


In 2004, Kishi and coworkers reported that the epoxidation of triene **1-87** with ketone **1-41** and subsequent epoxide opening with $LiAlH_4$ gave compound **1-88** in 52% yield over two steps. Compound **1-88** was transformed into (+)-glisoprenin A (**1-89**) in five steps (Scheme 1.17).[77]

[76] (a) Xiong, Z.; Corey, E.J. *J. Am. Chem. Soc.* **2000**, *122*, 4831. (b) Xiong, Z.; Corey, E.J. *J. Am. Chem. Soc.* **2000**, *122*, 9328.

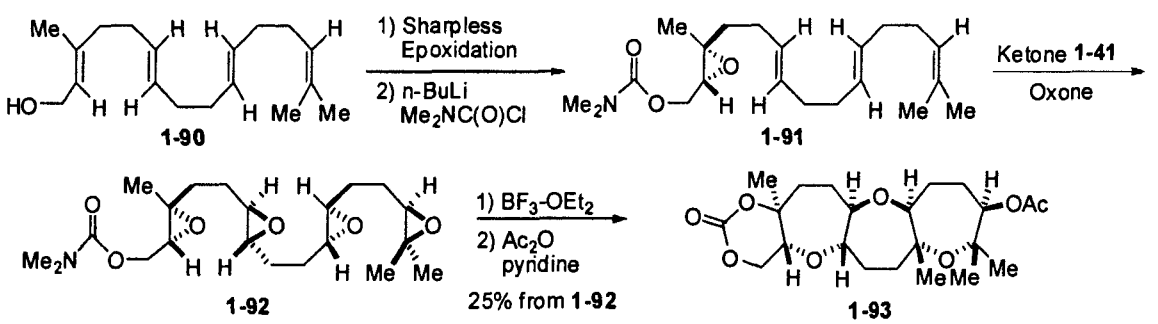
[77] Adams, C.M.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4723.

Scheme 1.17 Synthesis of (+)-Glisoprenin A (1-89)



McDonald and coworkers studied a series of biomimetic syntheses of fused polycyclic ethers.[78] For example, acyclic polyene **1-91** was epoxidized with ketone **1-41** to give polyepoxide **1-92** (Scheme 1.18). Fused polycyclic ether **1-93** can be obtained in good yield from **1-92** *via* the $BF_3{\cdot}Et_2O$ promoted *endo*-regioselective tandem oxacyclization.[78d]

Scheme 1.18 Polyepoxide Cyclization

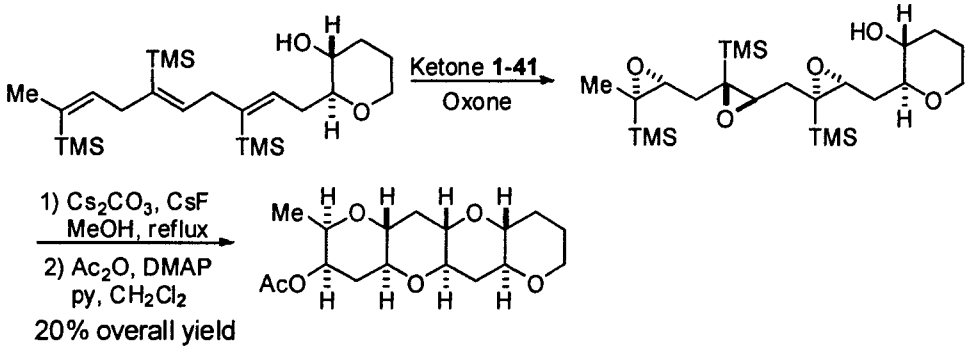


[78] (a) McDonald, F.E.; Wang, X.; Do, B.; Hardcastle, K.I. *Org. Lett.* **2000**, *2*, 2917. (b) McDonald, F.E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J.R.; Do, B.; Neiwert, W.A.; Hardcastle, K.I. *J. Org. Chem.* **2002**, *67*, 2515. (c) Bravo, F.; McDonald, F.E.; Neiwert, W.A.; Do, 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.

Recently, Jamison and coworkers reported a ladder fused polyether synthesis *via* cascade epoxidation and cyclization.[79] For example, vinylsilane **1-94** was epoxidized with ketone **1-41** to give triepoxide **1-95**, which was cyclized with Cs_2CO_3/CsF in MeOH to give tetracyclic tetrahydropyran **1-96** in 20% overall yield after acetylation (Scheme 1.19).[80] The $SiMe_3$ group acts as a "disappearing" directing group in the cyclization.

In more recent studies by Jamison and coworkers, 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 1.20).[81]

Scheme 1.19 Polyether Synthesis via Cascade Epoxide Opening

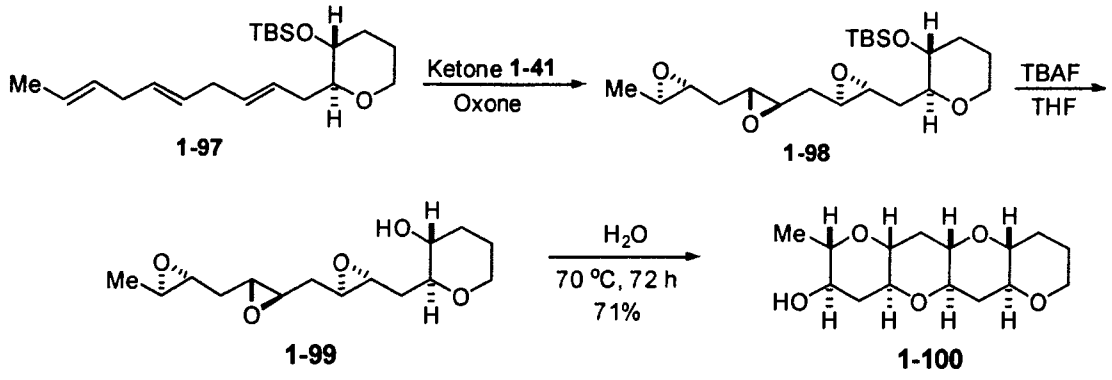


[79] Simpson, G.L.; Heffron, T.P.; Merino, E.; Jamison, T.F. *J. Am. Chem. Soc.* **2006**, *128*, 1056.

[80] For $SiMe_3$-based strategy for polyether synthesis, see: Heffron, T.P.; Jamison, T.F. *Org. Lett.* **2003**, *5*, 2339.

[81] (a) Vilotijevic, I.; Jamison, T.F. *Science* **2007**, *317*, 1189. (b) Morten, C.J.; Jamison, T.F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (c) Van Dyke, A.R.; Jamison, T.F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430.

Scheme 1.20 Water Promoted Cascade Epoxide Cyclization

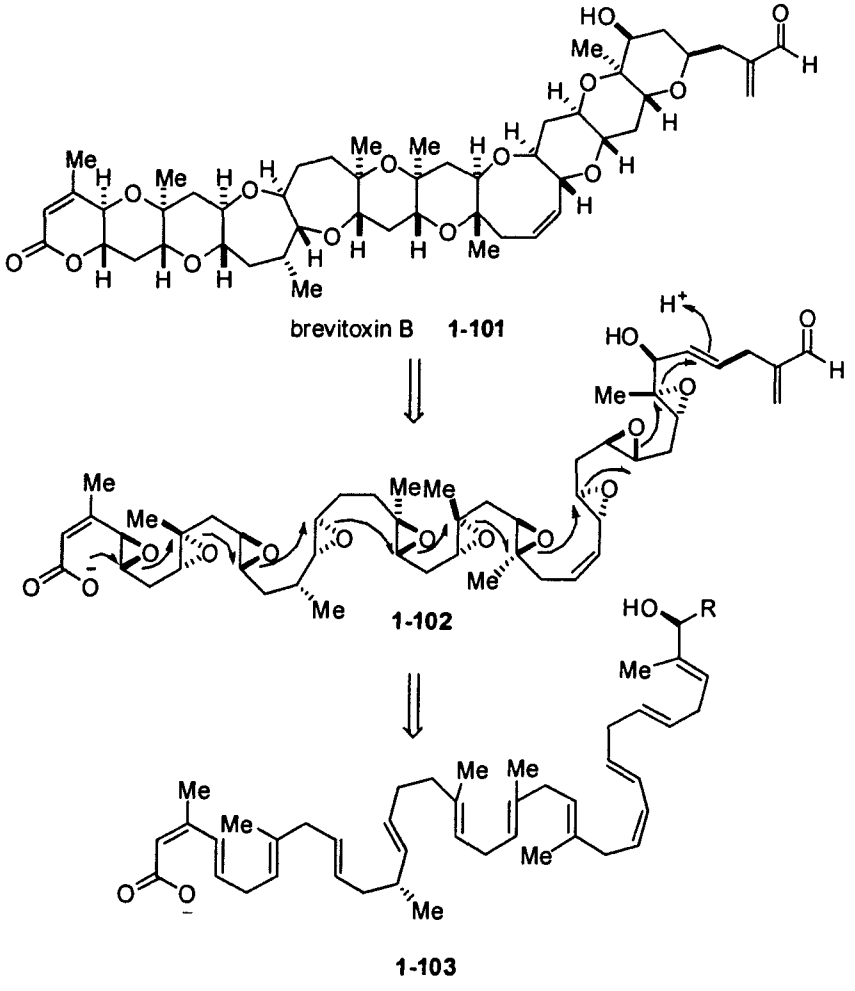


Polyethers such as brevitoxin B (**1-101**) are a class of compounds possessing important biological activities. It has been proposed that some naturally occurring polyethers are biosynthetically derived from the cyclization of polyepoxides which result from the epoxidation of polyene precursors (Scheme 1.21).[82,83]

[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, G.; 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.

Scheme 1.21 Biosynthetic Pathway of Brevitoxin B



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 **1-41** 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]

[84] For other synthetic applications of ketone **1-41**, 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.;

1.2.6.3. 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 **1-104** was reported to be a highly enantioselective catalyst for the epoxidation of cis-olefins (Figure 1.19) (Table 1.16).[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 **1-104** (Table 1.17). From the absolute configuration of several

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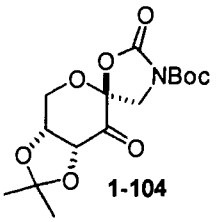
Kodama, M. *Angew, Chem. Int. Ed.* **2000**, *39*, 2552. (c) Bluet, G.; Campagne, J-M. *Synlett* **2000**, 221. (d) Morimoto, Y.; Iwai, T.; Kinoshita, T. *Tetrahedron Lett.* **2001**, *42*, 6307. (e) Shen, K-H.; Lush, S-F.; Chen, T-L.; Liu, R-S. *J. Org. Chem.* **2001**, *66*, 8106. (f) Guz, N.R.; Lorenz, 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) Madhushaw, 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) Cachoux, F.; Isarno, T.; Wartmann, M; Altmann, K-H. *ChemBioChem* **2006**, *7*, 54. (v) Ager, D.J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J. *Org. Proc. Res. Devel.* **2007**, *11*, 44. (w) Kananda, R.M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350. (x) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 1132. (y) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6481. (z) Wan, S.; Gunaydin, H.; Houk, K.N.; Floreancig, P.E. *J. Am. Chem. Soc.* **2007**, *129*, 7915. (aa) Tong, R.; McDonald, F.E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4377. (bb) Neighbors, J.D.; Mente, N.R.; Boss, K.D.; Zehnder, D.W. II, Wiemer, D.F. *Tetrahedron Lett.* **2008**, *49*, 516. (cc) Mente, N.R.; Neighbors, J.D.; Wiemer, D.F. *J. Org. Chem.* **2008**, *73*, 7963. (dd) Chapelat, J.; Buss, A.; Chougnet, A.; Woggon, W-D. *Org. Lett.* **2008**, *10*, 5123. (ee) Emmanuvel, L.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 5736. (ff) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M. Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230. (gg) Yu, M. Snider, B.B. *Org. Lett.* **2009**, *11*, 1031. (hh) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 2538.

[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 **1-104**, see: Shu, L.; Shen, Y-M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963.

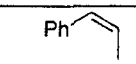
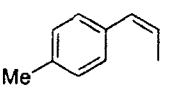
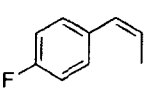
epoxides, it was revealed that the substitution with a π system, regardless of the size, prefers to be next to the spiro oxazolidinone of ketone **1-104** (spiro **M**, Figure 1.20). It seems that there exists some type of attraction between the R_π group of the olefin and the oxazolidinone of the ketone catalyst in the transition state. A prominent example is illustrated in Figure 1.21. When the epoxidation of 1-phenylcyclohexene was carried out with ketone **1-41**, 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 **1-104**, 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]

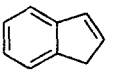
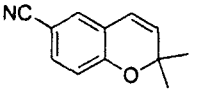
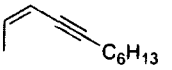
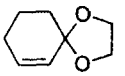


1-104

Figure 1.19

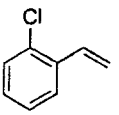
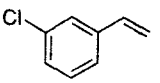
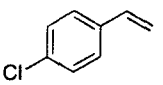
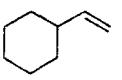
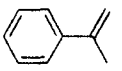
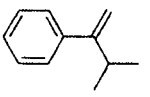
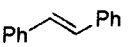
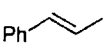
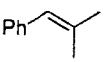
Table 1.16 Asymmetric Epoxidation of *cis*-Olefins with Ketone 1-104[a]

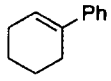
Entry	Substrate	Yield (%)	ee (%)
1		87	91 (1R,2S)
2		76	92 (1R,2S)
3		74	92 (1R,2S)

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.

Table 1.17 Asymmetric Epoxidation of Terminal, trans-, and Trisubstituted Olefins with Ketone 1-104[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.

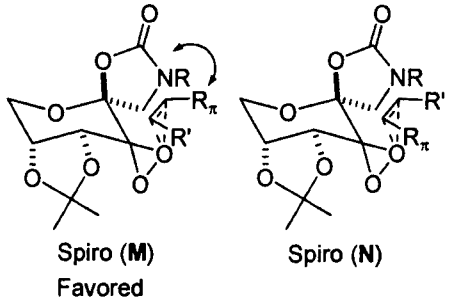


Figure 1.20

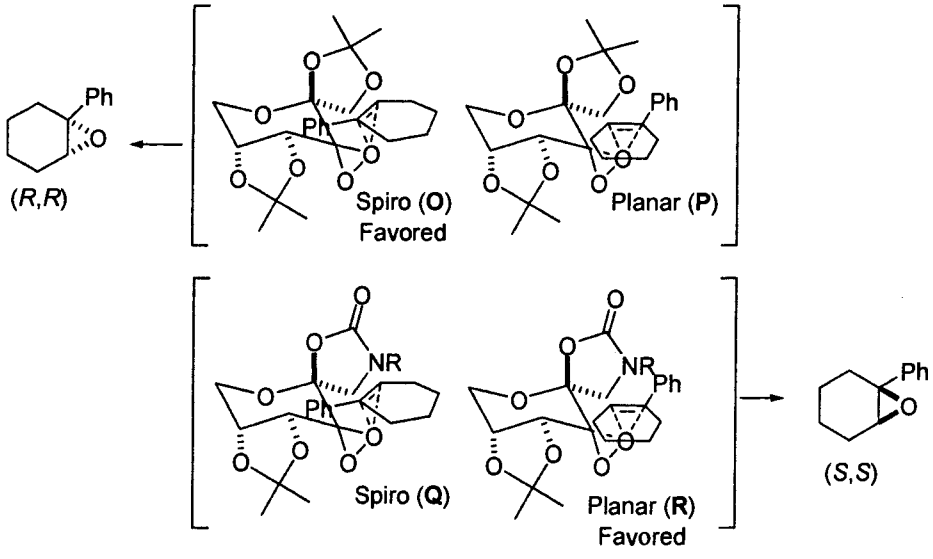


Figure 1.21

During studies of electronic and conformational effects of ketone catalysts on epoxidation ketone **1-105**, a carbocylic analogue of ketone **1-104** (Figure 1.22), was found to give higher ee's (89-93% ee) for styrenes (Table 1.18) and the opposite

enantiomer (*R,R*) for the epoxidation of 1-phenylcyclohexene (Figure 1.23) as compared to **1-104**.[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 **1-104** and **1-105** 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 effect. It is likely that the replacement of the pyranose oxygen in ketone **1-104** with a carbon in ketone **1-105** increases the interaction of the non-bonding orbital of the dioxirane with the π^* orbital of the alkene by raising the energy of the non-bonding 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 1.23). For styrenes, the replacement of an oxygen with a carbon in ketone **1-105** further favors desired spiro **U** and undesired spiro **V** over undesired planar **W** (Figure 1.24), 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 non-bonding orbital of the dioxirane, thus disfavoring the main spiro transition state and decreasing the epoxide ee's. The results obtained with ketones **1-104** and **1-105** indicates

[87] Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5794.

that an effective catalyst should have proper substituents that can provide a delicate balance between reactivity and enantioselectivity.

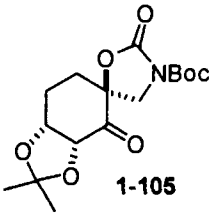


Figure 1.22

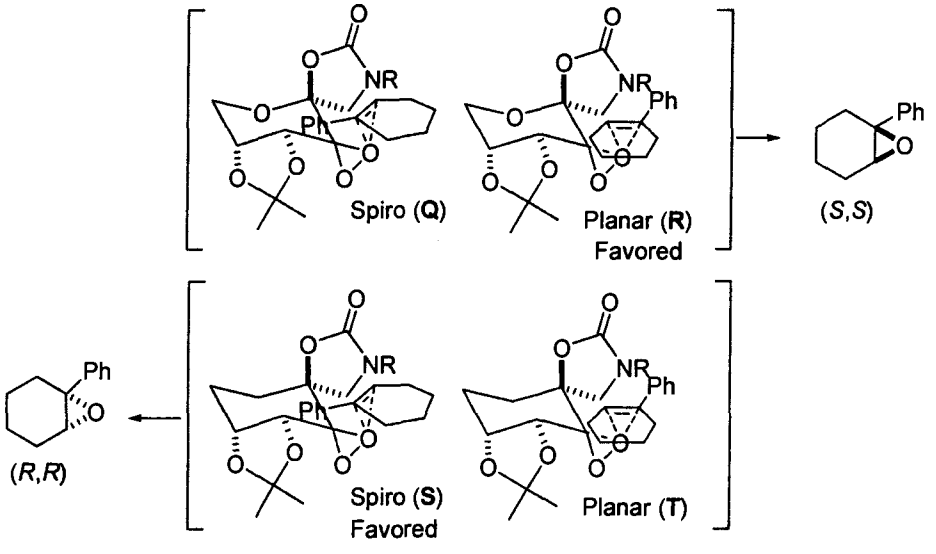


Figure 1.23

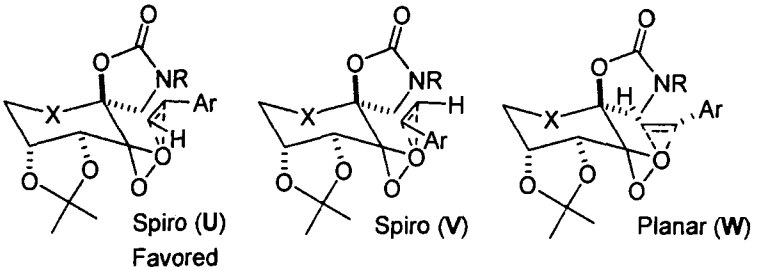
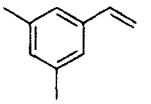
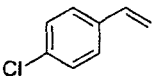
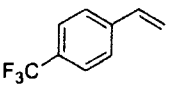
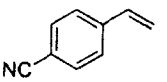


Figure 1.24

Table 1.18 Asymmetric Epoxidation of Styrenes with Ketone 1-105[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.

The spiro rings have been shown to be extremely important for the stereodifferentiation of the epoxidation for ketones **1-41** and **1-104**. To further probe the effects of different spiro ring substitution patterns on enantioselectivity of epoxidation, ketone catalysts with spiro ethers and lactones (**1-106** – **1-110**) (Figure 1.25) 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 1.19). 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 **1-104** 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

[88] Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409.

olefin substituents and the nitrogen substituents of the oxazolidinone are also significant contributing factors for stereodifferentiation.

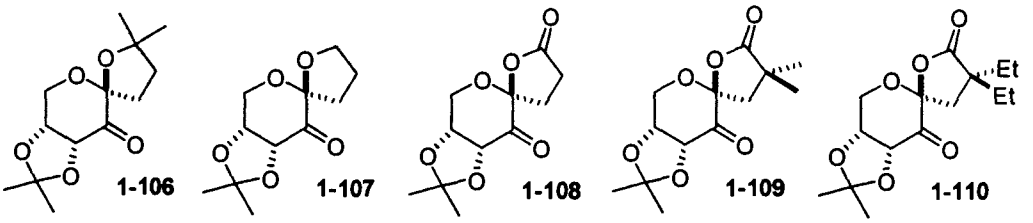
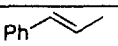
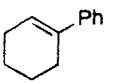


Figure 1.25

Table 1.19 Asymmetric Epoxidation with Ketones 1-106 – 1-110[a]

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

18	**1-108**	34	60 (*R*)
19	**1-109**	93	63 (*R*)
20	**1-110**	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 (0.1M K_2CO_3-AcOH, pH 9.3) at 0 °C, 1.5 h.

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 (**1-111**) were investigated. A few examples are shown in Figure 1.26.[89,90,91] Ketones such as **1-111b-e** are readily available in four steps from glucose and anilines (Scheme 1.22). Among the different aryl groups tested, phenyl groups substituted with hydrocarbons consistently gave better results than aryl groups with ethers or halogens.[90] Ketones **1-111b** and **1-111c** 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. 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 **1-111a**) generally giving the best ee's.[89]

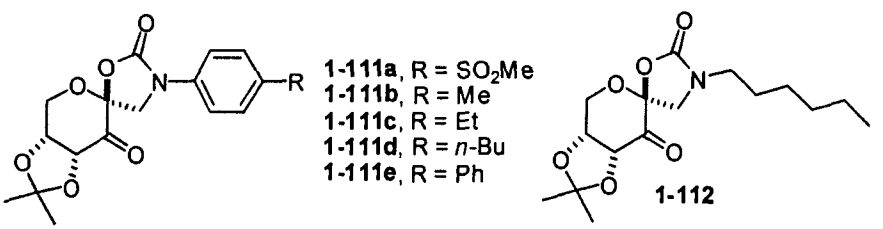


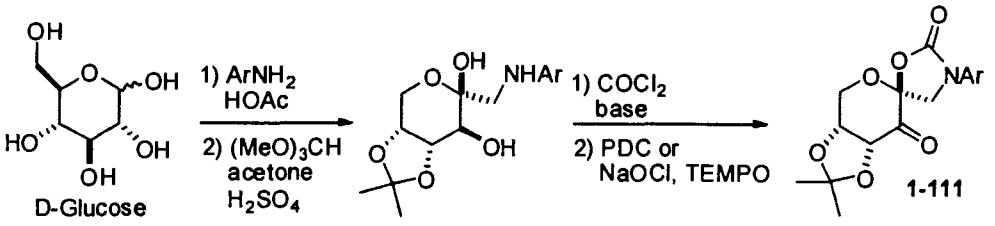
Figure 1.26

[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 **1-111**, see: Zhao, M-X.; Goeddel, D.; Li, K. and Shi, Y. *Tetrahedron* **2006**, *62*, 8064.

Scheme 1.22 Synthesis of Ketone 1-111



The epoxidation with ketones **1-111** provides high ee's for a variety of olefins. As shown in Table 1.20, *cis*-β-methylstyrenes can be epoxidized with ketone **1-111a** and **1-111b** 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 1.27).

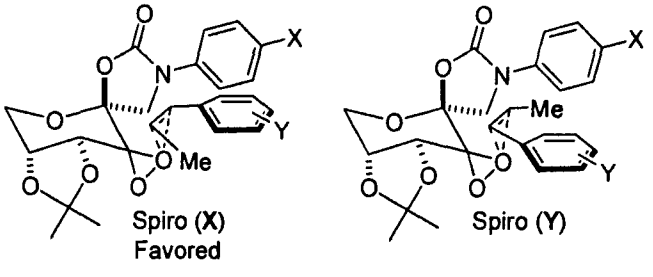


Figure 1.27

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

[92] Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115.

examined for the epoxidation using ketone **1-111c** and **1-112** (Figure 1.26, Table 1.21).[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 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 non-bonding 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 1.28). 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 1.29). 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*-substituent of the catalyst.

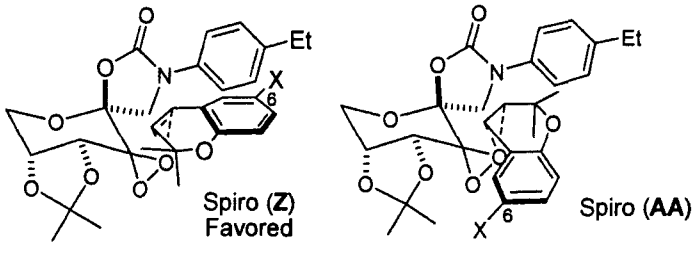


Figure 1.28

[93] Wong, O.A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973.

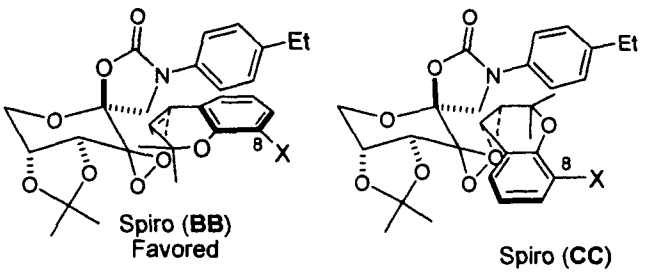


Figure 1.29

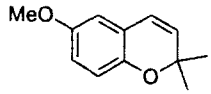
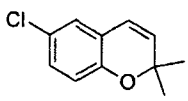
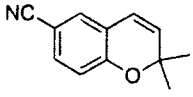
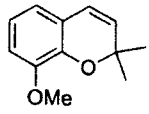
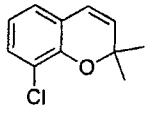
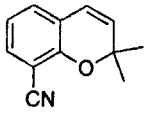
Table 1.20 Asymmetric Epoxidation of *cis*-ß-Methylstyrenes with Ketones 1-111[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1	Ph	**1-111a**	100	90
2		**1-111b**	99	84
3	Me	**1-111a**	96	92
4		**1-111b**	100	88
5	Cl	**1-111a**	90	95
6		**1-111b**	79	92
7	NC	**1-111a**	98	96
8		**1-111b**	94	96
9	O_2N	**1-111a**	91	97
10		**1-111b**	86	98
11	Me, Me	**1-111a**	100	94
12		**1-111b**	98	92

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

Table 1.21 Asymmetric Epoxidation of 2,2-Dimethyl Chromenes with Ketones 1-111c and 1-112[a]

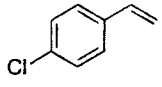
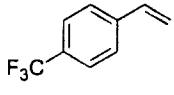
Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1	O	**1-111c**	100	84 (*R*,*R*)
2		**1-112**	100	84 (*R*,*R*)

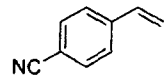
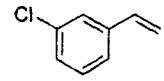
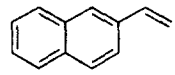
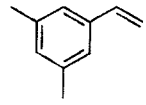
3		**1-111c**	100	90
4		**1-112**	100	88
5		**1-111c**	100	93
6		**1-112**	58	93
7		**1-111c**	83	93 (*R*,*R*)
8		**1-112**	71	89 (*R*,*R*)
9		**1-111c**	100	82
10		**1-112**	100	82
11		**1-111c**	85	83
12		**1-112**	76	86
13		**1-111c**	95	88
14		**1-112**	87	89

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

Epoxidation of styrenes with a wide variety of *N*-substituted oxazolidinone ketones was also investigated.[90] Among various ketone catalysts, **1-111c** was found to be one of the most effective catalysts. High ee's have been obtained for various styrenes (Table 1.22).

Table 1.22 Asymmetric Epoxidation of Styrenes with Ketone 1-111c[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

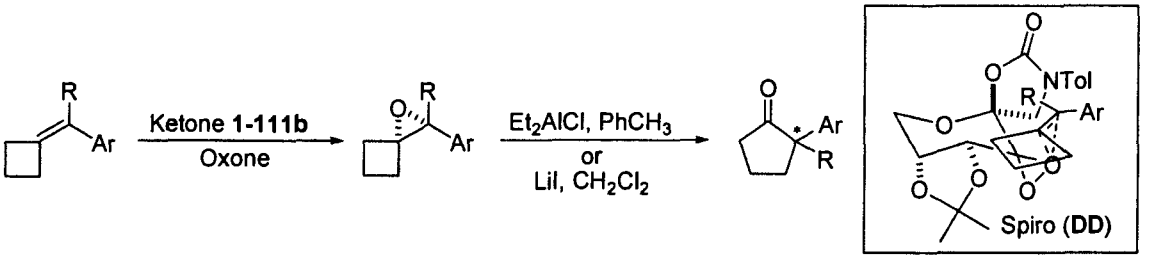
Ketone (0.15-0.3 equiv.), Oxone (2.7 equiv.), K_2CO_3 (10.6 equiv.), DME-DMM (5:1, v/v), buffer, -10 to -15 °C.

Trisubstituted benzylidenecyclobutanes (R = H) can be epoxidized with readily available ketone **1-111b** in high enantioselectivity *via* favored transition state spiro **DD** (Scheme 1.23).[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 1.24). High ee's have been obtained for 2-aryl cyclopentanones in most cases (Table 1.23). 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 1.24), 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

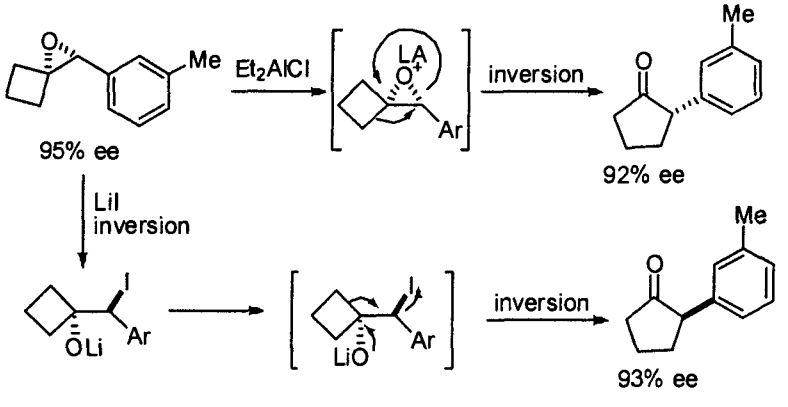
[94] (a) Shen, Y-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429. (b) Shen, Y-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.

Baeyer-Villiger oxidation (Scheme 1.25, Table 1.25).[95,96] Chiral cyclobutanones can also be obtained by supressing the Baeyer-Villiger oxidation with more ketone catalyst and less Oxone.

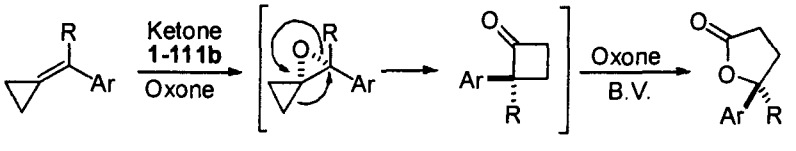
Scheme 1.23 Synthesis of Chiral 2-Aryl Cyclopentanones



Scheme 1.24 Rearrangement of Epoxide



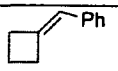
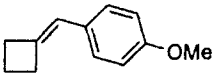
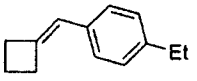
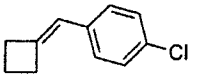
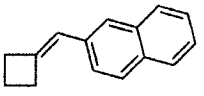
Scheme 1.25 Synthesis of Chiral γ-Aryl-γ-butyrolactones



[95] Wang, B.; Shen, Y-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519.

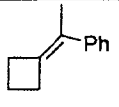
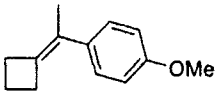
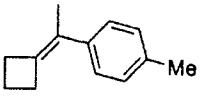
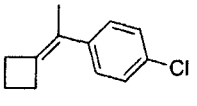
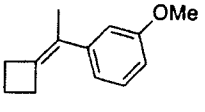
[96] For a synthesis of chiral 4-aryl-γ-butyrolactones using ketone **1-41**, see: (a) Yoshida, M.; Ismail, M.A-H.; Nemoto, H.; Ihara, M. *Heterocycles* **1999**, *50*, 673. (b) Yoshida, M.; Ismail, M.A-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629.

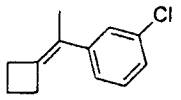
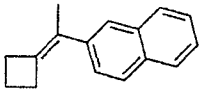
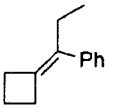
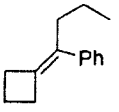
Table 1.23 Enantioselective Synthesis of 2-Aryl Cyclopentanones

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 **1-111b** (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.

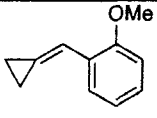
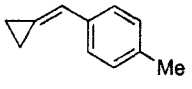
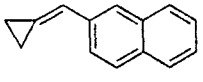
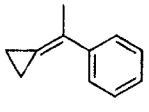
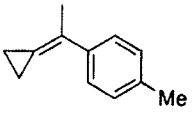
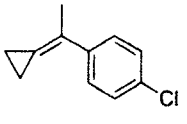
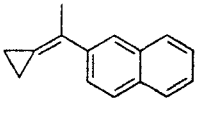
Table 1.24 Enantioselective Synthesis of 2-Alkyl-2-Aryl Cyclopentanones

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 **1-111b** (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 1.25 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 **1-111b** (0.2 equiv.), Oxone (3.2 equiv.), K_2CO_3 (13.4 equiv.), DME:DMM (3:1, v/v), buffer.

Conjugated *cis*-dienes[97] and *cis*-enynes[98] can also be epoxidized in high ee's, and no isomerization was observed during the reaction, giving cis-epoxides exclusively from cis-olefins (Table 1.26 and 1.27). Alkenes and alkynes appear to be effective directing groups to favor the desired transition states spiro **EE** and spiro **GG** (Figure 1.30 and 1.31). Non-bonding 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 **1-111** can also be carried out with H_2O_2 as primary oxidant (Table 1.28).[99]

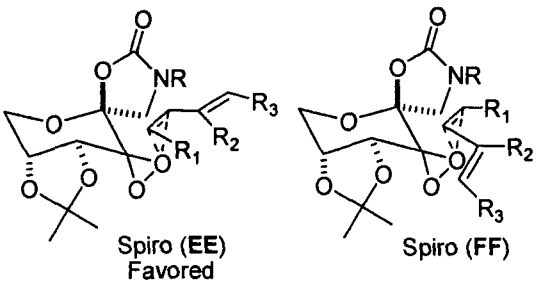


Figure 1.30

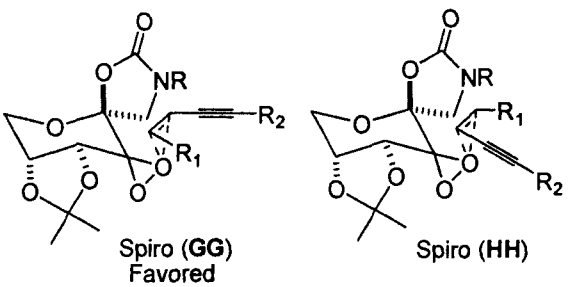


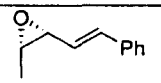
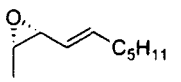
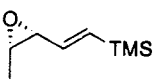
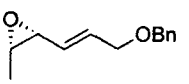
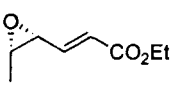
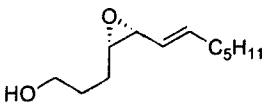
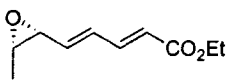
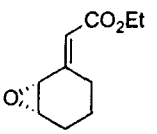
Figure 1.31

[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.

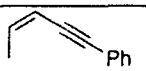
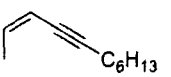
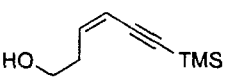
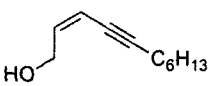
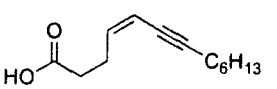
[99] Burke, C.P.; Shu, L.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 6320.

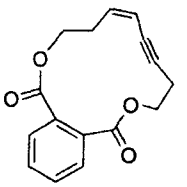
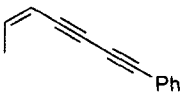
Table 1.26. Asymmetric Epoxidation of Conjugated *cis*-Dienes with Ketones 1-111[a]

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

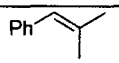
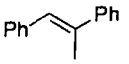
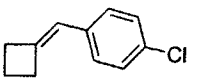
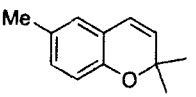
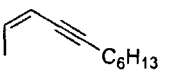
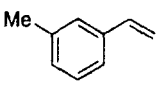
Table 1.27 Asymmetric Epoxidation of Conjugated *cis*-Enynes with Ketone 1-111c[a]

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 **1-111c** (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 **1-111b** (0.3 equiv.) with DME-dioxane as solvent.

Table 1.28 Asymmetric Epoxidation with Ketone 1-111c and H_2O_2[a]

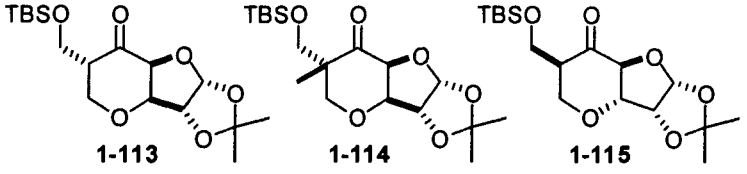
Entry	Substrate	Yield (%)	ee (%)
1		82	92
2		78	88 (R,R)
3		92	96 (R)
4		89	91
5		65	90 (2S,3R)
6		93	83

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

1.2.6.4. Other Carbohydrate-Based Catalysts

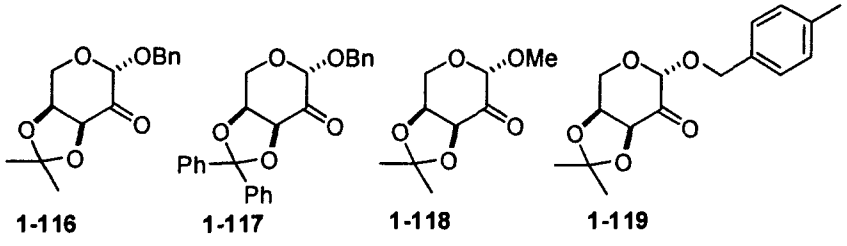
In 2002, Shing and coworkers reported three glucose-derived ketones (**1-113 – 1-115**) (Figure 1.32), and up to 71% ee was obtained for *trans*-stilbene oxide with ketone **1-**

113.[100] In 2003, Shing and coworkers also reported a series of L-arabinose-derived ketones (**1-116 – 1-122**); up to 90% ee was obtained for *trans*-stilbene with ketone **1-119** (Figure 1.33). High yield was obtained for epoxidation with the ester substituted ketones **1-120 – 1-122**, and up to 68% ee was obtained for phenylstilbene.[101]

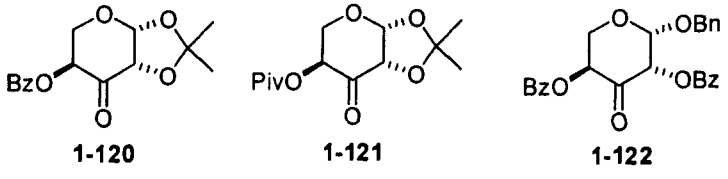


1-113 **1-114** **1-115**

Figure 1.32



1-116 **1-117** **1-118** **1-119**



1-120 **1-121** **1-122**

Figure 1.33

Later, Shing and coworkers also described ketone **1-123** and demonstrated that the enantioselectivity increased with the size of the R group (Figure 1.34). Up to 90% ee was obtained for phenylstilbene with ketone **1-123b**.[102] However, when *cis*-ethyl cinnamate

[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.

was used as the substrate, the ee's had an inverse relationship with the size of the R group. Epoxide **1-125** can be obtained in 68% ee using ketone **1-123a**, and it could be readily converted into a protected side chain of Taxol (Scheme 1.26).[103]

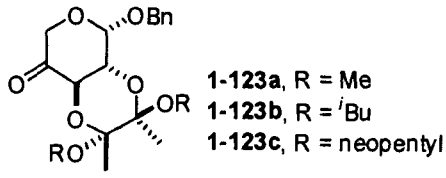
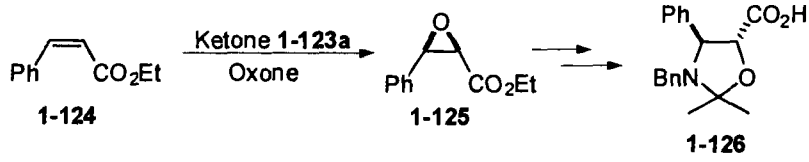


Figure 1.34

Scheme 1.26 Synthesis of Taxol Side Chain



In 2003, Zhao and coworkers reported the use of fructose-derived ketone and aldehydes **1-127 – 1-129** for asymmetric epoxidation reactions (Figure 1.35). Up to 94% ee was obtained for *trans*-stilbene with aldehyde **1-129**.[104]

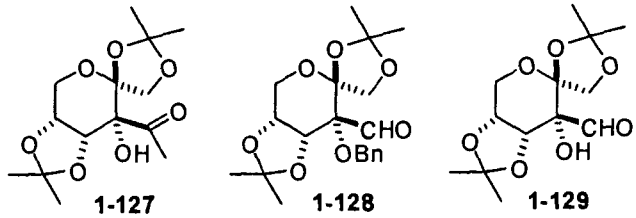


Figure 1.35

1.2.7. Carbocyclic Ketones

Ketones such as **1-41** and **1-111** use a fused ring and a quaternary carbon α to the carbonyl group as chiral control elements (Figure 1.36). In 1997, a series of pseudo C_2-

[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.

symmetric ketones bearing two fused rings at each side of the carbonyl group such as **1-130** was reported.[105] Among the ketones studied, ketones such as **1-130a** (R = CH_2OAc) and **1-130b** (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 1.29). Overall, ketone **1-130** is less enantioselective than **1-41** for the epoxidation of trans- and trisubstituted olefins.

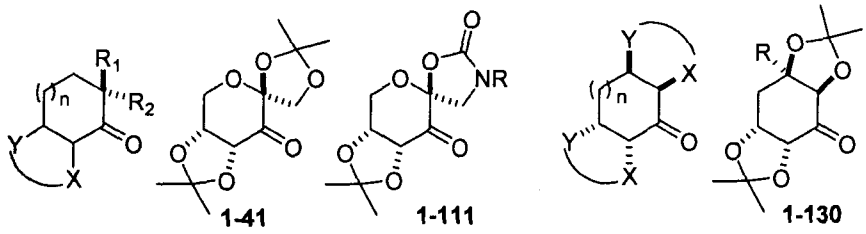
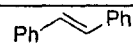
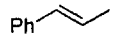
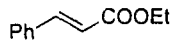
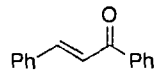
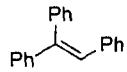
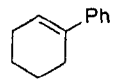


Figure 1.36

Table 1.29 Asymmetric Epoxidation with Ketones 1-130b[a]

Entry	Substrate	Yield (%)	ee (%)
1		91	96 (*R*,*R*)
2		94	80 (*R*,*R*)
3		35	89 (2*S*,3*R*)
4		85	96 (2*S*,3*R*)
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.

[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.

Ketones **1-131** and **1-132** having one of the ketals away from the α position (Figure 1.37), 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 coworkers also reported their studies on ketones **1-131** and **1-133**, and 85% ee was obtained for stilbene with **1-131**.[107]

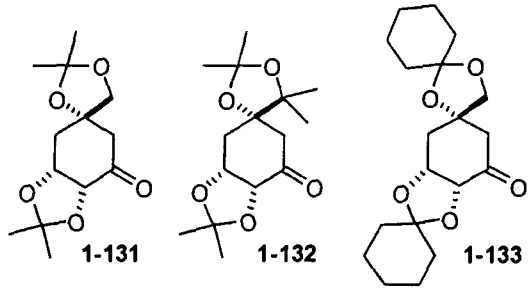


Figure 1.37

In 1999, Armstrong and coworkers reported two C_2-symmetric 5-membered ketones **1-134** and **1-135** (Figure 1.38).[108] Ketone **1-134** 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 of the carbonyl group. Studies showed that ketone **1-135** underwent rapid Baeyer-Villiger oxidation under reaction conditions to form the corresponding lactone.

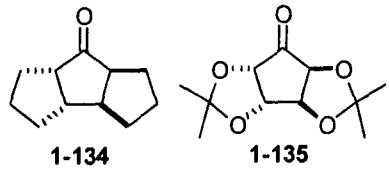


Figure 1.38

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[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.

In 1998, Yang and coworkers reported a series of ketones (**1-136**) containing a quarternary carbon at the C_2 position and various substituents at the C_8 position (Figure 1.39).[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 **1-136b** 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 1.30). Moreover, the substituents at C_8 significantly influence enantioselectivity through an electrostatic effect between the polarized C-X bond and the phenyl group on the stilbene (**1-136a**, 87.4% ee; **1-136b**, 85.4% ee; **1-136c**, 80.9% ee; **1-136d**, 73.8% ee; **1-136e**, 42.0% ee).

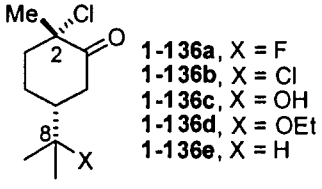
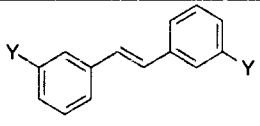
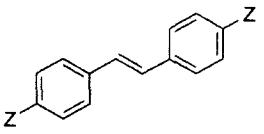


Figure 1.39

Table 1.30 Asymmetric Epoxidation of Stilbene with Ketones 1-136b[a]

Entry	Substrate	ee (%)
		
1	Y = Me	88.9
2	Y = H	85.9
3	Y = F	77.7
4	Y = Cl	74.3

[109] Yang, D.; Yip, Y-C.; Chen, J.; Cheung, K-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.

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.

In 2000, Solladié-Cavallo and coworkers reported fluorinated ketones **1-137** (Figure 1.40) which are derived from (+)-dihydrocarvone.[110] Higher conversion and ee were obtained for *p*-methoxycinnamate with **1-137a** than with **1-137b** (99% vs 43% conversion, 40% vs 6% ee), suggesting that axial fluorine (as in **1-137a**) is a more effective activating substituent than equatorial fluorine (as in **1-137b**) (Figure 1.40) (Table 1.31, entries 1-2).[111,112,113] Related cyclohexanones **1-138 – 1-141** (Figure 1.41) provide epoxides in high yields and good to high ee's (Table 1.31, entries 3-8).[114,115,116,117] These ketones are not prone to Baeyer-Villiger oxidation under the

[110] For the synthesis of ketones **1-137**, 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 much more active catalyst than the ketone with an axial F (ref. 29).

[114] For the synthesis of ketones **1-138** and **1-139**, see: Solladié-Cavallo, A.; Jierry, L.; Bouérat, L.; Taillasson, P. *Tetrahedron: Asymmetry*, **2001**, *12*, 883.

[115] For the determination of configuration of ketone **1-139**, see: Freedman, T.B.; Cao, X.; Nafie, L.A.; Solladié-Cavallo, A.; Jierry, L.; Bouérat, L. *Chirality* **2004**, *16*, 467.

reaction conditions as they were quantitatively recovered after epoxidation. Rigid *trans*-decalones **1-142** and **1-143** (Figure 1.41) whose dioxiranes do not undergo chair inversion, have been synthesized to investigate the role of axial and equatorial α-fluorine effect.[118] Decalone **1-142**, having an axial α-fluorine, gave complete conversion and 70% ee for the epoxidation of *trans*-ß-methylstyrene. On the other hand, equatorial α-fluorine-containing decalone **1-143**, only gave 88% conversion and 22% ee for the same substrate (Table 1.31, entries 11-12). This result correlates with the results obtained using ketones **1-137**.

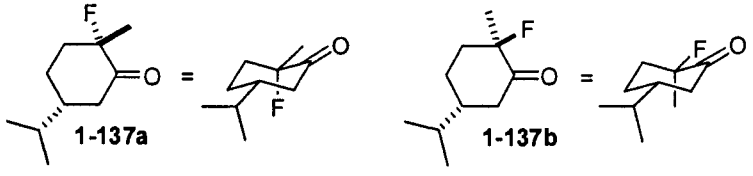


Figure 1.40

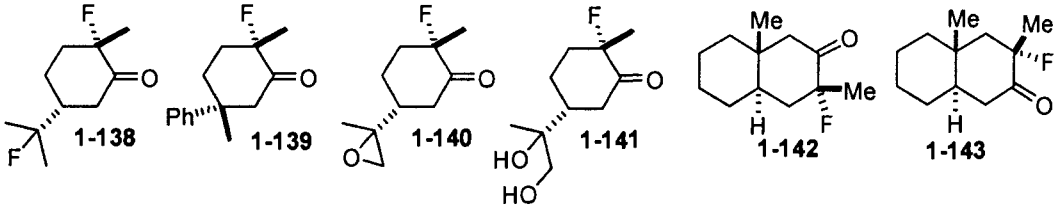


Figure 1.41

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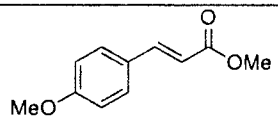
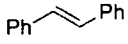
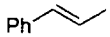
[116] Solladié-Cavallo, A.; Jierry, L.; Lupattelli, P.; Bovicelli, P.; Antonioletti, R. *Tetrahedron* **2004**, *60*, 11375.

[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 6* **2003**, 603.

[118] Solladié-Cavallo, A.; Jierry, L.; Klein. A.; Schmitt, M.; Welter, R. *Tetrahedron: Asymmetry* **2004**, *15*, 3891.

Table 1.31 Catalytic Asymmetric Epoxidation with Ketones 1-137 – 1-143[a]

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

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

In 2001, Bortolini and coworkers reported asymmetric epoxidation using a series of keto bile acids as dioxirane precursors (**1-144**, Figure 1.42).[119] *p*-Methylcinnamic acid can be epoxidized in good yield and high ee's with **1-144b-e** (Table 1.32, entries 2-5). To investigate the effect of substitution on carbons 7 and 12, a number of 3-keto-bile acid derivatives (**1-145** and **1-146**) were synthesized and studied for the epoxidation (Figure 1.43).[120] Up to 98% ee was obtained for *trans*-stilbene (Table 1.32, 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-

[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.

12-substituted bile acids generally afforded epoxides with higher enantiomeric excess compared to their 7-substituted counterparts (Table 1.32, entries 8,9 vs entries 6,7).[121]

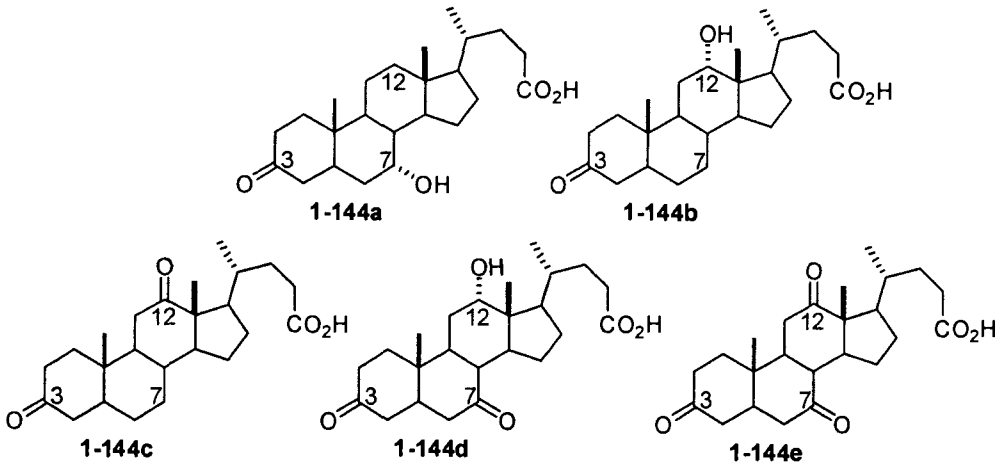


Figure 1.42

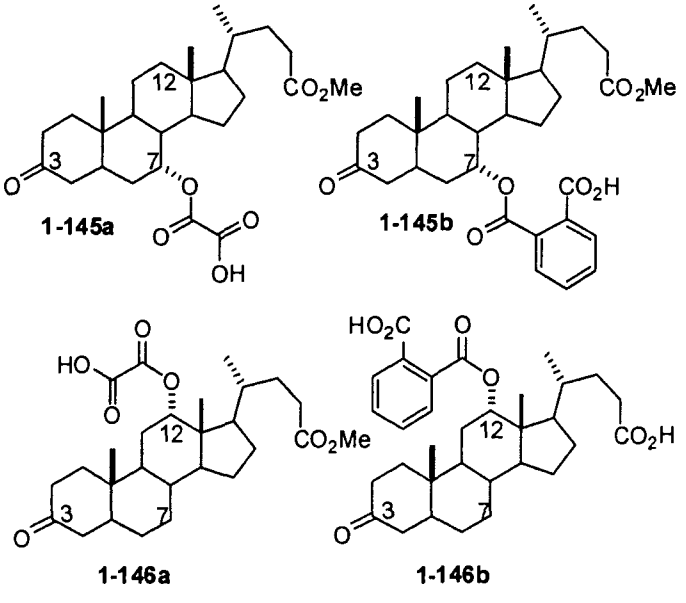
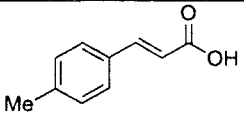
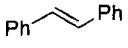


Figure 1.43

[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.

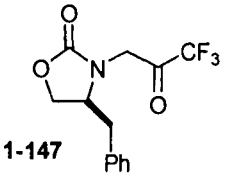
Table 1.32 Asymmetric Epoxidation with Ketones 1-144 – 1-146[a]

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

[a] Ketone (1.0 equiv.) at 0 °C.

1.2.8. Ketones with an Attached Chiral Moiety

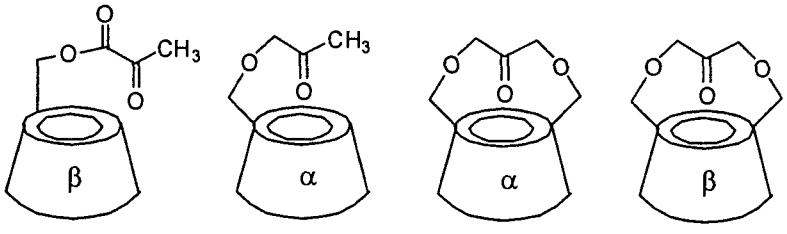
In 1999, Armstrong and coworkers reported the epoxidation of several olefins with chiral oxazolidinone trifluoromethyl ketone **1-147**, and up to 34% ee was obtained for 1-phenylcyclohexene (Figure 1.44).[108b] Ketone **1-147** underwent Baeyer-Villiger oxidation readily.



1-147

Figure 1.44

In 2003, Wong and coworkers reported a ß-cyclodextrin-modified ketoester (**1-148**) as epoxidation catalyst (Figure 1.45),[122] and up to 40% ee was obtained for 4-chlorostyrene. In 2004, Bols and coworkers reported three cyclodextrins containing an acetone moiety or bridge (**1-149** – **1-151**) as catalysts (Figure 1.45).[123] In many cases, substantial amounts of corresponding diols would also be obtained, and up to 12% ee was obtained for styrene with ketone **1-150**.



1-148 **1-149** **1-150** **1-151**

Figure 1.45

1.3. CHIRAL IMINIUM SALT-CATALYZED EPOXIDATION

1.3.1. Introduction

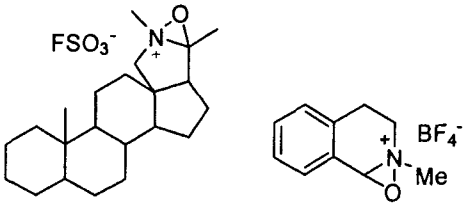
In 1976 and 1981, Lusinchi and coworkers reported the formation of steroidal oxaziridinium salt **1-152** by methylation of the corresponding oxaziridine with FSO_3Me or by oxidation of the corresponding iminium salt with peracid (Figure 1.46).[124] In 1987, Hanquet and coworkers prepared another example of an oxaziridinium salt (**1-153**) by oxidation of an *N*-methyl isoquinolinium fluoroborate salt with *p*-nitrobenzoyl peroxide

[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.

or methylation of its corresponding oxaziridine with trimethyloxonium fluoroborate.[125,126] In 1988, Hanquet, and coworkers reported that oxaziridinium salt **1-153** can efficiently epoxidize various olefins.[127,128] They further reported that the epoxidation can be carried out with *in situ* generated oxaziridinium salt **1-153** with catalytic amount of its corresponding iminium salt using Oxone-$NaHCO_3$ in CH_3CN-H_2O[128a,129] or mCPBA-$NaHCO_3$ in CH_2Cl_2.[128b] A reaction pathway for iminium salt-catalyzed epoxidation is shown in Scheme 1.27. The iminium salt catalyst is regenerated upon epoxidation of the olefin. Asymmetric epoxidation using chiral oxaziridinium salts have also been extensively investigated.



1-152 **1-153**

Figure 1.46

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[125] Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061.

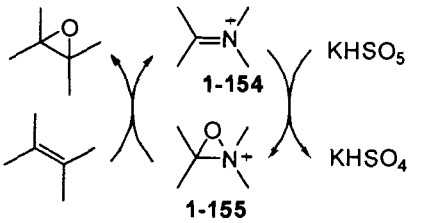
[126] Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *49*, 423.

[127] Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941.

[128] (a) Hanquet, G.; Lusinchi, X.; Milliet, P. *C.R. Acad. Sci. Paris, t. 313, Série II* **1991**, 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.

Scheme 1.27 Catalytic Cycle for Iminium Salt-Catalyzed Epoxidation

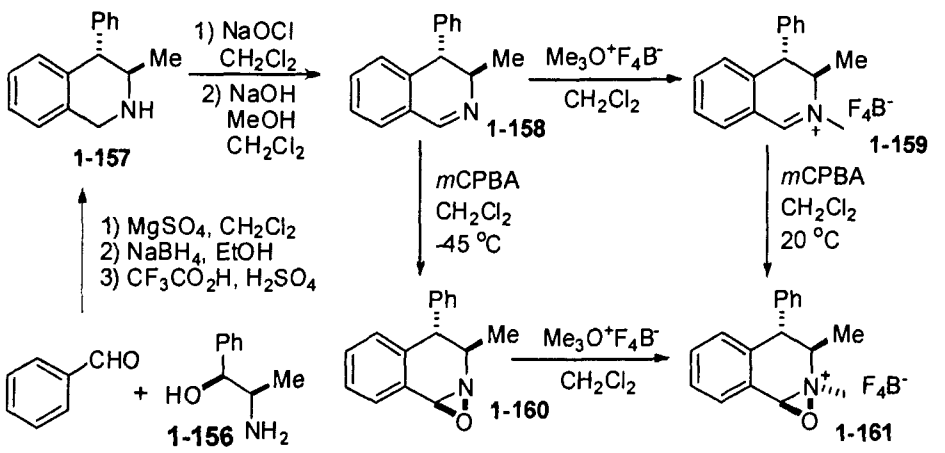


1.3.2. Chiral Cyclic Iminium Salts

1.3.2.1. Dihydroisoquinoline-Based Iminium Salts

In 1993, Bohé and coworkers reported their studies on asymmetric epoxidation of olefins with enantiomerically pure oxaziridinium salt **1-161** (Scheme 1.28).[130] Dihydroisoquinoline **1-158**, prepared from benzaldehyde and (1*S*, 2*R*)-(+)-norephedrine **1-156**, was converted into oxaziridinium salt **1-161** *via* two pathways: by methylation with Meerwein's salt to form iminium salt **1-159** and subsequent oxidation with *m*CPBA, or by oxidation with *m*CPBA to form oxaziridine **1-160** followed by methylation with Meerwein's salt. Oxaziridinium **1-161** was isolated by crystallization and characterized including X-ray diffraction.

Scheme 1.28 Synthesis of Oxaziridinium Salt 1-161



[130] (a) Ref 20 (b) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

Several olefins were effectively epoxidized with either isolated or *in situ* generated oxaziridinium **1-161** in CH_2Cl_2. For example, epoxidation of *trans*-stilbene with recrystallized **1-161** (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 **1-159** 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 non-polar solvents such as benzene and toluene, presumably due to the low solubility of oxaziridinium salt **1-161**. 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 coworkers reported a series of dihydroisoquinoline related iminium salt catalysts readily prepared from a chiral primary amine in a typical 30-65% overall yield (Scheme 1.29).[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 **1-162a**, the best result was obtained for *trans*-stilbene with 78% yield and 73% ee (Table 1.33, entry 10).

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[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.

A number of chiral iminium catalysts containing a secondary hydroxyl group were obtained by the same method (Scheme 1.29) using 1,2-amino alcohols as the chiral amine.[131c] These catalysts, such as **1-162b**, 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 **1-162c** gave higher enantioselectivity than catalyst **1-162a** for some olefins (Table 1.33, entry 12 vs 11).[131c,132] The results obtained with catalysts **1-162d** (Table 1.33, entries 4, 8, 15) and **1-162e** (Table 1.33, entries 9, 13, 16) showed that the epoxidation enantioselectivity can be influenced by the substituent on the phenyl ring.[133]

Scheme 1.29 Synthesis of Iminium Salt 1-162

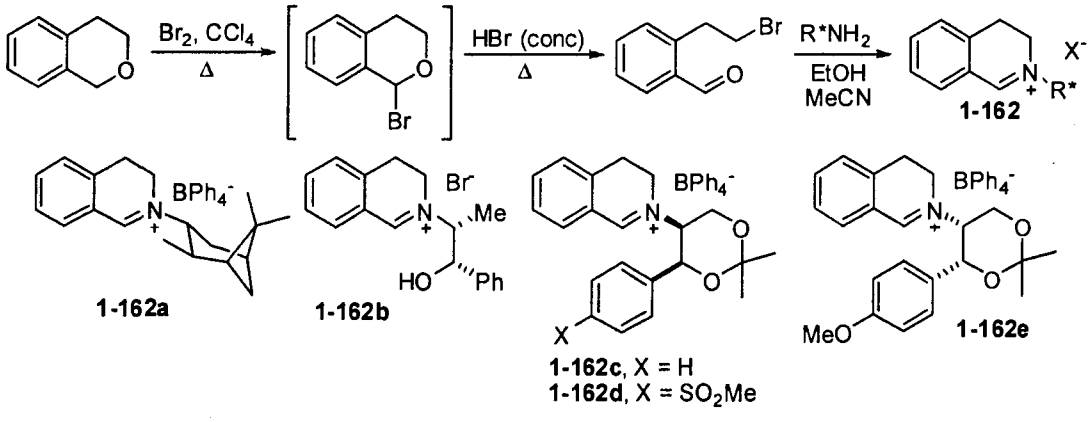
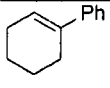
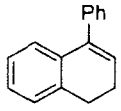
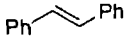
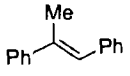
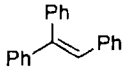


Table 1.33 Catalytic Asymmetric Epoxidation with Iminium Salts 1-162[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**1-162a**[b]	68	40 (*R*,*R*)

[132] For NMR studies on the formation of oxaziridinium salt from iminium **1-162c** 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.

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

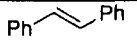
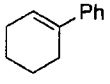
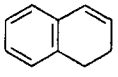
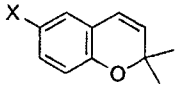
[a] Reactions were carried out at 0 °C. [b] 0.05 equiv. catalyst used. [c] 0.1 equiv. catalyst used. [d] Conversion (%).

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 coworkers introduced non-aqueous conditions for iminium salt-mediated asymmetric epoxidation using organic solvent-soluble stoichiometric oxidant tetraphenylphosphonium monoperoxysulfate (TPPP), which is synthesized by treating Oxone with tetraphenylphosphonium chloride.[134] When the epoxidation was carried out

[134] Page, P.C.B.; Barros, D.; Buckley, B.R.; Ardakani, A.; Marples, B.A. *J. Org. Chem.* **2004**, *69*, 3595.

with iminium salt **1-162d** 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 1.34, entry 7).[135] It was found that the reactions performed in $CHCl_3$ gave higher ee's than those in CH_3CN.

Table 1.34 Catalytic Asymmetric Epoxidation with Iminium Salt 1-162d[a]

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

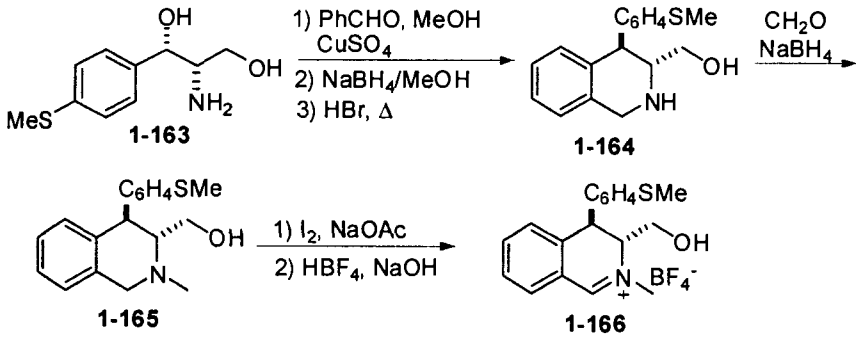
[a] Iminium salt **1-162d** (0.1 equiv.), TPPP (2.0 equiv.) in $CHCl_3$, at -40 °C.

Rozwadowska and coworkers reported the synthesis of the enantiomer of **1-159** (*ent*-**1-159**) from an industrial waste product, (+)-thiomicamine **1-163**, in several steps. This iminium salt *ent*-**1-159** produced enantioselectivities similar to those of **1-159** reported by Bohé and coworkers. A hydroxymethyl analogue of *ent*-**1-159** (**1-166**) was also prepared

[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.

from **1-163** and epoxidized *trans*-stilbene in 70% yield and 45% ee with *m*CPBA as oxidant (Scheme 1.30).[136]

Scheme 1.30 Synthesis of Iminium Salt 1-166



1.3.2.2. Binaphthylazepinium-Based Iminium Salts

In 1996, Aggarwal and coworkers reported binaphthyl-based iminium salt **1-168**, prepared from binaphthylamine **1-167** in two steps (Scheme 1.31).[137] The epoxidation with **1-168** (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 **1-168** was found to epoxidize trisubstituted olefins faster than disubstituted olefins.

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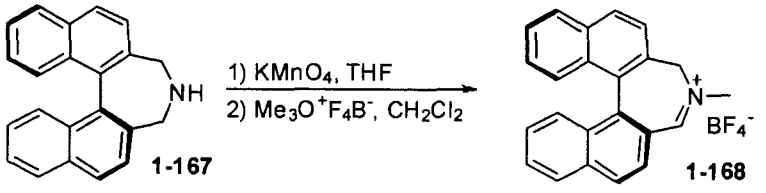
[136] (a) Brózda, D.; Koroniak, Ł.; Rozwadowska, M.D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017. (b) Głuzyńska, A.; MaćKowska, I.; Rozwadowska, M.D.; Sienniak, W. *Tetrahedron: Asymmetary* **2004**, *15*, 2499.

[137] Aggarwal, V.K.; Wang, M.F. *Chem. Commun.* **1996**, 191.

Scheme 1.31 Synthesis of Iminium Salt 1-168



1-167 1-168

In 2004, Page and coworkers reported a highly active and selective binaphthyl-based iminium salt catalyst **1-169a** (Figure 1.47).[138] This catalyst gave good to excellent ee's for several substrates (Table 1.35, 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 **1-169a** was also employed in non-aqueous 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% **1-169a** 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 coworkers reported another set of binaphthalene-fused azepinium salts. Among these catalysts, **1-169b** and **1-169c** (Figure 1.47) gave the best results (Table 1.35, entries 2, 4, 5, 7).[140]

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[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.

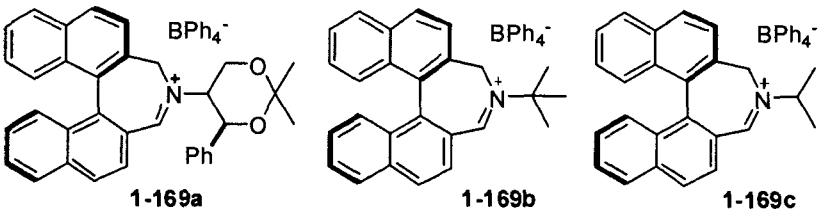
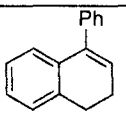
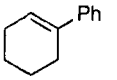
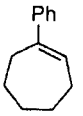


Figure 1.47

Table 1.35 Catalytic Asymmetric Epoxidation with Iminium Salts 1-169[a]

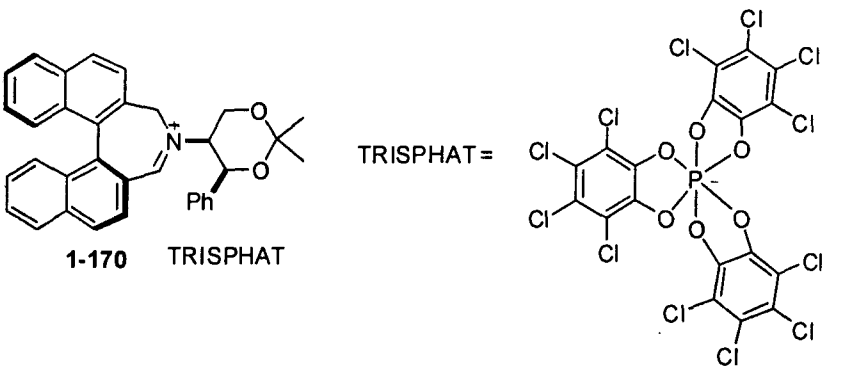
Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**1-169a**	66	95 (1*R*,2*S*)
2		**1-169c**	68	83 (1*R*,2*S*)
3[b]		**1-169a**	64	91 (1*S*,2*S*)
4		**1-169b**	54	84 (1*S*,2*S*)
5		**1-169c**	73	82 (1*S*,2*S*)
6[b]		**1-169a**	57	76 (1*S*,2*S*)
7		**1-169c**	60	65 (1*S*,2*S*)

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

Recently, Lacour and coworkers reported several catalysts (**1-170** and **1-171**) structurally similar to iminium salts **1-169** with TRISPHAT as the counter ion (Figure 1.48 and Figure 1.49).[141] They can be synthesized in three steps in good yields (Scheme 1.32) and provide good enantioselectivities for some trisubstituted olefins (Table 1.36). Iminium catalyts **1-170** and **1-171a**, having opposite binaphthyl configuration, gave epoxides of opposite configuration (Table 1.36, entries 1 vs 2 and 5 vs 6); and catalysts **1-171b** and **1-171c**, having the same binaphthyl configuration and opposite configuration on the *N*-substituent, gave epoxides with same absolute configuration (Table 1.36, entries

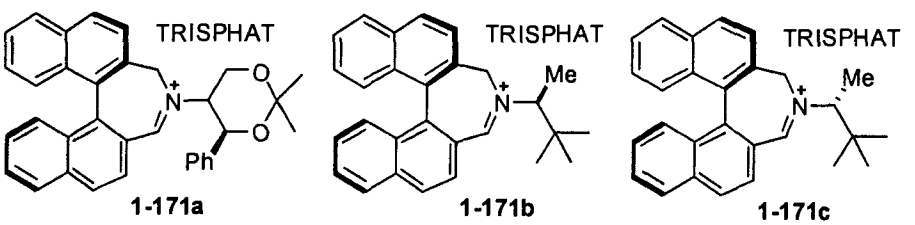
[141] (a) Gonçalves, M.-H.; Martinez, A.; Grass, S.; Page, P.C.B.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297. (b) Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334.

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]



1-170 TRISPHAT

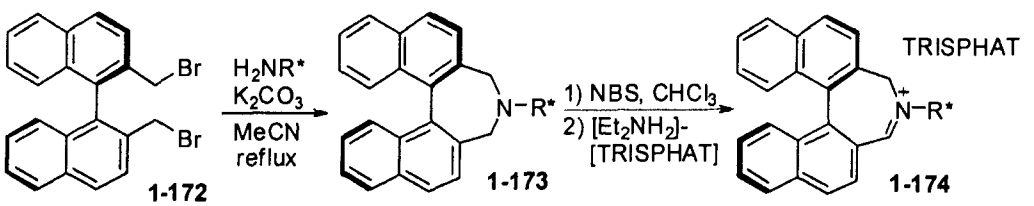
Figure 1.48



1-171a **1-171b** **1-171c**

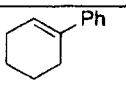
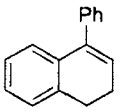
Figure 1.49

Scheme 1.32 Synthesis of Iminium Salt 1-174



1-172 **1-173** **1-174**

Table 1.36 Catalytic Asymmetric Epoxidation with Iminium Salts 1-170 and 1-171[a]

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

[a] 0.05 equiv. catalyst, 0 °C.

1.3.2.3. Biphenylazepinium-Based Iminium Salts

In 2002, Page and coworkers reported a series of biphenylazepinium salt catalysts (**1-175**) that are synthesized in the same manner as the dihydroisoquinoline-based iminium catalysts (Figure 1.50, Scheme 1.29).[142,133] In some cases, the enantioselectivity can be improved by using non-aqueous epoxidation conditions since the reaction can be carried out at lower temperature in organic solvent (Table 1.38).[139,134]

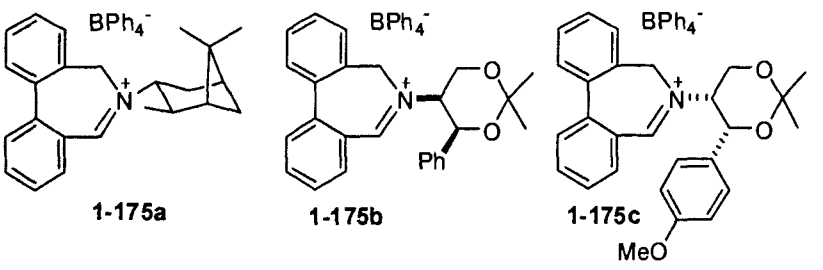
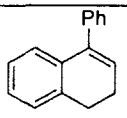
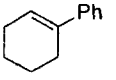
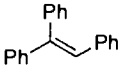
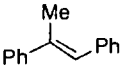


Figure 1.50

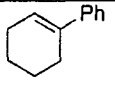
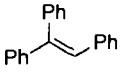
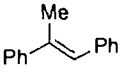
[142] Page, P.C.B.; Rassias, G.A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett*, **2002**, 580.

Table 1.37 Catalytic Asymmetric Epoxidation with Iminium Salts 1-175[a]

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

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

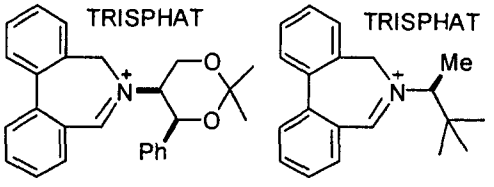
Table 1.38 Asymmetric Epoxidation with Iminium Salt 1-175b under Non-Aqueous Conditions[a]

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.

In 2002 and 2005, Lacour and coworkers reported catalysts **1-176** which are structurally similar to **1-175** but with the counter ion being replaced as TRISPHAT

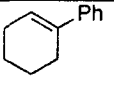
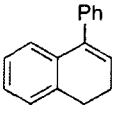
(Figure 1.51).[143,141] The lipophilicity of TRISPHAT keeps the iminium salt in the organic solvent, which can be beneficial to enantioselectivities.[143a] Up to 80% ee was obtained for the epoxidation of 4-phenyl-1,2-dihydronaphthalene with **1-176b** (Table 1.39, entry 6).



1-176a **1-176b**

Figure 1.51

Table 1.39 Catalytic Asymmetric Epoxidation with Iminium Salts 1-176[a]

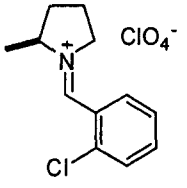
Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**1-176a**	100	69 (*S,S*)
2		**1-176b**	100	65 (*S,S*)
3		**1-176a**	85	76 (1*R*,2*S*)
4		**1-176b**	72	70 (1*R*,2*S*)
5[b]		**1-176a**	91	79
6[b]		**1-176b**	100	80 (1*R*,2*S*)

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

[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.

1.3.3. 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 coworkers 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 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 **1-177** (Figure 1.52) was successfully prepared and gave 100% conversion and 22% ee for 1-phenylcyclohexene with stoichiometric amount of **1-177**.



1-177

Figure 1.52

In 1999, Armstrong and coworkers also reported a highly stereoselective intramolecular epoxidation with oxaziridinium salts generated from unsaturated oxaziridines such as **1-179** and **1-180** by methylation with MeOTf (Scheme 1.33).[145,146]

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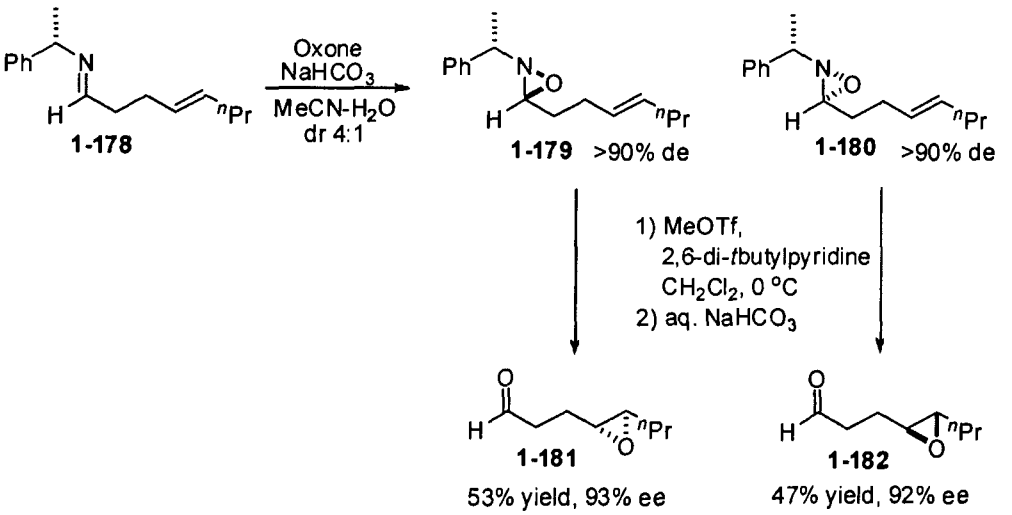
[144] (a) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K. *Synlett* **1997**, 1075. (b) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J.S. *Tetrahedron* **1999**, *55*, 2341.

[145] Armstrong, A.; Draffan, A.G. *Tetrahedron Lett.* **1999**, *40*, 4453.

Oxaziridines **1-179** and **1-180** were formed by the oxidation of imine **1-178** with Oxone. The resulting diastereomeric mixture (4:1) could be separated and purified to >20:1. The purified **1-179** and **1-180** were individually treated with MeOTf to form the corresponding oxaziridinium salts, which underwent a stereoselective intramolecular epoxidation to give epoxide **1-181** and **1-182** in 93% ee and 92% ee, respectively, upon hydrolysis of the imine epoxide (Scheme 1.33).

Scheme 1.33 Intramolecular Epoxidation with Iminium Salt



In 2000, Komatsu and coworkers 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 **1-183** (Figure 1.53) and Oxone-$NaHCO_3$ in CH_3CN-H_2O at 25 °C for 16 h gave the epoxide in 70% yield and 39% ee.

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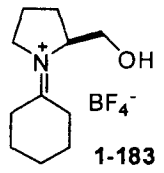
[146] For calculational studies on transition states for this system and for epoxidations by oxaziridinium salts, see: Washington, I.; Houk, K.N. *J. Am. Chem. Soc.* **2000**, *122*, 2948.

[147] Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810.

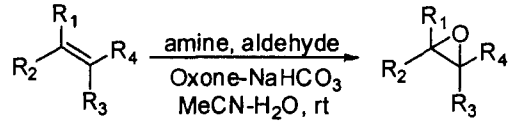


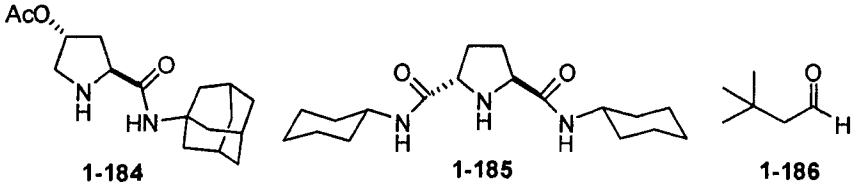
1-183

Figure 1.53

In 2001, Yang and coworkers developed an epoxidation system using catalytic iminium salts generated *in situ* from chiral amines and aldehydes (Scheme 1.34).[148] Up to 59% ee was obtained with amine **1-184** and aldehyde **1-186** (Figure 1.54) (Table 1.40, entry 2). When amine **1-185** (1.0 equiv.) and aldehyde **1-186** (1.0 equiv.) were used, *trans*-stilbene epoxide was obtained in 80% conversion and 65% ee.

Scheme 1.34 Asymmetric Epoxidation with *in situ* Generated Iminium Salt

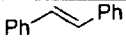
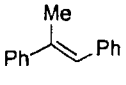




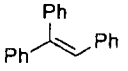
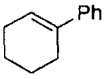
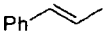
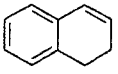
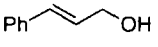
1-184 1-185 1-186

Figure 1.54

Table 1.40 Catalytic Asymmetric Epoxidation of Olefins with Amine 1-184 and Aldehyde 1-186[a]

Entry	Substrate	Reaction time (h)	Conv. (%)	ee (%)
1		5	81	46 (*S,S*)
2[b]		1.3	100	59 (*S,S*)

[148] Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587.

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 **1-184** (0.5 equiv.), aldehyde **1-186** (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 **1-184** (0.2 equiv.) and aldehyde **1-186** (0.2 equiv.)

4. CONCLUSION

Asymmetric epoxidation of olefins catalyzed by chiral ketones and iminum salts has been intensively studied over the past few years. 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.

CHAPTER TWO

ASYMMETRIC EPOXIDATION OF STYRENES AND STUDIES OF SUBSTITUENT EFFECT ON EPOXIDATION OF CHROMENES

2.1. INTRODUCTION

Asymmetric epoxidation of styrenes using chiral dioxirane has been challenging despite the fact that trans-, trisubstituted and certain cis-olefins are effective substrates.[1] During our earlier studies, encouraging enantioselectivity (81% ee) was obtained for styrene oxide with ketone **1-104** (Figure 1.19, page 50).[2] However, the synthesis of ketone **1-104** is nontrivial which will limit its practical use. It was necessary to design a new class of catalyst that has a short and straightforward synthetic route and can provide improved reactivity and selectivity. The effect of the sprio ring on the ketone catalysts has been studied by varying the ring structure for a number of ketones (Figure 1.25, page

[1] For reviews, see: (a) Denmark, S.E.; Wu, Z., *Synlett* **1999**, 847. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.

[2] (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.

56).[3] The results suggested that the carbonyl group as well as the nonbonding interactions adjacent to the carbonyl contribute significantly to obtaining high enantioselectivities for conjugated terminal and cis-olefins for ketones such as **1-104**. To ensure the highest efficiency for the epoxidation of conjugated terminal and cis-olefins, these advantageous features should be included in the design of the new class of catalyst.

Anilines can be introduced into sugars directly by Amadori rearrangement and the substituents on the nitrogen can be easily varied by changing the starting anilines. A series of oxazolidinone-containing catalysts were prepared by David Goeddel, Lianhe Shu and, Yi Yuan. Selected examples are listed in Figure 2.1. In general, catalysts with hydrocarbon substitution on the aniline showed consistently high enantioselectivities compared to the ether- or halogen-containing catalysts when styrene was used as a test substrate (Table 2.1). The low cost of 4-methyl and 4-ethyl anilines as well as their effectiveness toward asymmetric epoxidation makes catalysts **1-111b** and **1-111c** ideal catalysts for substrate scope investigation.

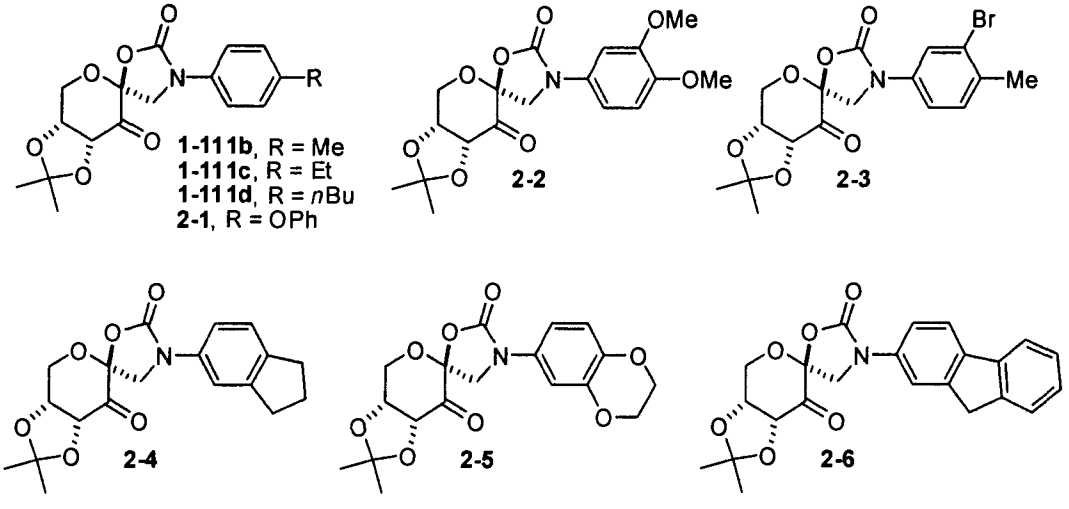


Figure 2.1

[3] Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409.

Table 2.1 Asymmetric Epoxidation of Styrene with Chiral Ketones

entry	catalyst	conv. (%)	ee (%)
1	**1-111b**	100	84
2	**1-111c**	100	86
3	**1-111d**	99	84
4	**2-1**	89	85
5	**2-2**	77	70
6	**2-3**	49	78
7	**2-4**	87	84
8	**2-5**	89	79
9	**2-6**	100	86

The asymmetric epoxidation of various substituted *cis*-β-methylstyrenes was also investigated with catalyst **1-111b**.[4] 84% ee was obtained for *cis*-β-methylstyrene and an increase of 4-7% ee was obtained for methyl substituted *cis*-β-methylstyrenes (*o*-Me, 88% ee; *m*-Me, 91% ee, *p*-Me, 88% ee). Earlier studies in our laboratory suggested that the stereodifferentiation for the epoxidation of cis-olefins with oxazolidinone-containing catalysts such as **1-104** originates from the apparent attraction between the oxazolidinone moiety of the catalyst and the R_π group of the substrate.[2] This apparent attraction causes spiro **A** to be favored over spiro **B** (Figure 2.2). The higher ee obtained for methyl substituted *cis*-β-methylstyrene indicated that the substituent on the phenyl ring has a beneficial effect on the enantioselectivity of the epoxidation, thus further favoring spiro **A**. In the case of *meta*-methyl substituted *cis*-β-methylstyrene, there could be two possible reacting approaches for the favored transition state (**A-1** and **A-2**, Figure 2.3). We can determine which of these reacting approaches is in operation if we restrict the

[4] (a) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (b) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115.

rotation by using analogous cyclic olefins. Consequently, the asymmetric epoxidation of a series of substituted 2,2-dimethylchromenes were studied.

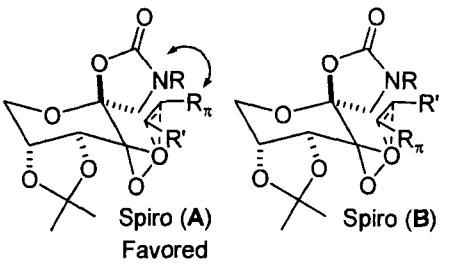


Figure 2.2

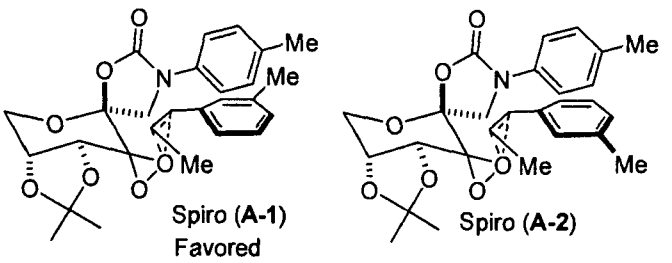


Figure 2.3

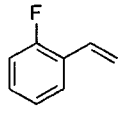
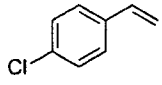
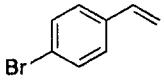
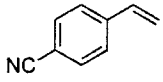
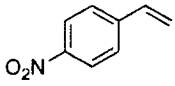
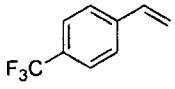
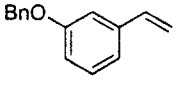
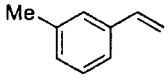
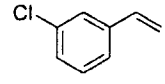
2.2. RESULTS AND DISSCUSION

2.2.1. Asymmetric Epoxidation of Styrenes

The noncommercially available styrenes were synthesized by Wittig reactions from the corresponding commercially available benzaldehydes. Working alongside David Goeddel, many substituted styrenes were found to be effective substrates for the asymmetric epoxidation using ketone **1-111c**. As shown in Table 2.2, up to 92% ee is

obtained for substituted styrenes. The enantioselectivity is dependent on the substituent of the styrene.

Table 2.2 Asymmetric Epoxidation of Styrenes with Ketone 1-111c[a]

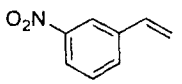
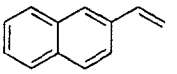
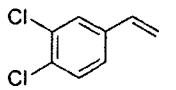
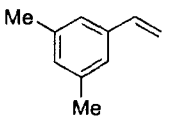
entry	substrate	yield[b] (conv.[c]) (%)	ee (%)	config.[h]
1[i,m]		72 (100)	86[d]	(-)-(*R*)[5]
2[j,m]		89 (95)	80[d]	(-)[6]
3[j,m]		85 (100)	86[d]	(-)-(*R*)[5]
4[j,m]		71 (99)	87[d]	(-)-(*R*)[7]
5[k,n]		86 (100)	90[d]	(-)-(*R*)[7]
6[l,n]		73 (99)	90[d]	(-)-(*R*)[7]
7[l.n]		73 (100)	92[d]	(-)[8]
8[k,n]		66 (79)	87[e]	(-)
9[i,m]		87 (100)	90[d]	(-)
10[k,n]		72 (100)	86[f]	(-)[5]

[5] Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112.

[6] Doussot, J.; Guy, A.; Siaugue, J-M.; Ferroud, C.; Guieres, A.F. *Chirality* **1999**, *11*, 541.

[7] (a) Pedragosa-Moreau, S.; Morisseau, C.; Zylber, J.; Archelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1999**, *61*, 7402. (b) Moussou, P.; Archeals, A.; Baratti, J.; Furstoss, R. *J. Org.Chem.* **1998**, *63*, 3532.

[8] Zhang, R.; Yu, W-Y.; Wong, K-Y.; Che, C-M. *J. Org. Chem.* **2001**, *66*, 8145.

11[k,n]		77 (100)	88[f]	(-)[9]
12[k,o]		91 (100)	87[g]	(-)-(*R*)[7b]
13[k,n]		75 (95)	90[d]	(-)[10]
14[i,m]		86 (99)	90[d]	(-)

[a] All reactions were carried out with olefin (0.40 mmol), ketone **1-111c** (0.06-0.12 mmol), Oxone (1.07 mmol), K_2CO_3 (4.23 mmol), and Bu_4NHSO_4 (0.04 mmol) in DME (6.0 mL) and buffer (0.1 M K_2CO_3-AcOH, pH 9.3) (4.0 mL) at -10 to -15 °C (bath temperature). For entry 12, the reaction was carried out at -5 °C. For entry 13, the reaction was carried out in DME (5.0 mL)/dioxane (1.0 mL) at 0 °C. [b] Isolated yield. [c] The conversion was determined by GC, except for entries 8, 10, 11, and 12 which were determined by ^{1}H NMR. [d] The ee was determined by chiral GC (Chiraldex B-DM). [e] The ee was determined by chiral HPLC (Chiralcel AD). [f] The ee was determined by chiral HPLC (Chiralcel OD). [g] The ee was determined by chiral HPLC (Chiralcel OJ). [h] The absolute configurations were determined by comparing the measured optical rotations with the reported ones. [i] Reaction time of 6 h. [j] Reaction time of 8 h. [k] Reaction time of 12 h. [l] Reaction time of 16 h. [m] 0.06 mmol of ketone **1-111c** was used. [n] 0.12 mmol of ketone **1-111c** was used. [o] The reaction was carried out with 3.24 mmol of olefin and 0.98 mmol of ketone **1-111c**.

As discussed before, the asymmetric induction for oxazolidinone-containing ketone catalysts, such as ketone **1-111c**, is likely due to an attraction between the oxazolidinone moiety of the ketone and the conjugated aryl group of the substrate.[2,4] For styrenes, spiro **C** is likely to be the favored transition state with spiro **D** and planar **E** being the competing transition states (Figure 2.4). For *ortho*-substituted styrenes, such as *o*-F-styrene (Table 2.2, entry 2), the substituent at the *ortho* position causes an unfavorable steric interaction between the substituent and the oxazolidinone moiety of the catalyst in the favored spiro **C**. Thus, the ee of the *ortho*-substituted styrene is lower than styrene itself. For *para*-substituted styrenes (Table 2.2, entries 3-7), certain

[9] Collman, J.P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460.

[10] Solladié-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494.

substituents do not affect the competition between transition states. However, the styrenes bearing electron-withdrawing substituents can be epoxidized in higher ee than their electron-rich counterparts, presumably because of enhanced secondary orbital interactions further favoring spiro **C** (Figure 1.16, page 35).[11] For *meta*-substituted styrenes (Table 2.2, entries 8-11), certain substituent on the phenyl ring appear to further favor spiro **C**, resulting in an increase in overall ee. Styrenes bearing multiple substituents gave ee's that are consistent with the various electronic and structural patterns of the simpler monosubstituted styrenes (Table 2.2, entries 12-14). The addition of dioxane was found to significantly improve the conversion of the relatively insoluble and unreactive substrates (Table 2.2, entry 13).

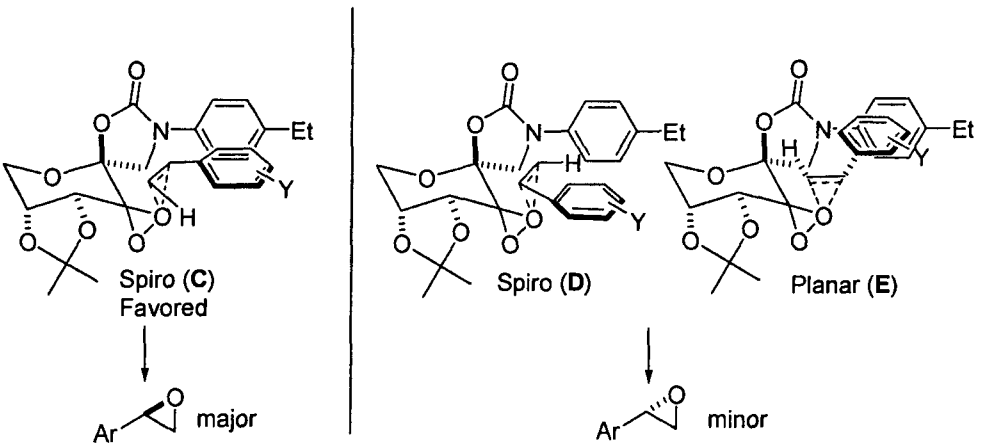


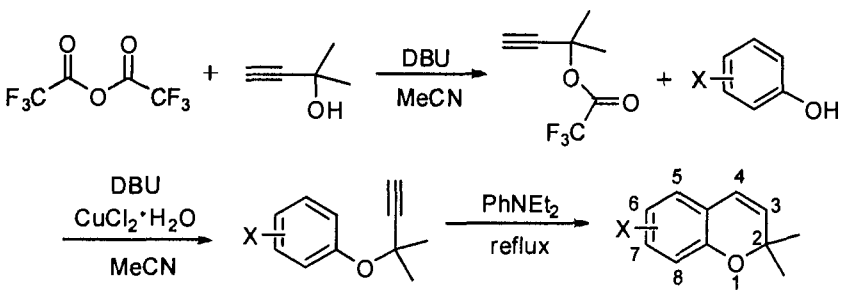
Figure 2.4

[11] Hicky, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

2.2.2. Studies of Substituent Effect on Asymmetric Epoxidation of Chromenes

The substituted chromenes were prepared on the basis of a reported procedure (Scheme 5.1).[12,13] 6-Substituted chromenes were prepared from the corresponding *para*-substituted phenols, while 8-substituted chromenes were prepared from the corresponding *ortho*-substituted phenols.

Scheme 2.1 Synthesis of 2,2-Dimethylchromenes



The epoxidation was initially investigated using ketone **1-111c** (Figure 2.1). Subjecting 2,2-dimethylchromene to the epoxidation conditions with 20 mol% of ketone **1-111c** at 0 °C gave (3*R*, 4*R*)-(+)-2,2-dimethylchromene in 100% conversion and 84% ee (Table 2.3, entry 1). By introducing a substituent, electron-withdrawing or electron-donating, at the 6-position, the ee's increased (Table 2.3, entries 2-12). Furthermore, 6-methyl-2*H*-chromene was studied to investigate the effect of the *gem*-dimethyl groups on enantioselectivity (Table 2.3, entry 13). The epoxidation of this substrate gave 90% ee, only slightly lower than 6-methyl-2,2-dimethylchromene (Table 2.3, entry 3), suggesting that the *gem*-dimethyl groups do not have significant effect on the enantioselectivity.

---

[12] Godfrey, J.D., Jr.; Mueller, R.H.; Sedergran, T.C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.

[13] Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148.

When the substituents are introduced at the 8-position, the ee's are generally lower with electron-donating groups but increase with electron-withdrawing groups (Table 2.3, entries 14-20). The enantioselectivity is higher for both 5-chloro and 7-chloro-2,2-dimethylchromenes compared to 2,2-dimethylchromene itself, with higher ee being achieved for the latter (Table 2.3, entries 21 and 22). When both the 5- and 7-positions are chlorinated, the enantioselectivity increased with respect to its 5-chloro counterpart but decrease with respect to its 7-chloro counterpart (Table 2.3, entry 23). When the 5, 6 and 7-positions are substituted, as in 6-chloro-2,2,5,7-tetramethylchromene, the ee for the epoxidation with ketone **1-111c** is only slightly higher than non-substituted chromene (Table 2.3, entry 24 vs. entry 1).

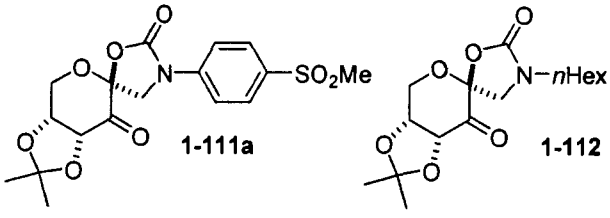
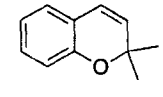
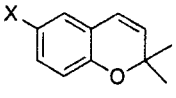
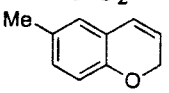
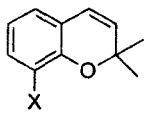
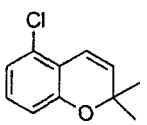
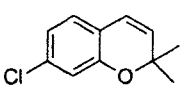
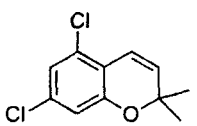
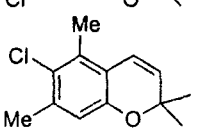


Figure 2.5

Table 2.3 Asymmetric Epoxidation of 2,2-Dimethylchromenes

		ketone **1-111a**[a]		ketone **1-111c**[b]		ketone **1-112**[a]	
entry	substrate	conv. (yield) (%)[e]	ee (%)	conv. (yield) (%)[e]	ee (%)	conv. (yield) (%)[e]	ee (%)
1[c,f,j]	 	100 (71)	86	100 (86)	84	100 (60)	84

2[c,f]	X = OMe	100 (73)	89	100 (65)	90	100 (71)	88
3[c,f]	X = Me	100 (79)	89	100 (75)	92	100 (71)	92
4[c,i]	X = Et			80 (59)	90		
5[c,f]	X = ^{n}Pr			75 (70)	91		
6[c,f]	X = ^{i}Pr			79 (69)	90		
7[c,f]	X = ^{t}Bu	37 (30)	90	86 (71)	91	58 (30)	89
8[d,g]	X = F	81 (64)	87	100 (77)	89	94 (64)	89
9[d,g]	X = Cl	55 (40)	94	100 (81)	93	58 (52)	93
10[d,f]	X = Br	63 (61)	91	81 (66)	91	76 (71)	93
11[d,f,j]	X = CN	77 (75)	93	83 (75)	93	71 (64)	89
12[d,f]	X = NO_2	40 (36)	90	76 (72)	93	44 (41)	89
13[c,f]				100 (38)	90		
							
14[d,h]	X = OMe	100 (73)	84	100 (63)	82	100 (78)	82
15[d,h]	X= Me	100 (71)	87	80 (63)	81	100 (53)	85
16[d,h]	X = F	87 (59)	80	100 (82)	84	81 (67)	84
17[d,h]	X = Cl	59 (48)	87	85 (71)	83	76 (60)	86
18[d,h]	X = Br	57 (43)	83	83 (70)	82	76 (61)	85
19[d,g]	X = CN	76 (70)	86	95 (88)	88	87 (83)	89
20[d,h]	X = NO_2	35 (30)	85	67 (63)	85	75 (73)	87
21[d,f]				54 (52)	85		
22[d,f]				87 (86)	91		
23[d,f]				25 (23)	88		
24[d,f]				80 (64)	85		

[a] All reactions were carried out with olefin (0.20 mmol), ketone **1-111a** or **1-112** (0.04 mmol), Oxone (0.53 mmol), K_2CO_3 (2.12 mmol), Bu_4NHSO_4 (0.0015 mmol) in DME/DMM (3:1 v/v) (3.0 mL), and buffer (0.1 M K_2CO_3-AcOH, pH 9.3) (2.0 mL) at 0 °C (bath temperature). [b] All reactions were carried out with olefin (0.40 mmol), ketone **1-111c** (0.08 mmol), Oxone (1.07 mmol), K_2CO_3 (4.23 mmol), Bu_4NHSO_4 (0.003 mmol) in DME/DMM (3:1 v/v) (6.0 mL), and buffer (0.1 M K_2CO_3-AcOH, pH 9.3) (4.0 mL) at 0 °C (bath temperature). [c] Reaction time 6 h. [d] Reaction time 12 h. [e] The conversion was determined by ^{1}H NMR. The yield is the isolated yield. The epoxides were purified by flash chromatography (buffered with 1% NEt_3) and gave satisfactory spectroscopic characterization. For entry 13, a diol resulting from the opening of the epoxide was also isolated in 42% yield. [f] Enantioselectivity was determined by chiral HPLC (Chiralcel

OD). [g] Enantioselectivity was determined by chiral GC (Chiraldex B-DM). [h] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [i] Enantioselectivity was determined by chiral HPLC (Chiralcel OB). [j] The epoxides have (3*R*,4*R*) configurations as determined by comparing the measured optical rotations with reported ones (ref 14).

The effect of substituents at the 8-position is likely to be electronic in nature. In the case of 6-substituted chromenes, besides the electronic effect, the proximity of the substituents on the chromenes to the phenyl group of the catalyst in spiro **F** might cause additional beneficial nonbonding interactions between the substituent at the 6-position of the substrate and the phenyl group of the catalyst, further favoring spiro **F** over spiro **G** (Figure 2.5) (examples of Chem3D molecular modeling of transition states spiro **F** and **G** for the epoxidation of 6-methyl-2,2-dimethylchromene with ketone **1-111c** are shown in Figures 2.6 and 2.7). On the other hand, such interaction is not feasible for 8-substituted substrates (Figure 2.8) (examples of Chem3D molecular modeling of transition states spiro **H** and **I** for the epoxidation of 8-methyl-2,2-dimethylchromene with ketone **1-111c** are shown in Figures 2.9 and 2.10).

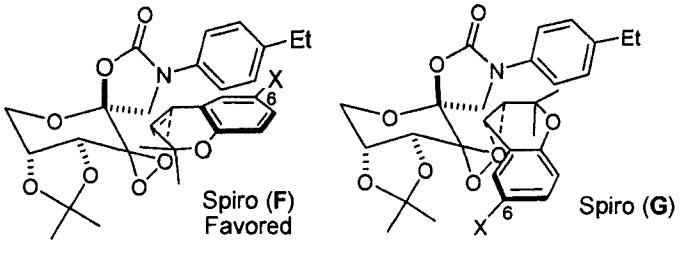


Figure 2.5 Two Competing Spiro Transition States for the Epoxidations of 6-Substituted 2,2-Dimethylchromenes

[14] The absolute configuration was determined by comparing the measured optical rotations with reported ones; see: (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055. (c) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541. (d) Scheurer, A.; Mosset, P.; Spiegel, M.; Saalfrank, R. W. *Tetrahedron* **1999**, *55*, 1063. (e) Page, P.C.B.; Buckley, B.R.; Heaney, H.; Blacker, A.J. *Org. Lett.* **2005**, *7*, 375.

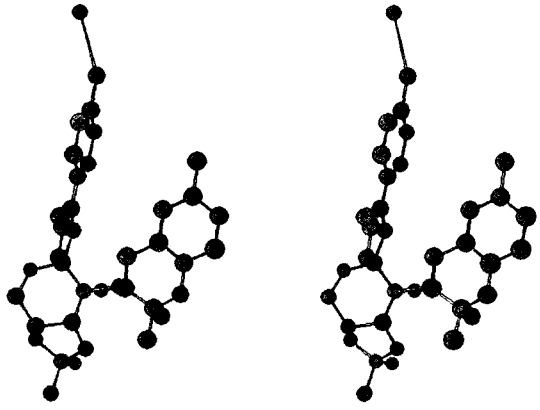


Figure 2.6 Chem3D Molecular Modeling of TS Spiro **F** for the Epoxidation of 6-Methyl-2,2-Dimethylchromene with Ketone **1-111c** (stereoview)

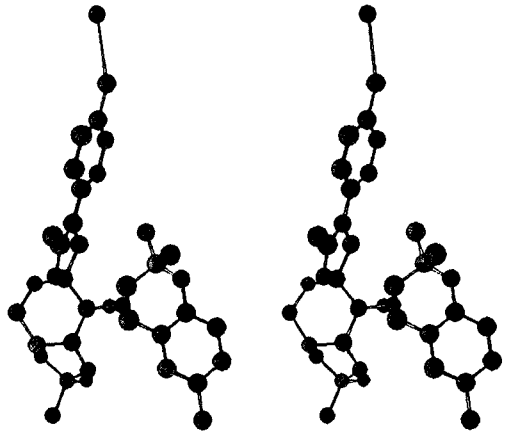


Figure 2.7 Chem3D Molecular Modeling of TS Spiro **G** for the Epoxidation of 6-Methyl-2,2-Dimethylchromene with Ketone **1-111c** (stereoview)

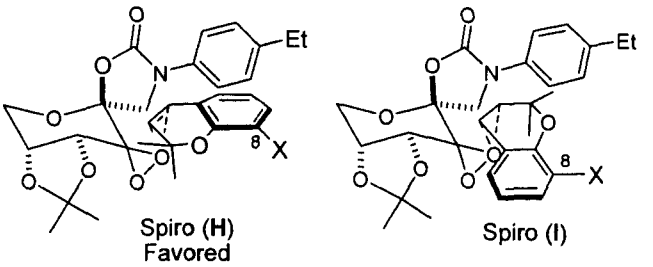


Figure 2.8 Two Competing Spiro Transition States for the Epoxidations of 8-Substituted 2,2-Dimethylchromenes

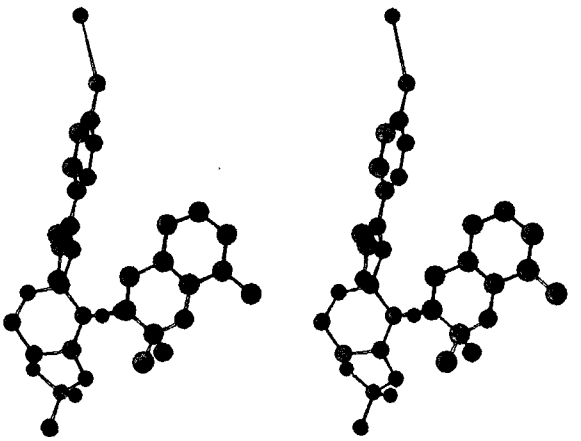


Figure 2.9 Chem3D Molecular Modeling of TS Spiro **H** for the Epoxidation of 8-Methyl-2,2-Dimethylchromene with ketone **1-111c** (stereoview)

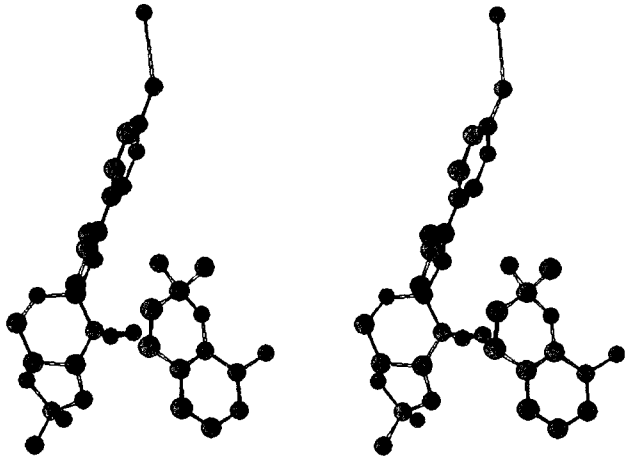


Figure 2.10 Chem3D Molecular Modeling of TS Spiro **I** for the Epoxidation of 8-Methyl-2,2-Dimethylchromene with Ketone **1-111c** (stereoview)

To further probe the interaction between the catalyst and the substrate, the epoxidation of some chromenes were also carried out with *N*-phenylmethylsulfonyl-substituted ketone **1-111a** and *N*-hexyl-substituted ketone **1-112** (Figure 2.5).[15] As shown in Table 2.3, a similar trend (the ee's of 6-substituted chromenes are higher than the 8-substituted chromenes) is observed, suggesting that an electron-withdrawing group or a non-aromatic group on the nitrogen of the oxazolidinone could also provide a beneficial interaction between the 6-substituent of the substrate and the *N*-substituent of the ketone catalyst. The fact that both electron-withdrawing and electron-donating groups at the 6-position enhance the enantioselectivity of the epoxidation with all three ketones suggests that nonbonding interaction, such as van der Waals forces and/or hydrophobic

[15] Ketones **1-111a** and **112** were synthesized by Drs. Lianhe Shu and Yi Yuan.

interactions, are important components of the interaction between the substituent on the phenyl group of the olefin and the *N*-substituent of the ketone catalyst.

2.3. CONCLUSIONS

In summary, the asymmetric epoxidation of various styrenes has been investigated with readily available oxazolidinone-containing ketone **1-111c**. Styrenes bearing electron-withdrawing or electron-donating groups can be epoxidized in high ee's. Additionally, the substituent effect on the epoxidation of various 2,2-dimethylchromenes has been studied with ketones **1-111a**, **1-111c**, and **1-112**. The results indicated that the substituents at the 6-position of the chromenes have significant beneficial effects on enantioselectivity. Both *N*-aryl (**1-111a** and **1-111c**) and *N*-alkyl (**1-112**) ketones provided similar results, suggesting that van der Waals forces and/or hydrophobic interactions play important roles in the beneficial interaction between the substituent of the substrate and the *N*-substituent of the ketone catalyst.

2.4. EXPERIMENTAL

Representative Procedure for the Synthesis of Styrenes by Wittig Reaction (Table 2.2, entry 8). 3-Benzyloxystyrene (OAW0123). To a mixture of $MePPh_3Br$ (8.57 g, 24 mmol), KO^{t}Bu (2.69 g, 24 mmol) and 18-crown-6 (0.05 g, 0.2 mmol) was added dry THF (100 mL). Upon stirring for 30 min, 3-benzyloxybenzaldehyde (4.25 g, 20 mmol) was added dropwise and the bright yellow suspension turned pink upon the aldehyde addition.

The suspension was stirred at rt under Ar overnight (~14 h). The reaction was concentrated and diluted with hexanes. The hexanes solution was decanted and the leftover solid was extracted with hexanes. The combined hexanes solution was concentrated and purified by flash column chromatography (Hex:Et_2O, 1:0 to 6:1) to obtain 3.66 g of the product (87% yield).

Table 2.2, entry 8 (OAW0123)

3-Benzyloxystyrene. IR (film): 1576, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.43-7.40 (m, 2H), 7.36-7.32 (m, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.06-7.02 (m, 2H), 6.94 (dd, J = 8.0, 2.4 Hz, 1H), 6.70 (dd, J = 17.6, 10.8 Hz, 1H), 5.75 (d, J = 17.6 Hz, 1H), 5.26 (d, J = 10.8 Hz, 1H), 5.26 (d, J = 10.8 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 139.0, 137.0, 136.8, 129.5, 128.5, 127.9, 127.5, 119.1, 114.2, 114.1, 112.7.

Table 2.2, entry 13 (OAW0111)

3,4-Dichlorostyrene. IR (film): 1473, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.1 Hz, 1H), 6.63 (dd, J = 17.4, 10.8 Hz, 1H), 5.76 (d, J = 17.4 Hz, 1H), 5.34 (d, J = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.7, 134.6, 132.7, 131.5, 130.4, 128.0, 125.4, 115.8.

Representative Asymmetric Epoxidation Procedure (Table 2.2, entry 8). (-)-3-Benzyloxystyrene Oxide (OAW0226). To a solution of 3-benzyloxystyrene (0.084 g, 0.4 mmol) and ketone **1-111c** (0.042 g, 0.12 mmol) in DME (6.0 mL) were added buffer

(0.1 M K_2CO_3-AcOH in 4 x 10^{-4}M aq. Na_2EDTA, pH = 9.3) (4.0 mL) and Bu_4NHSO_4 (0.010 g, 0.03 mmol) with stirring. After the mixture was cooled to about –10 to –15 °C (bath temperature) via a NaCl-ice bath, a solution of Oxone (0.21 M in 4 x 10^{-4}M aq. Na_2EDTA, 5.04 mL) and a solution of K_2CO_3 (0.84 M in 4 x 10^{-4} M aq. Na_2EDTA, 5.04 mL) were added dropwise separately and simultaneously over 12 h via syringe pump. The reaction was quenched by the addition of pentane and extracted with pentane. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography (the silica gel was buffered by 1% Et_3N in pentane; pent:Et_2O, 1:0 to 10:1 was used as the eluent) to give 3-benzyloxystyrene oxide as a white solid (0.0594 g, 66% yield, 87% ee).

Table 2.2, entry 8 (OAW0226)

3-Benzyloxystyrene Oxide. White solid; $[\alpha]^{20}_D$ = -3.37 (*c* 1.75, $CHCl_3$); IR (film): 2980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.24 (m, 6H), 6.95-6.89 (m, 3H), 5.07 (s, 2H), 3.84 (dd, *J* = 4.0, 2.8 Hz, 1H), 3.13 (dd, *J* = 5.6, 4.0 Hz, 1H), 2.77 (dd, *J* = 5.6, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 139.5, 137.0, 129.8, 128.8, 128.2, 127.7, 118.4, 114.9, 111.7, 70.2, 52.5, 51.4.

Table 2.2, entry 13 (DLG-XII-21)

3,4-Dichlorostyrene Oxide. Yellow oil; $[\alpha]^{20}_D$ = -9.95 (*c* 2.08, $CHCl_3$); IR (film): 2993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.81 (dd, *J* = 3.9, 2.4 Hz, 1H), 3.15 (dd, *J* = 5.4, 4.2 Hz,

1H), 2.73 (dd, J = 5.4, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.0, 132.3, 130.7, 127.6, 125.0, 51.5, 51.4.

Representative Procedure for the Synthesis of 2,2-Dimethylchromenes (Table 2.3, entry 1) (OAW0324, OAW0325). To a solution of 2-methyl-3-butyn-2-ol (4.88 g, 58.0 mmol) in dry MeCN (30 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (11.40 g, 11.2 mL, 74.9 mmol) at –5 °C (NaCl-ice bath) under Ar. Trifluoroacetic anhydride (12.18 g, 0.06 mL, 58.0 mmol) was added over 25 min via syringe pump, the resulting solution was allowed to stir for 30 min. Another round-bottom flask was charged with phenol (5.46 g, 58.0 mmol) in dry MeCN (30 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (11.40 g, 11.2 mL, 74.9 mmol) and $CuCl_2 \cdot 2H_2O$ (0.009 g, 0.055 mmol) was added at –4 °C. The trifluoroacetic anhydride solution was cannulated into the phenol solution over 30 min and the resulting solution was allowed to stir for 5 h. The solution was then concentrated, and partitioned between hexanes and H_2O. The layers were separated and the aqueous phase was extracted with hexanes three times. The combined organic layers was washed with 1N HCl, 1N NaOH, 1N $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated to give 6.70 g of yellow liquid (crude yield 72%). The crude propargyl ether was refluxed in distilled $PhNEt_2$ (80 mL) for 6 h. Upon cooling to rt, it was poured into a 1-L sep funnel charged with diluted HCl. The aqueous layer was washed with Et_2O three times. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, concentrated and purified by flash column chromatography to give 5.45 g of yellow oil (81% yield). (Table 2.3, entries 23 and 24.

5-Chloro-2,2-dimethylchromene and 7-Chloro-2,2-dimethylchromene (OAW0408) were obtained as a 1.9 to 1.0 mixture)

Procedure for the Synthesis of 6-Methyl-2*H*-Chromene (Table 2.3, entry 13). (OAW0421). To a solution of phenol (6.53 g, 60.0 mmol) in acetone (40 mL) was added K_2CO_3 (10.76 g, 78.0 mmol). Propargyl bromide (9.20 g, 6.89 mL, 78.0 mmol) was added slowly to the solution. Upon refluxing for 8 h, the solvent was evaporated. The resulting residue was partitioned between Et_2O and H_2O. The layers were separated, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography (eluted with hex:Et_2O 8:1) to obtain 10.70 g of product (79% yield). The cyclization is carried out with $PhNEt_2$ using the same method as 2,2-dimethylchromenes.

Table 2.3, entry 1 (OAW0324, OAW0325)

2,2-Dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dt, J = 8.0, 1.6 Hz, 1H), 6.98 (dd, J = 7.2, 1.6 Hz, 1H), 6.85 (dd, J = 7.6, 1.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 10.0 Hz, 1H), 5.62, (d, J = 9.6 Hz, 1H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 130.9, 129.2, 126.5, 122.5, 121.5, 120.9, 116.5, 76.3, 28.2.

Table 2.3, entry 2 (OAW0338)

6-Methoxy-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 8.8 Hz, 1H), 6.68 (dd, J = 8.8, 2.8 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 6.30 (d, J = 9.6 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 3.76 (s, 1H), 1.43, (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 146.9, 131.9, 122.6, 122.1, 117.0, 114.3, 111.7, 76.0, 55.9, 27.8.

Table 2.3, entry 3 (OAW0413)

6-Methyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 10.0 Hz, 1H), 5.62 (d, J = 9.6 Hz, 1H), 2.28 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 131.0, 13.0, 129.6, 126.9, 122.6, 121.2, 116.2, 76.1, 28.0, 20.7.

Table 2.3, entry 4 (OAW0517-1, OAW0525-1)

6-Ethyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, J = 8.4, 2.4 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 10.0 Hz, 1H), 5.62 (d, J = 9.6 Hz, 1H), 2.59 (q, J = 7.2 Hz, 2H), 1.46 (s, 6H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 136.6, 130.9, 128.5, 125.8, 122.6, 121.2, 116.2, 76.1, 28.2, 28.1, 16.0.

Table 2.3, entry 5 (OAW0517-2, OAW0525-2)

6-*n*-Propyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, J = 8.0, 2.0 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 9.6 Hz, 1H), 5.62 (d, J = 10.0 Hz, 1H), 2.52 (t, J = 7.2 Hz, 2H), 1.46 (s, 6H), 1.64 (sextet, J = 7.2 Hz, 2H), 1.46 (s, 6H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 135.0, 130.8, 129.1, 126.4, 122.7, 121.1, 116.1, 76.1, 37.4, 28.1, 24.9, 14.0.

Table 2.3, entry 6 (OAW0526-1, OAW0527-1)

6-*i*-Propyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 9.6 Hz, 1H), 5.61

(d, J = 9.6 Hz, 1H), 2.84 (septet, J = 7.2 Hz, 1H), 1.45 (s, 6H), 1.24 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 141.3, 130.8, 127.1, 124.4, 122.7, 121.1, 116.1, 76.2, 33.5, 28.2, 24.4.

Table 2.3, entry 7 (OAW0526-2, OAW0527-2)

6-*t*-Butyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.4, 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.34 (d, J = 9.6 Hz, 1H), 5.61 (d, J = 10.0 Hz, 1H), 1.45 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 143.5, 130.7, 126.1, 123.4, 122.9, 120.7, 115.8, 76.2, 34.2, 31.7, 28.3.

Table 2.3, entry 8 (OAW0342)

6-Fluoro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dt, J = 8.4, 2.8 Hz, 1H), 6.74-6.69 (m, 2H), 6.27 (d, J = 9.6 Hz, 1H), 5.68 (d, J = 10.0 Hz, 1H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.2, 148.9, 132.4, 122.4, 122.3, 121.9, 117.3, 117.2, 115.3, 112.7, 112.5, 76.4, 27.8.

Table 2.3, entry 9 (OAW0336)

6-Chloro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 8.4, 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.26 (d, J = 9.6 Hz, 1H), 5.66 (d, J = 10.0 Hz, 1H), 1.43, (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 132.2, 128.8, 126.0, 125.5, 122.8, 121.6, 117.8, 76.7, 28.1.

Table 2.3, entry 10 (OAW0406)

6-Bromo-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.4, 2.4 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.26 (d, J = 9.6 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 132.1, 131.7, 128.9, 123.3, 121.5, 118.3, 11.8, 76.7, 28.1.

Table 2.3, entry 11 (OAW0245)

6-Cyano-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.8, 2.4 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 10.0 Hz, 1H), 5.71 (d, J = 10.0 Hz, 1H), 1.47, (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 133.5, 132.4, 130.3, 121.9, 120.9, 119.5, 117.4, 104.0, 78.1, 28.6, 28.6.

Table 2.3, entry 12 (OAW0337)

6-Nitro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.8, 2.8 Hz, 1H), 7.90 (d, J = 2.8 Hz, 1H), 6.82 (d, J = 10.0 Hz, 1H), 6.36 (d, J = 10.0 Hz, 1H), 5.75 (d, J = 10.0 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.7, 142.4, 132.1, 125.6, 122.6, 121.3, 121.1, 116.8, 78.4, 28.5.

Table 2.3, entry 13 (OAW0421)

6-Methyl-2*H*-Chromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J = 8.4, 2.0 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 9.6 Hz, 1H), 5.72 (dt, J = 9.6, 3.6 Hz, 1H), 4.82 (d, J = 3.2 Hz, 1H), 4.81 (d, J = 3.6 Hz, 1H), 2.29 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 152.0, 130.7, 129.7, 127.2, 124.9, 122.4, 122.2, 115.6, 65.6, 20.7.

Table 2.3, entry 14 (OAW0528-1, OAW0530-1)

8-Methoxy-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83-6.77 (m, 2H), 6.64 (dd, J = 6.0, 2.4 Hz, 1H), 6.32 (d, J = 9.6 Hz, 1H), 5.63 (d, J = 9.6 Hz, 1H), 3.87 (s, 3H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.0, 131.0, 122.5, 122.2, 120.4, 119.0, 112.4, 70.5, 56.4, 28.0.

Table 2.3, entry 15 (OAW0414)

8-Methyl-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 7.2 Hz, 1H), 6.85 (dd, J = 7.2, 1.6 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.33 (d, J = 9.6 Hz, 1H), 5.62 (d, J = 9.6 Hz, 1H), 2.21 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 130.6, 125.7, 124.1, 122.8, 120.9, 120.2, 76.1, 28.2, 15.7.

Table 2.3, entry 16 (OAW0528-2, OAW0523-2)

8-Fluoro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97-6.91 (m, 1H), 6.80-6.76 (m, 2H), 6.35 (dd, J = 10.0, 1.6 Hz, 1H), 5.68 (d, J = 9.6 Hz, 1H), 1.50 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 150.3, 140.8, 140.6, 131.7, 123.7, 122.0, 121.6, 120.4, 120.3, 116.2, 116.1, 77.0, 28.1.

Table 2.3, entry 17 (OAW0347)

8-Chloro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 10.8, 2.4 Hz, 1H), 6.88 (dd, J = 9.6, 1.6 Hz, 1H), 6.77 (t, J = 10.0 Hz, 1H), 6.32 (d, J = 13.2 Hz, 1H), 5.67 (d, J = 13.2 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 131.6, 129.7, 124.8, 122.9, 122.1, 121.5, 121.1, 77.6, 28.2.

Table 2.3, entry 18 (OAW0350)

8-Bromo-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.4, 1.6 Hz, 1H), 6.92 (dd, J = 7.6, 1.6 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 6.30 (d, J = 9.6 Hz, 1H), 5.66 (d, J = 10.0 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 132.6, 131.7, 125.5, 123.0, 122.2, 121.7, 110.7, 77.7, 28.2.

Table 2.3, entry 19 (OAW0406)

8-Cyano-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 7.6, 1.2 Hz, 1H), 7.13 (dd, J = 7.2, 1.6 Hz, 1H), 6.85 (t, J = 7.2 Hz, 1H), 6.29 (d, J = 10.0 Hz, 1H), 5.70 (d, J = 10.0 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 132.2, 132.2, 130.5, 122.0, 120.9, 120.8, 116.4, 100.5, 78.7, 28.4.

Table 2.3, entry 20 (OAW0348)

8-Nitro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.0, 1.6 Hz, 1H), 7.17 (dd, J = 7.6, 1.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.36 (d, J = 10.0 Hz, 1H), 5.77 (d, J = 10.0 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 138.9, 132.5, 130.7, 124.8, 124.0, 121.4, 120.0, 78.7, 28.2.

Table 2.3, entry 23 (OAW0407)

5,7-Dichloro-2,2-dimethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 2.0, 0.8 Hz, 1H), 6.64 (d, J = 10.0 Hz, 1H), 5.72 (d, J = 10.4 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 133.9, 132.0, 131.7, 121.6, 118.4, 118.3, 115.9, 77.2, 28.0.

Table 2.3, entry 24[16]

6-Chloro-2,2,5,7-tetramethylchromene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.52 (d, J = 10.4 Hz, 1H), 5.65 (d, J = 10.0 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 136.8, 131.7, 130.8, 126.8, 119.9, 119.2, 116.8, 75.4, 27.7, 21.4, 15.9.

General Procedure for the Aysmmetric Epoxidation of 2,2-Dimethylchromenes. (Table 2.3) To a mixture of olefin (0.4 mmol), Bu_4NHSO_4 (0.001 g, 0.003 mmol), and ketone **1-111c** (0.028 g, 0.08 mmol) was added DME/DMM (v/v 3:1) (6.0 mL). After the mixture was stirred at rt for 20 min, buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous Na_2EDTA, pH 9.3) (4.0 mL) was added. After being stirred at rt for 10 more min, the mixture was cooled by an ice bath (0 °C). Oxone (5.04 mL, 0.21 M in 4 x 10^{-4} M aqueous Na_2EDTA) and K_2CO_3 (5.04 mL, 0.84 M in 4 x 10^{-4} M aqueous Na_2EDTA) were added simultaneously and separately via syringe pump over the period of time indicated. The reaction was quenched by the addition of diethyl ether and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered,

[16] This substrate was synthesized by Dr. Yi Yuan.

concentrated, and purified by flash chromatography (silica gel was buffered with 1% NEt_3) to afford the corresponding epoxide.

Table 2.3, entry 1 (OAW 0645, OAW0511-1, OAW0624-1)

2,2-Dimethylchromene Oxide.[14d,17] Yellow solid; mp 27-29 °C; $[\alpha]^{20}_D$ = +28.0 (*c* 0.82, THF) (84% ee); IR (film): 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.25 (td, *J* = 7.6, 1.6 Hz, 1H), 6.94 (td, *J* = 7.2, 0.8 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.92 (d, *J* = 4.2 Hz, 1H), 3.51, (d, *J* = 4.2 Hz, 1H), 1.59 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 130.5, 129.8, 121.3, 120.1, 118.2, 73.2, 63.1, 51.2, 25.9, 22.8; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.20; H, 6.92.

Table 2.3, entry 2 (OAW0650-2, OAW0444-1, OAW0625-1)

6-Methoxy-2,2-dimethylchromene Oxide.[14d,18] White solid; mp 61-64 °C; $[\alpha]^{20}_D$ = +12.4 (*c* 0.66, $CHCl_3$) (90% ee); IR (film): 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 3.2 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.75 (dd, *J* = 8.8 Hz, 1H), 3.87 (d, *J* = 4.2 Hz, 1H), 3.79 (s, 3H), 3.48 (d, *J* = 4.2 Hz, 1H), 1.57, (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.4, 120.8, 118.9, 115.8, 114.9, 72.9, 63.0, 56.0, 51.3, 25.9, 22.5. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.89.

Table 2.3, entry 3 (OAW0650-3, OAW0508-1, OAW0624-2)

6-Methyl-2,2-dimethylchromene Oxide. White solid; mp 42-44 °C; $[\alpha]^{20}_D$ = +15.5 (*c* 0.73, $CHCl_3$) (92% ee); IR (film): 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* =

[17] Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827.

[18] Wang, Q.; She, X.; Ren, X.; Ma, J.; Pan, X. *Tetrahedron: Asymmetry* **2004**, *15*, 29.

2.0 Hz, 1H), 7.04 (dd, J = 8.0, 1.2 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.87 (d, J = 4.4 Hz, 1H), 3.48 (d, J = 4.4 Hz, 1H), 2.30 (s, 3H), 1.58 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 150.4, 131.0, 130.6, 130.2, 119.8, 118.0, 73.0, 63.1, 51.3, 25.9, 22.7, 20.7; HRMS calcd for $C_{12}H_{15}O_2$ (M+1) 191.1072, found 191.1072.

Table 2.3, entry 4 (OAW0540-1)

6-Ethyl-2,2-dimethylchromene Oxide. Yellow oil; $[\alpha]^{20}_D$ = +11.5 (*c* 0.89, $CHCl_3$) (90% ee); IR (film): 1499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.4, 2.4 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 3.89 (d, J = 4.4 Hz, 1H), 3.49 (d, J = 4.4 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 1.58 (s, 3H), 1.25, (s, 3H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 137.1, 129.8, 129.0, 119.8, 117.9, 73.0, 63.0, 51.3, 28.2, 25.9, 22.7, 16.0; HRMS calcd for $C_{13}H_{17}O_2$ (M+1) 205.1229, found 205.1225.

Table 2.3, entry 5 (OAW0535-2)

6-*n*-Propyl-2,2-dimethylchromene Oxide. Yellow oil; $[\alpha]^{20}_D$ = +11.3 (*c* 0.69, $CHCl_3$) (91% ee); IR (film): 1499, 1167 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 8.0, 2.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 3.88 (d, J = 4.4 Hz, 1H), 3.49 (d, J = 4.4 Hz, 1H), 2.53 (t, J = 7.6 Hz, 2H), 1.62 (sextet, J = 7.6 Hz, 2H), 1.58, (s, 3H), 1.25 (s, 3H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 135.5, 130.4, 129.6, 119.7, 117.9, 73.0, 63.0, 51.4, 37.3, 25.9, 24.9, 22.7, 13.9; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.94; H, 8.22.

Table 2.3, entry 6 (OAW0536-1)

6-*i*-Propyl-2,2-dimethylchromene Oxide.[19] White solid; mp 27-29 °C; $[\alpha]^{20}_D$ = +9.8 (*c* 0.99, $CHCl_3$) (90% ee); IR (film): 1498, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 3.90 (d, *J* = 4.2 Hz, 1H), 3.49 (d, *J* = 4.2 Hz, 1H), 2.86 (septet, *J* = 7.2 Hz, 1H), 1.58 (s, 3H), 1.26, (s, 3H), 1.23 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 141.8, 128.5, 127.6, 119.6, 117.9, 73.0, 63.1, 51.5, 33.5, 25.9, 24.4, 24.3, 22.8; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.88; H, 8.47.

Table 2.3, entry 7 (OAW0645-2, OAW0536-2, OAW0625-2)

6-*t*-Butyl-2,2-dimethylchromene Oxide. White solid; mp 41-45 °C; $[\alpha]^{20}_D$ = +11.2 (*c* 0.81, $CHCl_3$) (90% ee); IR (film): 2966, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.4 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 4.8 Hz, 1H), 3.50 (d, *J* = 4.4 Hz, 1H), 1.58 (s, 3H), 1.31 (s, 9H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 144.0, 127.4, 126.7, 119.2, 117.5, 73.0, 63.1, 51.6, 34.3, 31.7, 25.9, 22.9. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.38; H, 8.53.

Table 2.3, entry 8 (OAW0643-2, OAW0449-2, OAW0622-2)

6-Fluoro-2,2-dimethylchromene Oxide. White solid; mp 38-39 °C; $[\alpha]^{20}_D$ = -2.0 (*c* 0.97, $CHCl_3$) (89% ee); IR (film): 1494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.4, 3.2 Hz, 1H), 6.94 (td, *J* = 8.8, 3.2 Hz, 1H), 6.77 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.86 (d, *J* = 4.2 Hz, 1H), 3.49 (d, *J* = 4.2 Hz, 1H), 1.58, (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz,

[19] Burrell, G.; Cassidy, F.; Evans, J.M.; Lightowler, D.; Stemp, G. *J. Med. Chem.* **1990**, *33*, 3023.

$CDCl_3$) δ 158.4, 156.0, 148.7, 121.4, 119.33, 119.36, 117.1, 116.9, 116.2, 116.0, 73.3, 62.8, 50.8, 25.8, 22.5. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 67.69; H, 5.65.

Table 2.3, entry 9 (OAW0649-1, OAW0504, OAW0620-1)

6-Chloro-2,2-dimethylchromene Oxide.[14e] Yellow solid; mp 57-59 °C; $[\alpha]^{20}_D$ = +36.6 (*c* 0.95, $CHCl_3$) (93% ee); IR (film): 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.4 Hz, 1H), 7.20 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 4.2 Hz, 1H), 3.50 (d, *J* = 4.2 Hz, 1H), 1.58, (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 130.4, 129.4, 125.9, 121.8, 119.6, 73.6, 62.8, 50.6, 25.8, 22.7. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 63.00; H, 5.30.

Table 2.3, entry 10 (OAW0644-2, OAW0443-2, OAW0622-1)

6-Bromo-2,2-dimethylchromene Oxide. Yellow solid; mp 53-55 °C; $[\alpha]^{20}_D$ = +36.7 (*c* 1.06, $CHCl_3$) (91% ee); IR (film): 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 3.85 (d, *J* = 4.4 Hz, 1H), 3.50 (d, *J* = 4.4 Hz, 1H), 1.58, (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 133.3, 132.3, 122.3, 120.0, 113.0, 73.6, 62.8, 50.5, 25.8, 22.7; Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 52.13; H, 4.39.

Table 2.3, entry 11 (OAW0644-1, OAW0509-2, OAW0619-2)

6-Cyano-2,2-dimethylchromene Oxide.[14d,e] White solid; mp 100-101 °C; $[\alpha]^{20}_D$ = +68.3 (*c* 1.05, $CHCl_3$) (93% ee); IR (film): 2227, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 7.66 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.92 (d, J = 4.4 Hz, 1H), 3.55 (d, J = 4.4 Hz, 1H), 1.61, (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 134.7, 134.1, 121.3, 119.3, 119.0, 104.6, 74.9, 62.6, 50.1, 25.8, 23.3.

Table 2.3, entry 12 (OAW0649-2, OAW0447-1, OAW0620-2)

6-Nitro-2,2-dimethylchromene Oxide. Yellow solid; mp 86-88 °C; $[\alpha]^{20}_D$ = +141.9 (*c* 1.05, $CHCl_3$) (94% ee); IR (film): 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 1.6 Hz, 1H), 8.15 (dd, J = 4.8, 1.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.00 (d, J = 4.4 Hz, 1H), 3.57 (d, J = 4.4 Hz, 1H), 1.63, (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 141.6, 126.5, 126.0, 120.5, 118.7, 75.4, 62.3, 50.2, 25.7, 23.3. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33; O, 28.93. Found: C, 59.81; H, 5.13.

Table 2.3, entry 13 (OAW0849)

6-Methyl-2*H*-Chromene Oxide. White solid; mp 32-33 °C; $[\alpha]^{20}_D$ = +64.9 (*c* 0.54, $CHCl_3$) (90% ee); IR (film): 1501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 8.2, 1.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 4.54 (dd, J = 12.8, 1.0 Hz, 1H), 4.11 (d, J = 12.8 Hz, 1H), 3.88 (d, J = 4.4 Hz, 1H), 3.80 (dd, J = 4.4, 1.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 131.0, 130.9, 130.5, 120.3, 117.3, 62.9, 56.5, 49.6, 20.7. HRMS calcd for $C_{10}H_{11}O_2$ (M+1) 163.0759, found 163.0761.

Table 2.3, entry 14 (OAW0725-1, OAW0538-1, OAW0628-1)

8-Methoxy-2,2-dimethylchromene Oxide. Yellow solid; $[\alpha]^{20}_D$ = +23.5 (*c* 0.51, CHCl3) (82% ee); IR (film): 1493, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 5.2, 3.6, 1H), 6.89-6.87 (m, 2H), 3.89 (d, *J* = 4.6 Hz, 1H), 3.82 (s, 3H), 3.49 (d, *J* = 4.6 Hz, 1H), 1.65 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 141.8, 121.7, 121.0, 120.9, 113.4, 73.4, 63.0, 56.4, 51.0, 25.9, 22.6; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.60; H, 7.02.

Table 2.3, entry 15 (OAW0716-2, OAW0524-1, OAW0711-2)

8-Methyl-2,2-dimethylchromene Oxide. White solid; mp 37-38 °C; $[\alpha]^{20}_D$ = +12.0 (*c* 0.67, $CHCl_3$) (81% ee); IR (film): 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.12 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 3.91 (d, *J* = 4.6 Hz, 1H), 3.51 (d, *J* = 4.6 Hz, 1H), 2.17 (s, 3H), 1.61 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 131.8, 127.4, 120.7, 119.5, 73.1, 63.1, 51.5, 25.9, 22.9, 15.7. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.60.

Table 2.3, entry 16 (OAW0716-1, OAW0538-2, OAW0711-1)

8-Fluoro-2,2-dimethylchromene Oxide. Yellow oil; $[\alpha]^{20}_D$ = +13.1 (*c* 0.53, $CHCl_3$) (84% ee); IR (film): 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.08-7.03 (m, 1H), 6.85 (td, *J* = 7.6, 4.4 Hz, 1H), 3.93 (dd, *J* = 4.4, 1.6 Hz, 1H), 3.52 (d, *J* = 4.4 Hz, 1H), 1.64 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 150.9, 140.6, 140.5, 124.9, 124.8, 122.7, 120.9, 120.8, 117.4, 117.2, 74.0, 62.8, 50.6, 25.6, 22.7; Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 68.15; H, 5.90.

Table 2.3, entry 17 (OAW0715-1, OAW0450-2, OAW0710-1)

8-Chloro-2,2-dimethylchromene Oxide. Yellow solid; mp 42-44 °C; $[\alpha]^{20}_D$ = +30.8 (*c* 0.57, $CHCl_3$) (83% ee); IR (film): 1459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 3.91 (d, *J* = 4.4 Hz, 1H), 3.52 (d, *J* = 4.4 Hz, 1H), 1.65 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 131.0, 128.2, 123.1, 121.9, 121.4, 74.4, 62.8, 50.9, 25.7, 22.9; Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.90; H, 5.28.

Table 2.3, entry 18 (OAW0715-2, OAW0539-2, OAW0710-2)

8-Bromo-2,2-dimethylchromene Oxide. Yellow oil; $[\alpha]^{20}_D$ = +45.3 (*c* 0.57, $CHCl_3$) (82% ee); IR (film): 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.82 (dd, *J* = 8.0, 7.6 Hz, 1H), 3.90 (d, *J* = 4.4 Hz, 1H), 3.52 (d, *J* = 4.4 Hz, 1H), 1.66 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.0, 129.0, 122.0, 121.8, 112.5, 74.6, 62.9, 51.0, 25.7, 22.9; Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 51.54; H, 4.39.

Table 2.3, entry 19 (OAW0643-1, OAW0523-2, OAW0623-1)

8-Cyano-2,2-dimethylchromene Oxide. Yellow solid; mp 86-88 °C; $[\alpha]^{20}_D$ = +88.7 (*c* 0.71, $CHCl_3$) (88% ee); IR (film): 2229, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.00 (dd, *J* = 8.0, 7.6 Hz, 1H), 3.93 (d, *J* = 4.4 Hz, 1H), 3.56 (d, *J* = 4.4 Hz, 1H), 1.64 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 134.3, 134.0, 121.4, 121.2, 115.9, 102.5, 75.6, 62.4, 50.1, 25.5, 23.1. HRMS calcd for $C_{12}H_{12}NO_2$ (M+1) 202.0868, found 202.0867.

Table 2.3, entry 20 (OAW0726-1, OAW0543-1, OAW0623-2)

8-Nitro-2,2-dimethylchromene Oxide. Yellow solid; mp 79-86 °C; $[\alpha]^{20}_D$ = +41.1 (*c* 0.68, $CHCl_3$) (84% ee); IR (film): 1537, 1371 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (dd, *J* = 11.2, 1.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 3.99 (d, *J* = 4.4 Hz, 1H), 3.58 (d, *J* = 4.0 Hz, 1H), 1.65 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 140.1, 134.3, 126.1, 123.3, 120.5, 75.7, 62.2, 50.4, 25.5, 23.0. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01. Found: C, 59.90; H, 4.91.

Table 2.3, entry 21 (OAW0529-3)

5-Chloro-2,2-dimethylchromene Oxide. Clear oil; $[\alpha]^{20}_D$: +14.3 (c 0.63, $CHCl_3$) (85%ee); IR (film): 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.42 (d, *J* = 4.4 Hz, 1H), 3.52 (d, *J* = 4.4 Hz, 1H), 1.58 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 135.0, 130.4, 122.3, 118.2, 117.0, 73.4, 62.7, 48.0, 25.7, 22.8. HRMS calcd for $C_{11}H_{11}ClO_2$ (M+1) 211.0526, found 211.0522.

Table 2.3, entry 22 (OAW0529-3)

7-Chloro-2,2-dimethylchromene Oxide. White solid; mp 60-62 °C; $[\alpha]^{20}_D$: +30.0 (*c* 0.54, $CHCl_3$) (91% ee); IR (film): 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 3.89 (d, *J* = 4.0 Hz, 1H), 3.50 (d, *J* = 4.4 Hz, 1H), 1.58 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 135.8, 130.6, 121.5, 118.8, 118.6, 73.9, 62.7, 50.6, 25.7, 22.9. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.89; H, 5.44.

Table 2.3, entry 23 (OAW0520-1)

5,7-Dichloro-2,2-dimethylchromene Oxide. White solid; mp 76-78 °C; $[\alpha]^{20}_D$ = +42.2 (*c* 0.46, $CHCl_3$) (88% ee); IR (film): 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 1.2 Hz, 1H), 6.76 (d, *J* = 1.6 Hz, 1H), 4.37 (d, *J* = 4.4 Hz, 1H), 3.51 (d, *J* = 4.4 Hz, 1H), 1.58 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 135.5, 122.4, 117.6, 116.9, 74.2, 62.4, 47.7, 25.6, 23.0. Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.11; found: C, 53.90; H, 4.04.

Table 2.3, entry 24 (OAW0514-1)

6-Chloro-2,2,5,7-tetramethylchromene Oxide. White solid; mp 62-64 °C; $[\alpha]^{20}_D$ = +38.1 (c 0.55, $CHCl_3$) (86% ee); IR (film): 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, s), 4.14 (d, *J* = 4.4 Hz, 1H), 3.47 (d, *J* = 4.4 Hz, 1H), 2.50 (3H, s), 2.31 (3H, s), 1.58 (s, 3H), 1.2[illegible] (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 138.2, 136.0, 127.3, 118.3, 117.1, 72.6, 62.5, 48.4, 25.7, 22.9, 21.3, 15.9, Anal. Calcd for $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33. Found: C, 65.19; H, 6.26.

CHAPTER THREE

ASYMMETRIC EPOXIDATION OF FLUOROOLEFINS — FLUORINE EFFECT ON ENANTIOSELECTIVITY

3.1. INTRODUCTION

Our earlier studies have shown that ketones **1-41** and **1-53** are highly effective for the epoxidation of trans- and trisubstituted olefins,[1,2] and ketones **1-111** are highly effective for the epoxidation of cis- and related olefins (Figure 3.1).[3] The electronic and steric properties of substituents on an olefin have an important impact on the enantioselectivity for the epoxidation. The epoxidation with ketones **1-41** and **1-53**

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[1] For leading references on ketone **1-41**, see: (a) Tu, Y.; Wang, Z-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

[2] Wu, X-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.

[3] For leading references on ketones **1-111**, see: (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. (d) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (e) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115. (f) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O.A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. (g) Wong, O.A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973. (h) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429. (i) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (j) Wang, B.; Shen, Y-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519. (k) Burke, C. P.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4475. (l) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093.

proceeds mainly via spiro transition state **A**, which is favored over spiro **B** due to the steric effect and favored over planar **C** due to the stabilizing secondary orbital interaction between the oxygen non-bonding orbital of the dioxirane and the π^* orbital of the olefin in the spiro transition state (Figure 3.2).[1,2,4] The stereodifferentiation for the epoxidation with ketones **1-111** likely results from electronic interactions.[3] It appears that there exists an attraction between the R_π substituent of the olefin and the oxazolidinone moiety of the catalyst (spiro **D** is favored over spiro **E**) (Figure 3.3).[3]

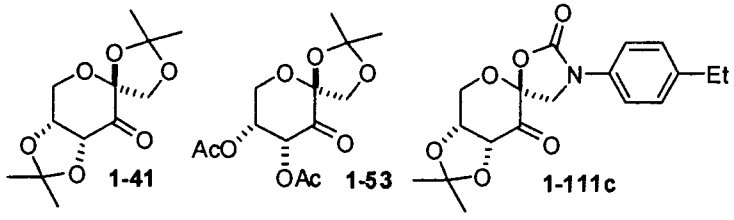


Figure 3.1

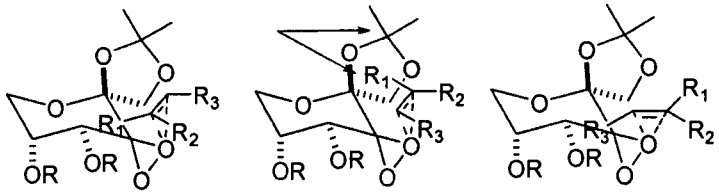


Figure 3.2

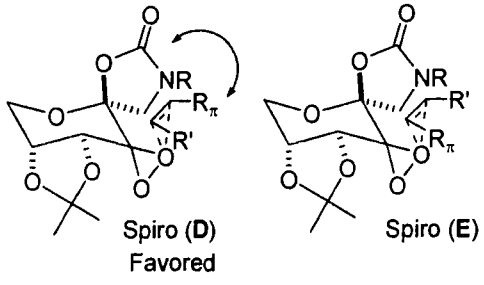


Figure 3.3

[4] For leading references on theoretic studies on transition states for the dioxirane epoxidation, see: (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. (e) Singleton, D.A.; Wang, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6679.

Fluorine has unique steric and electronic properties, and is widely used to alter the properties of organic molecules.[5,6] It is foreseeable that fluorinated olefins may display different steric and electronic properties for the epoxidation with chiral ketones as compared to their non-fluorinated counterparts. Moreover, fluorine atoms have been studied as cation-stabilizing auxiliary for the enhancement of polyene cyclizations.[7] In our case, it is possible that a fluorine atom on an alkene can both direct epoxidation and subsequent epoxide opening. The fluorine atom may stabilize a cation to favor 6-endo ring formation over 5-exo, which is normally favored, to form ladder polyethers as shown in Scheme 3.1.[8] With that in mind, we decided to investigate the asymmetric epoxidation of mono-fluorinated olefins using ketones **1-41**, **1-53**, and **1-111c** to explore the effect of fluorine on reactivity and enantioselectivity.[9,10,11,12,13]

---

[5] Chambers, R.D. *Fluorine in Organic Chemistry*; Blackwell Publishing: Boca Raton, 2004.

[6] Smart, B.E. In *Organofluorine Chemistry. Principles and Commercial Applications.* Banks, R.E., Smart, B.E., Tatlow, J.C. Ed.; Plenum Press: New York, 1994; Chapter 3.

[7] (a) Johnson, W.S.; Telfer, S.J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517. (b) Johnson, W.S.; Chenera, B.; Tham, F.S.; Kullnig, R.K. **1993**, *115*, 493. (c) Johnson, W.S.; Fletcher, V.R.; Chenera, B.; Bartlett, W.R.; Tham, F.S.; Kullnig, R.K. *J. Am. Chem. Soc.* **1993**, *115*, 497. (d) Johnson, W.S.; Buchanan, R.A.; Bartlett, W.R.; Tham, Kullnig, R.K. *J. Am. Chem. Soc.* **1993**, *115*, 504. (e) Johnson, W.S.; Plummer, M.S.; Reddy, S.P.; Bartlett, W.R. *J. Am. Chem. Soc.* **1993**, *115*, 515.

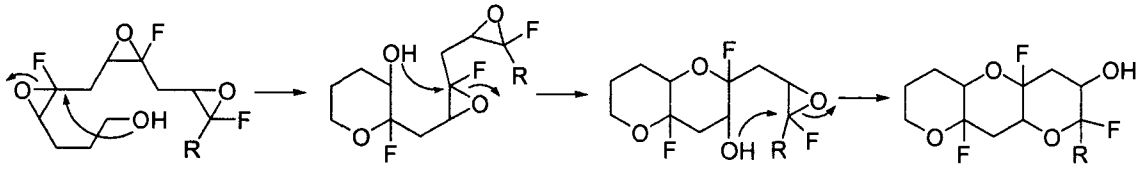
[8] Vilotijevic, I.; Jamison, T.F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250.

[9] For examples of asymmetric epoxidation of fluoroallylic alcohols and nucleophilic epoxide opening, see: (a) Dubuffet, T.; Bidon, C.; Sauvêtre, R.; Normant, J.-F. *J. Organomet. Chem.* **1990**, *393*, 173. (b) Gosmini, C.; Dubuffet, T.; Sauvêtre, R.; Normant, J.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 223. (c) Gosmini, C.; Sauvêtre, R.; Normant, J.F. *Bull. Soc. Chim. Fr.* **1993**, *130*, 236.

[10] For additional examples of asymmetric epoxidation of fluoroolefins, see: Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113.

[11] For examples of epoxidation of fluoroolefins, see: (a) Elkik, E.; Le Blanc, M. *Bull. Soc. Chim. Fr.* **1971**, *38*, 870. (b) Camps F.; Messeguer, A.; Sánchez F.-J. *Tetrahedron* **1988**, *44*, 5161. (c) Dubuffet, T.; Sauvêtre, R.; Normant, J.F. *Tetrahedron Lett.* **1988**, *29*, 5923. (d) Lluch, A.-M.; Sánchez-Baeza, F.; Messeguer, A.; Fusco, C.; Curci, R. *Tetrahedron* **1993**, *49*, 6299. (e) Kornilov, A.M.; Sorochinsky, A.E.;

Scheme 3.1 Polyfluoroepoxide Opening



3.2. RESULTS AND DISCUSSION

The syntheses of various fluoroolefins are outlined in Schemes 3.2 – 3.5. Fluoroolefins **3-1**, **3-2**, **3-5**, **3-6**, and **3-8** were synthesized by fluorobromination[14] followed by HBr elimination using DBU[15] or KO^{t}Bu[16] (Scheme 3.2). (*Z*)-Fluorostilbene (**3-3**) was synthesized by iodofluorination of *cis*-stilbene[17] followed by the elimination of HI with KO^{t}Bu (Scheme 3.3), and (*E*)-fluorostilbene (**3-4**) was synthesized via Suzuki coupling of phenyl boronic acid and the corresponding bromide[18] (Scheme 3.4). (1-

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Kukhar, V.P. *Tetrahedron: Asymmetry* **1994**, *5*, 1015. (f) Michel, D.; Schlosser, M. *Tetrahedron* **1996**, *52*, 2429. (g) Tranel, F.; Haufe, G. *J. Fluor. Chem.* **2004**, *125*, 1593.

[12] For examples of fluorinated epoxide synthesis by ring closure of halogenated alcohols, see: (a) Kirrmann, A.; Nouri-Bimorghi, R. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2328. (b) Duhamel, P.; Leblond, B.; Poirier, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 476. (c) Duhamel, P.; Leblond, B.; Bidois-Séry, L.; Poirier, J.-M. *J. Chem. Soc. Perkin Trans. I*, **1994**, 2265. (d) Shimizu, M.; Takebe, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* **1996**, *37*, 7387. (e) Hollenstein, H.; Luckhaus, D.; Pochert, J.; Quack, M.; Seyfang, G. *Angew. Chem.* **1997**, *109*, 136. (f) Shimizu, M.; Yamada, N.; Takebe, Y.; Hata, T.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2903.

[13] For an example of fluorinated epoxide synthesis by halogen substitution of chlorinated or brominated epoxides, see: Leroy, J.; Bensoam, J.; Humiliere, M.; Wakselman, C.; Mathey, F. *Tetrahedron* **1980**, *36*, 1931.

[14] Haufe, G.; Alvernhe, G.; Laurent, A.; Ernet, T.; Goj, O. *Org. Synth.* **1999**, *76*, 159.

[15] Wolkoff, P. *J. Org. Chem.*, **1982**, *47*, 1944.

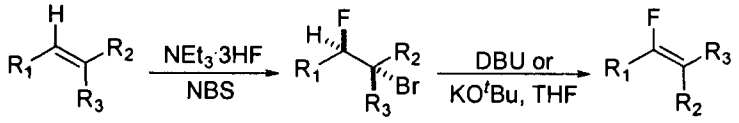
[16] Suga, H.; Hamatani, T.; Guggisberg, Y.; Schlosser, M. *Tetrahedron* **1990**, *46*, 4255.

[17] Olah, G.A.; Welch. J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J. *J. Org. Chem.* **1979**, *44*, 3872.

[18] (a) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 741. (b) Chen, C.; Wilcoxen, K.; Huang, C.Q.; Strack, N.; McCarthy, J.R. *J. Fluor. Chem.* **2000**, *101*, 285.

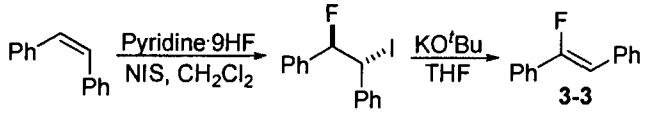
Fluoro-2-methylprop-1-enyl)benzene (**3-7**) was synthesized in three steps from diethylphosphite via the fluorination of diethyl-α-hydroxybenzylphosphonate with DAST (Scheme 3.5).[19]

Scheme 3.2 Synthesis of Fluoroolefins 3-1, 3-2, 3-5, 3-6, and 3-8



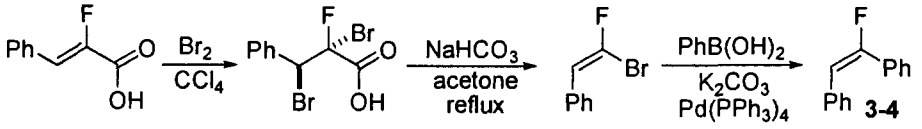
3-1, R_1=Ph, R_2=H, R_3=Me
3-2, R_1=Ph, R_2=Me, R_3=H
3-5, R_1=^{n}Bu, R_2=H, R_3=^{n}Bu
3-6, R_1=^{n}Bu, R_2=^{n}Bu, R_3=H
3-8, R_1=Ph, R_2=R_3=H

Scheme 3.3 Synthesis of Fluoroolefin 3-3



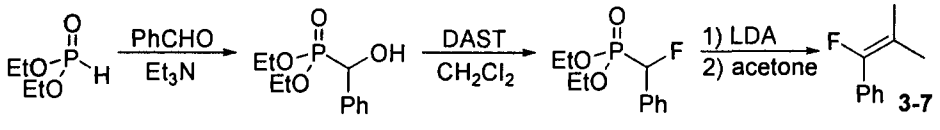
3-3

Scheme 3.4 Synthesis of Fluoroolefin 3-4



3-4

Scheme 3.5 Synthesis of Fluoroolefin 3-7



3-7

Solvent screening was carried out with olefin **3-6** and ketone **1-41** (Table 3.1). Among the solvents tested, MeCN:DMM (2:1 v/v) gave the best results (Table 3.1, entry 8). Using this solvent, the epoxidation of fluoroolefins **3-1** – **3-8** were carried

[19] (a) Taylor, W.P.; Zhang, Z.-Y.; Widlanski, T.S. *Bioorg. Med. Chem.* **1996**, *4*, 1515. (b) Tsai, H.-J.; Lin, K.-W.; Ting, T.-h.; Burton, D.J. *Helv. Chem. Acta.* **1999**, *82*, 2231.

out with 28-30 mol% ketones **1-41**, **1-53**, and **1-111c** at 0 °C for 8 h (Table 3.2). Good to high ee's (74-93%) were obtained for the epoxidation of olefins **3-1** and **3-2** with ketones **1-41** and **1-53** (Table 3.2, entries 1-2, 4-5). Modest ee (41%) was obtained for the epoxidation of olefin **3-2** with ketone **1-111c** (Table 1, entry 6) and the configuration of the resulting epoxide is opposite to that of epoxides resulting from ketones **1-41** and **1-53**. The epoxidation of olefins **3-3** – **3-6** generally gave good to high ee's (65-91%) with ketones **1-41** and **1-53** (Table 3.2, entries 7-8, 10-11, 13-14, 16-17). However, the ee's obtained for these olefins with ketone **1-111c** are generally low (6-56% ee) (Table 3.2, entries 12, 15, 18) except in the case of olefin **3-3** (85% ee) (Table 3.2, entry 9). The ee's for the epoxidation of (1-fluoro-2-methylprop-1-enyl)benzene (**3-7**) and α-fluorostyrene (**3-8**) are generally modest (27-62% ee) as these are not effective substrates for the ketones tested (Table 3.2, entries 19-24).[20]

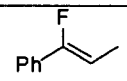
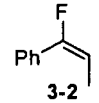
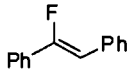
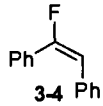
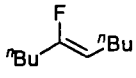
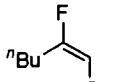
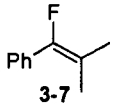
Table 3.1 Solvent Screening for the Asymmetric Epoxidation of Fluoroolefin 3-6[a]

entry	solvent	conv.[b] (%)	ee[b] (%)
1	MeCN	32	74
2	DME	17	80
3	Dioxane	30	79
4	DMF	6	75
5	THF	16	75
6	MeCN:DMM (1:1)	30	77
7	MeCN:DMM (1:2)	40	79
8	**MeCN:DMM (2:1)**	**51**	**78**
9	DME:DMM (3:1)	20	81
10	MeCN:DMM (3:1)	38	76
11	MeCN:DMM (4:1)	34	75
12	MeCN:DMM (1:4)	32	82
13	MeCN:DMM (1:3)	34	82
14	MeCN:DMM:DME (1:1:1)	47	79

[20] The fluoroepoxides are reasonably stable except the epoxide from olefin **3-4**, which readily decomposes on silica gel. The epoxides from olefins **3-1**, **3-2**, and **3-8** are extremely volatile.

[a] All reactions are carried out with olefin (0.20 mmol), ketone **1-41** (0.04 mmol), Oxone (0.28 mmol), K_2CO_3 (1.16 mmol), and Bu_4NHSO_4 (0.012 mmol) in organic solvent and buffer at 0 °C (bath temperature) for 3.5 h. Notebook page: OAW1048. [b] The conversion and ee were determined by chiral GC (Chiraldex B-DM).

Table 3.2 Asymmetric Epoxidation of Fluoroolefins with Ketones 1-41, 1-53, and 1-111c[a]

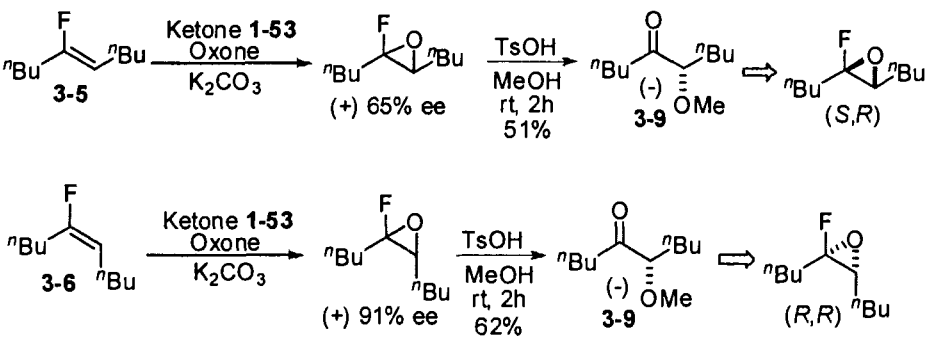
entry	substrate	ketone	yield[b] (%)	ee[c] (%)	config.[d]
1	 **3-1**	**1-41**	70	93	(+)
2		**1-53**	60	90	(+)
3		**1-111c**	71	30	(+)
4	 **3-2**	**1-41**	63	74	(-)-(*R,R*)
5		**1-53**	68	92	(-)-(*R,R*)
6		**1-111c**	67	41	(+)-(*S,S*)
7	 **3-3**	**1-41**	39	91	(+)
8		**1-53**	67	85	(+)
9		**1-111c**	88	85	(+)
10	 **3-4**	**1-41**	56	83	(-)
11		**1-53**	86	91	(-)
12		**1-111c**	60	56	(-)
13	 **3-5**	**1-41**	83	77	(+)
14		**1-53**	83	65	(+)
15		**1-111c**	71	46	(+)
16	 **3-6**	**1-41**	83	80	(+)-(*R,R*)
17		**1-53**	77	91	(+)-(*R,R*)
18		**1-111c**	80	6	(+)-(*R,R*)
19	 **3-7**	**1-41**	42	43	(+)
20		**1-53**	70	33	(+)
21		**1-111c**	79	62	(+)
22	 **3-8**	**1-41**	64	27	(-)
23		**1-53**	75	39	(-)
24		**1-111c**	68	32	(+)

[a] All reactions are carried out with olefin (0.20 mmol), ketone (0.06 mmol), Oxone (0.28 mmol), K_2CO_3 (1.16 mmol), and Bu_4NHSO_4 (0.012 mmol) in MeCN:DMM (2:1 v/v) and buffer at 0 °C (bath temperature) for 8 h. [b] Isolated yield. [c] The ee's were determined by chiral GC (Chiraldex B-DM), except for entries 16-18 which

were determined by chiral HPLC (Chiralcel OD). [d] The absolute configurations of entries 7-9, 19-21 were determined using the VCD spectra by BioTools.

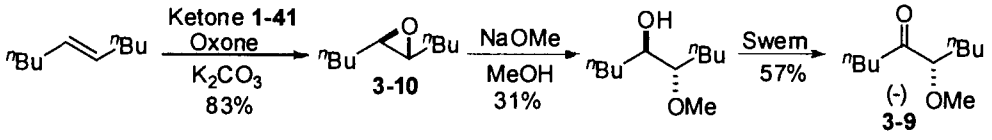
In order to determine the absolute configuration of the fluorinated epoxides, the epoxides obtained from olefins **3-5** and **3-6** with ketone **1-53** (Table 3.2, entries 14 and 17) were treated with anhydrous TsOH-MeOH at rt for 2 h, giving (-)-(*S*)-6-methoxydecan-5-one (**3-9**) in both cases (Scheme 3.6).[1] The absolute configuration of 6-methoxydecan-5-one was determined by comparing the absolute configuration of the methoxyketone synthesized from the epoxide (**3-10**) with known configuration (Scheme 3.7).[Error! Bookmark not defined.c] When the deuterated (*E*)-5-fluorodec-5-ene oxide (**3-11**) was treated with anhydrous TsOH-MeOH at rt for 2 h, deuterated 6-methoxydecan-5-one (**3-12**) was obtained, suggesting that MeOH attacks on the non-fluorinated carbon to form the corresponding ketone (Scheme 3.8). The absolute configuration determined by the above reaction sequence confirmed the absolute configuration obtained with the VCD data from BioTools (Table 3.2, entry 17).

Scheme 3.6 Absolute Configuration Determination by Epoxide Opening

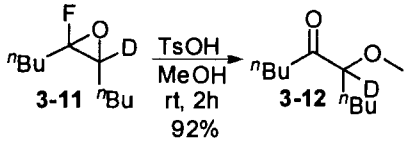


[1] The determination of the ee of compound **3-9** was attempted, but with no success.

Scheme 3.7 Synthesis of (*S*)-6-Methoxydecan-5-one (3-9)

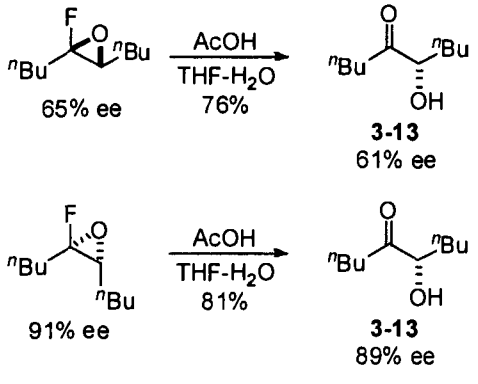


Scheme 3.8 Ring Opening of Deuterated Epoxide 3-11



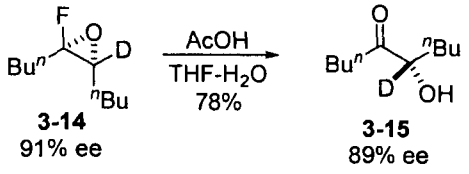
When the epoxide obtained from olefins **3-5** and **3-6** were treated with acetic acid in THF-H_2O at 60 °C for 20 h, (*S*)-6-hydroxydecan-5-one (**3-13**) was obtained with only a slight loss of ee (Scheme 3.9).[2] When deuterated epoxide **3-14** was subjected to the same conditions (acetic acid in THF-H_2O at 60 °C for 20 h), (*S*)-deuterated-6-hydroxydecan-5-one (**3-15**) was obtained in 89% ee, which further supports that nucleophilic attack occurs on the non-fluorinated carbon (Scheme 3.10).

Scheme 3.9 Epoxide Opening with AcOH



[2] The absolute configuration of 6-hydroxydecan-5-one is reported in Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115.

Scheme 3.10 Epoxide Opening with AcOH



High enantioselectivities were obtained for *Z*-olefins **3-1** and **3-3** with ketones **1-41** and **1-53** (Table 3.2, entries 1-2, 7-8), suggesting that spiro **F** is favored over spiro **G** due to steric interaction between the phenyl ring on the olefin and the spiro ketal group of the catalyst (Figure 3.4). Lower ee's obtained for *E*-olefins **3-2** and **3-4** with ketone **1-41** as compared to that of olefins **3-1** and **3-3** (Table 3.2, entry 4 vs 1 and 10 vs 7) indicates that fluorine is not as effective in disfavoring spiro **I** as phenyl group in disfavoring spiro **G** (Figures 3.4 and 3.5, R = CMe_2). Higher ee's obtained for the epoxidation of olefins **3-2** and **3-4** with ketone **1-53** compared to that of ketone **1-41** (Table 3.2, entry 5 vs 4 and 11 vs 10) could be due to additional beneficial interactions between the F and/or Ph group of the olefin and the acetate group of the catalyst in transition state spiro **H** (R = Ac), thus increasing the ee's (Figure 3.5).[Error! Bookmark not defined.b]

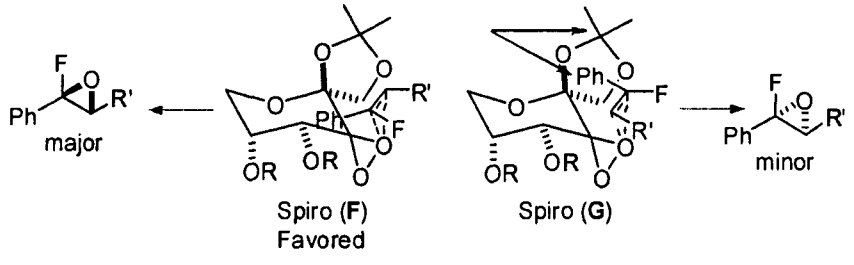


Figure 3.4 Proposed transition states for the epoxidation of olefins **3-1** and **3-3** with ketones **1-41** and **1-53**

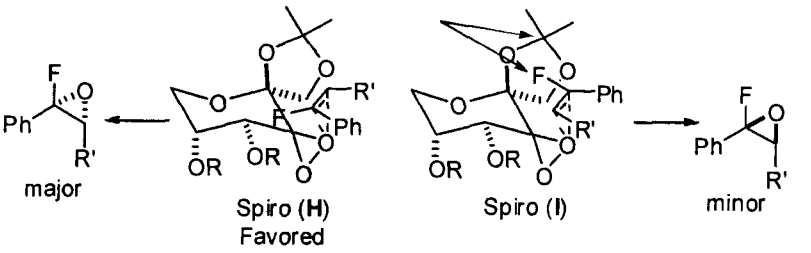


Figure 3.5 Proposed transition states for the epoxidation of olefins **3-2** and **3-4** with ketones **1-41** and **1-53**

Higher ee's obtained for the epoxidation of olefin **3-6** than that of olefin **3-5** with ketones **1-41** and **1-53** suggests that the fluorine atom may be more effective in disfavoring spiro **M** than the *n*-butyl group is in disfavoring spiro **K** (Figure 3.6). High ee (91%) obtained for olefin **3-6** with ketone **1-53** again suggests that there may be beneficial interactions between the fluorine of the olefin and the OAc group of the catalyst in transition state spiro **L** (R = Ac) as in the case of spiro **H** (Figure 3.5), thus increasing the ee.

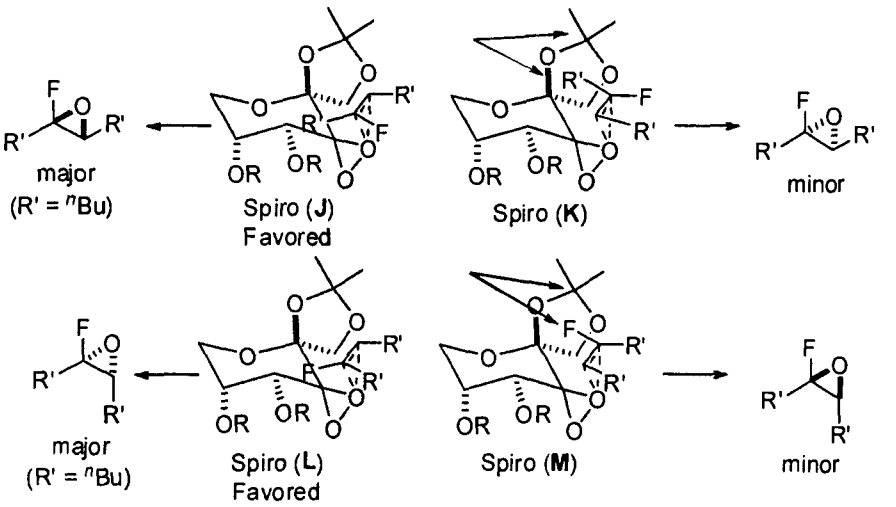


Figure 3.6 Proposed transition state for the epoxidation of olefins **3-5** and **3-6** with ketones **1-41** and **1-53**.

Lower ee obtained for the epoxidation of olefin **3-5** with ketone **1-41** (Table 3.2, entry 13) as compared to its non-fluorinated counterpart (77% ee for **3-5** vs 91% ee

(*E*)-dec-5-ene with ketone **1-41**[1c]) could be due to the fact that the lone pair of the fluorine substituent raises the π^* orbital of the olefin causing the weakening of the secondary orbital interaction between the π^* orbital of the olefin and the non-bonding orbital of the dioxirane in spiro **J**, thus leading to more competition from planar **C**-like transition state and decreasing the ee.

The fluorine atom did not show a beneficial effect on the epoxidation with ketone **1-111c**. In fact, in most cases, lower ee's were obtained for fluorinated olefins than non-fluorinated olefins (Table 3.2).[3] For example, only 41% and 32% ee were obtained, respectively, for olefins **3-2** and **3-8** with ketone **1-111c** (Table 3.2, entries 6 and 24). Compared to spiro **D** (Figure 3.3), spiro **N** (Figure 3.7) is disfavored by the fluorine possibly via steric[23] and/or electronic repulsion.

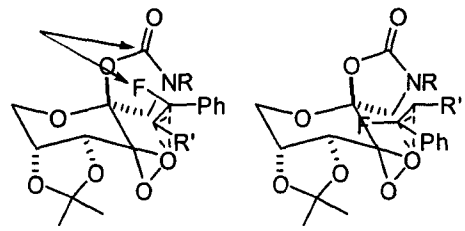


Figure 3.7 Proposed transition state for the epoxidation of olefins **3-2** and **3-8** with ketone **1-111c**.

3.3. CONCLUSIONS

In conclusion, a series of fluoroolefins were epoxidized with ketones **1-41**, **1-53**, and **1-111c**, and up to 93% ee was obtained. In some cases, the fluorine can act as an effective directing group via its steric and/or electronic interactions with ketone catalysts. In other cases, however, the fluorine is detrimental to the enantioselectivity

[23] The van der Waals' radii of fluorine is larger than hydrogen (1.47 Å vs 1.20 Å) (see ref. 6)

for the epoxidation. It was found that the epoxide opening occurs on the non-fluorinated carbon under the conditions studied. The proposal of synthesizing ladder polyethers using polyfluoroepoxides may not be viable, however, these epoxidation results provide us better understanding of the effect of the olefin substituent on the chiral ketone-catalyzed epoxidation.

3.4. EXPERIMENTAL

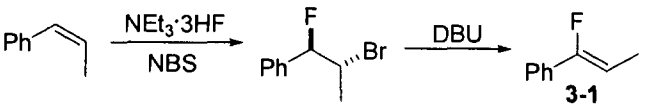
Representative asymmetric epoxidation procedure with ketone 1-41 (Table 3.2, entry 16). (OAW2333-1). To a solution of olefin **3-6** (0.20 mmol, 0.032 g), ketone **1-41** (0.06 mmol, 0.015 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN:DMM (2:1, v/v) (3.0 mL) was added buffer (0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M aq Na_2EDTA, pH 9.3) (2.0 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.27 mmol, 0.21 M in 4 x 10^{-4} M aq Na_2EDTA, 1.30 mL) and a solution of K_2CO_3 (1.16 mmol, 0.89 M in 4 x 10^{-4} M aq EDTA, 1.30 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane-Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.029 g, 83% yield, 80% ee).

Representative asymmetric epoxidation procedure with ketone 1-53 (Table 3.2, entry 17). (OAW1105). To a solution of olefin **3-6** (0.20 mmol, 0.032 g), **1-53·H_2O** (0.056 mmol, 0.018 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN:DMM (2:1, v/v)

(3.6 mL) was added buffer (0.05 M aq Na_2HPO_4-0.05 M aq KH_2PO_4, pH 7.0) (1.2 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.40 mmol, 0.21 M in 4 x 10^{-4} M aq EDTA, 1.92 mL) and a solution of K_2CO_3 (0.81 mmol, 0.42 M in 4 x 10^{-4} M aq EDTA, 1.92 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane-Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.027 g, 77% yield, 91% ee).

Representative asymmetric epoxidation procedure with ketone 1-111c (Table 3.2, entry 18). (OAW2347). To a solution of olefin **3-6** (0.20 mmol, 0.032 g), ketone **1-111c** (0.06 mmol, 0.021 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN:DMM (2:1, v/v) (3.0 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aq Na_2EDTA, pH 9.3) (2.0 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.53 mmol, 0.21 M in 4 x 10^{-4} M aq EDTA, 2.52 mL) and a solution of K_2CO_3 (2.12 mmol, 0.84 M in 4 x 10^{-4} M aq EDTA, 2.52 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane-Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.028 g, 80% yield, 6% ee).

Synthesis and characterization of olefins 3-1 – 3-8 and (*E*)-5-fluoro-6-deutero-dec-5-ene



3-1

(*Z*)-α-Fluoro-β-methylstyrene (3-1) (OAW0940).[24,25] To a solution of *cis*-β-methyl styrene (2.95 g, 25.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added NEt_3·3HF (6.05 g, 6.11 mL, 37.5 mmol), followed by *N*-bromosuccinimide (4.89 g, 27.5 mmol). Upon stirring at 0 °C for 15 min then at rt overnight, the reaction mixture was poured into slightly basic ice water adjusted with NH_4OH, extracted with CH_2Cl_2 eight times, washed with 1N HCl then 1N $NaHCO_3$, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give the bromofluoride as a colorless oil (4.58 g, 84 % yield).[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.34 (m, 5H), 5.41 (dd, J = 45.9, 6.9 Hz, 1H), 4.42-4.28 (m, 1H), 1.60 (d, J = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.4, 129.2, 128.7, 128.5, 126.6, 126.5, 97.9, 95.5, 50.6, 50.3, 21.92, 21.89.

(OAW0942) To the above bromofluoride (4.58 g, 21.1 mmol) was added DBU (3.21 g, 3.16 mL, 21.1 mmol) at rt. The reaction mixture was heated at ~85 °C for 30 min. The resulting solid was partitioned between water and pentane. Pentane was distilled off at normal pressure and then the product was distilled off at 43 mmHg (bp 96 °C) as a colorless oil (1.54 g, 54 % yield).[26] IR (film): 1683, 1280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.49 (m, 2H), 7.37-7.28 (m, 3H), 5.44 (dq, J = 37.2, 7.2 Hz, 1H), 1.82 (dd, J = 7.2, 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 156.3, 133.2, 132.9, 128.6,

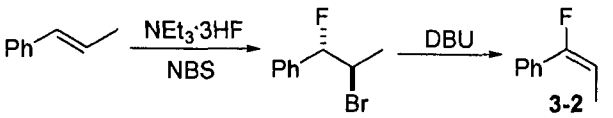
[24] Merritt, R.F. *J. Am. Chem. Soc.* **1967**, *89*, 609.

[25] Baklouti, A.; Chaabouni, M.M. *J. Fluor. Chem.* **1981**, *19*, 181.

[26] Wolkoff, P. *J. Org. Chem.*, **1982**, *47*, 1944.

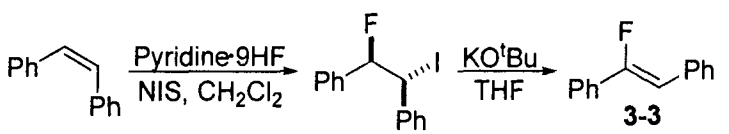
128.5, 124.0, 123.9, 100.9, 100.8, 9.7, 9.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –122.1 (d, J = 37.2 Hz).

(*E*)-α-Fluoro-β-methylstyrene (3-2).[24,25,27] Prepared from *trans*-β-methylstyrene using the same method as for olefin **3-1**.



(OAW0937) Bromofluoride (87% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.36 (m, 5H), 5.57 (dd, J = 46.0, 5.6 Hz, 1H), 4.40-4.29 (m, 1H), 1.74 (dd, J = 6.8, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.9, 129.2, 128.6, 126.53, 126.46, 97.3, 95.5, 49.8, 49.5, 20.4, 20.3.

(OAW0947) Olefin **3-2** (64% yield): Colorless oil; bp 92 °C (42 mmHg); IR (film): 1683, 1351 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.46-7.36 (m, 3H), 5.50 (dq, J = 22.8, 7.6 Hz, 1H), 1.83 (dd, J = 7.6, 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.0, 132.4, 132.1, 128.9, 128.4, 127.8, 127.7, 103.0, 102.7, 11.7, 11.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.5 (d, J = 22.6 Hz).

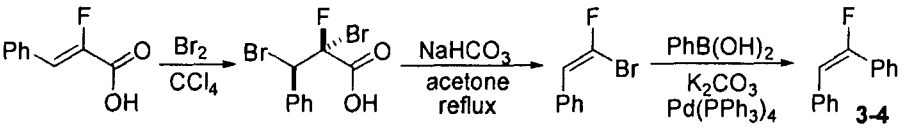


(*Z*)-Fluorostilbene (3-3) (OAW1020). To a solution of *cis*-stilbene (4.50 g, 25.0 mmol) in CH_2Cl_2 (25 mL) in a plastic bottle equipped with a septum at 0 °C was added

[27] Yoshino, H.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Flour. Chem.* **2004**, *125*, 455.

pyridine·9HF (6.50 mL, 27.5 mmol), followed by *N*-iodosuccinimide (8.50 g, 37.5 mmol). Upon stirring at 0 °C for 30 min then at rt overnight, the reaction mixture was poured into slightly basic ice water adjusted by NH_4OH, extracted with CH_2Cl_2 eight times, washed with 1N HCl, 1N $NaHCO_3$, and 1N $Na_2S_2O_3$, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes to hexanes:Et_2O = 10:1, v/v) to give the iodofluoride (3.25 g, 40% yield).[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.07 (m, 10H), 5.77-5.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 134.8, 134.6, 134.5, 129.7, 129.2, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.6, 127.1, 127.0, 126.9, 126.6, 125.9, 96.6, 96.3, 95.9, 95.5, 94.2, 93.9, 93.5, 93.1, 53.6, 51.6.

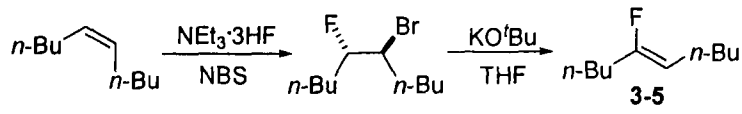
(OAW1022-2) To a solution of the above iodofluoride (3.25 g, 10.0 mmol) in THF (10 mL) was added KO^{t}Bu (2.68 g, 23.9 mmol) at 0 °C. Upon stirring at 0 °C for 5 h, the reaction mixture was filtered, concentrated, and purified by recrystallization from hexanes to give olefin **3-3** as a white solid (1.84 g, 93% yield).[16,28] mp 82-86 °C; IR (film): 1655, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.62 (m, 4H), 7.42-7.16 (m, 6H), 6.30 (d, J = 39.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 155.7, 133.9, 133.2, 132.9, 131.8, 129.2, 129.1, 128.8, 128.5, 127.8, 127.5, 126.7, 124.5, 124.4, 106.1, 106.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.6 (d, J = 39.5 Hz).



[28] Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.-i.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476.

(*E*)-Fluorostilbene (3-4) (OAW1329, OAW1330). To a solution of α-fluorocinnamic acid (3.40 g, 20.0 mmol) in CCl_4 (60 mL) was added Br_2 (1.20 mL, 22 mmol) dropwise at rt. The reaction mixture was refluxed for 5 h, then left to cool to rt, washed with saturated aqueous $Na_2S_2O_3$ and water, concentrated, and purified by recrystallization from CCl_4 to give the dibromoacid as white crystals (6.63 g, 20.3 mmol), which was dissolved in acetone (70 mL). Upon addition of $NaHCO_3$ (5.16 g, 61.4 mmol), the reaction mixture was refluxed for 6 h and concentrated. Water and Et_2O were added to the residue and the aqueous layer was extracted with Et_2O, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give the bromoolefin (3.28 g, 82% yield over two steps).[18a]

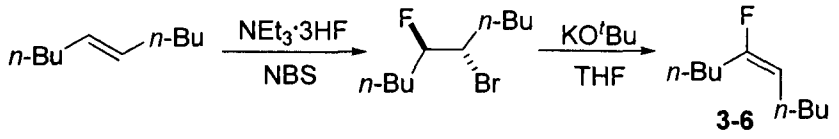
(OAW1335) To a solution of the above bromoolefin (2.01 g, 10.0 mmol), $PhB(OH)_2$ (1.50 g, 12.3 mmol), and K_2CO_3 (4.20 g, 30.0 mmol) in benzene:EtOH:H_2O (5:1:1, v/v/v) (210 mL) was added $Pd(PPh_3)_4$ (0.60 g, 0.52 mmol). The reaction mixture was heated at ~100 °C for 6 h, cooled, and poured into a separatory funnel. The aqueous layer was removed. The organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give olefin **7** as a colorless oil (1.96 g, 99% yield).[18b] IR (film): 1661, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (m, 2H), 7.26-7.18 (m, 3H), 7.15-7.07 (m, 5H), 6.37 (d, J = 21.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 156.8, 134.1, 133.9, 132.2, 131.9, 129.7, 129.0, 128.6, 128.51, 128.46, 127.3, 109.7, 109.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.5 (d, J = 21.8 Hz).



(*Z*)-5-fluorodec-5-ene (3-5) (OAW1006). To a solution of *cis*-5-decene (4.06 g, 29.0 mmol) in CH_2Cl_2 (29 mL) at 0 °C was added $NEt_3 \cdot 3HF$ (6.05 g, 6.11 mL, 37.8 mmol), followed by *N*-bromosuccinimide (4.89 g, 27.5 mmol). Upon stirring at 0 °C for 15 min then at rt overnight, the reaction mixture was poured into slightly basic ice water adjusted with NH_4OH, extracted with CH_2Cl_2 eight times, washed with 1N HCl, then 1N $NaHCO_3$, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give the bromofluoride as a colorless oil (5.41 g, 78 % yield).[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56-4.35 (m, 1H), 4.06-3.93 (m, 1H), 1.94-1.26 (m, 12 H), 0.93 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.7, 93.4, 57.3, 57.0, 34.5, 32.5, 32.3, 30.0, 27.5, 27.4, 22.6, 22.3, 14.1.

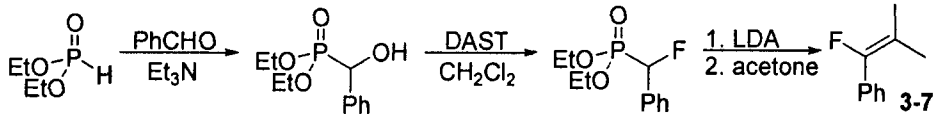
(OAW1008) To a suspension of KO^{t}Bu (5.83 g, 51.9 mmol) in THF (22 mL) at 0 °C was added the above bromofluoride (5.17 g, 21.6 mmol). The reaction mixture was stirred at 0 °C for 5 h, partitioned between water and hexanes, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give olefin **3-5** as a colorless oil (2.53 g, 74 % yield).[16] IR (film): 1707, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (dt, J = 38.4, 7.2 Hz, 1H), 2.14 (dt, J = 17.2, 7.2 Hz, 2H), 2.08-2.03 (m, 2 H), 1.51-1.43 (m, 2H), 1.39-1.28 (m, 6H), 0.95-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 158.6, 105.1, 105.0, 32.05, 32.01, 31.8, 28.7, 23.42, 23.36, 22.4, 22.2, 14.1, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –110.7 (dt, J = 38.4, 16.9 Hz).

(*E*)-5-fluorodec-5-ene (3-6): Prepared from *trans*-5-decene using the same method as for olefin **3-5**.



(OAW0949) Bromofluoride (86% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62-4.40 (m, 1H), 4.07-3.97 (m, 1H), 2.04-1.22 (m, 12 H), 0.93 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.5, 94.2, 57.0, 56.8, 33.6, 33.5, 32.4, 32.1, 29.7, 27.33, 27.28, 22.7, 22.3, 14.1.

(OAW1009) Olefin **3-6** (80% yield): Colorless oil; IR (film): 1701, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dt, J = 22.8, 8.4 Hz, 1H), 2.22 (dt, J = 23.2, 7.6 Hz, 2H), 1.95-1.90 (m, 2 H), 1.55-1.46 (m, 2H), 1.40-1.28 (m, 6H), 0.95-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 159.1, 105.8, 105.6, 32.5, 28.8, 28.0, 27.7, 25.4, 25.3, 22.4, 22.3, 14.11, 14.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.8 (q, J = 23.0).

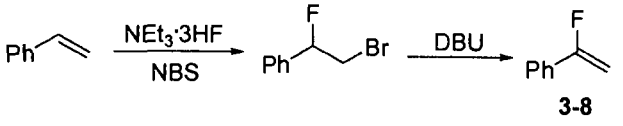


(1-Fluoro-2-methylprop-1-enyl)benzene (3-7) (OAW1331). To a mixture of diethyl phosphite (15.19 g, 14.20 mL, 110.0 mmol) and distilled benzaldehyde (10.60 g, 10.20 mL, 100.0 mmol) was added triethyl amine (22.26 g, 30.66 mL, 220.0 mmol) at rt. Upon stirring at rt overnight (white precipitate appeared in the reaction flask after 2 h), the reaction mixture was filtered to give a white solid, which was washed with cold Et_2O, then dried under high vacuum, and recrystallized from hot Et_2O to give the hydroxybenzylphosphonate as white needles (21.05 g, 86% yield).[19a]

(OAW1336) To a solution of diethylaminosulfur trifluoride (5.66 g, 4.64 mL, 35.1 mmol) in CH_2Cl_2 (35 mL) was added a solution of the above hydroxybenzylphosphonate (7.20 g, 30.0 mmol) in CH_2Cl_2 (75 mL) *via* syringe pump at -78 °C over 2 h. Upon warming to rt and stirring at rt for 2 h, the reaction mixture was poured into a solution of pyridine (10 mL) in EtOH (240 mL) and stirred for 1 h, then poured into ice water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with 1N HCl and H_2O, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes:Et_2O = 1:4, v/v) to give the fluoride as a pale yellow oil (6.13 g, 83% yield).

(OAW1339) To a solution of the above fluoride (6.10 g, 24.8 mmol) in THF (50 mL) was added freshly prepared LDA (diisopropylamine: 4.50 mL, 32.2 mmol; *n*-BuLi: 20 mL, 1.6 M in hexanes; THF: 30 mL) at –78 °C. The dark reaction mixture was stirred at –78 °C for 30 min, at which point acetone (1.80 g, 2.30 mL, 31.0 mmol) was added and the reaction stirred at –78 °C for an additional 30 min. Upon warming to rt slowly and stirring at rt overnight, the reaction mixture was then poured into H_2O and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with 1N HCl, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes) to give olefin **3-7** as a colorless oil (2.59 g, 70% yield).[19b] IR (film): 1693, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.43-7.39 (m, 2H), 7.37-7.34 (m, 1H), 1.90 (d, J = 3.6 Hz, 3H), 1.83 (d, J = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.0, 133.5, 133.2, 128.44, 128.39, 128.2, 111.2, 111.0, 19.00, 18.97, 17.0, 16.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.2 (s).

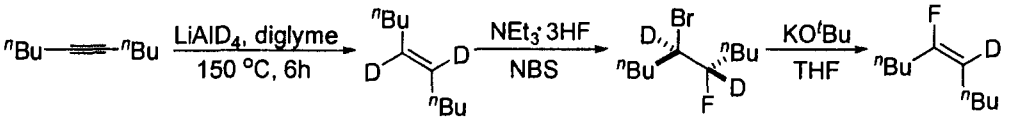
α-Fluorostyrene (3-8).[29] Prepared from styrene using the same method as for olefin **3-1**.



3-8

(OAW0943) Bromofluoride (86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.37 (m, 5H), 5.65 (ddd, J = 46.8, 7.6, 4.0 Hz, 1H), 3.75-3.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 137.2, 129.5, 128.9, 125.95, 125.89, 93.9, 92.1, 34.7, 34.4.

(OAW0944) Olefin **3-8** (48% yield): Colorless oil; bp 65 °C (42 mmHg); IR (film): 1650, 1277 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.44-7.36 (m, 3H), 5.06 (dd, J = 49.5, 3.3 Hz, 1H), 4.87 (dd, J = 18.0, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 161.5, 132.4, 132.0, 129.6, 128.7, 124.8, 124.7, 89.9, 89.6; ^{19}F (376 MHz, $CDCl_3$) δ –108.4 (dd, J = 49.3, 17.7 Hz).



(*E*)-5-fluoro-6-deutero-dec-5-ene (OAW2426).[30] A round-bottom flask equipped with a reflux condenser is charged with a slurry of $LiAlD_4$ (2.50 g, 59.6 mmol) in diglyme (50.0 mL). Upon addition of 5-decyne (9.02 mL, 6.91 g, 50.0 mmol), the reaction

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[29] Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004**, *60*, 7731.

[30] (a) Kroll, J.H.; Donahue, N.M.; Cee, V.J.; Demerjian, K.L.; Anderson, J.G. *J. Am. Chem. Soc.* **2002**, *124*, 8518. (b) Coseri, S.; Mendenhall, G.D.; Ingold, K.U. *J. Org. Chem.* **2005**, *70*, 4629.

mixture was heated at 150 °C for 6 h, cooled to rt, quenched by D_2O (10 mL), D_2O/DCl (20% w/w, 5 mL), HCl (6 N, 12.5 mL), then saturated aqueous NH_4Cl, stirred for 15 min, extracted with pentane, washed with water, dried over Na_2SO_4, and filtered to give the deuterated olefin as a colorless oil (5.35 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (t, J = 6.4 Hz, 4H), 1.36-1.29 (m, 8H), 0.93-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 130.1, 129.9, 32.4, 32.1, 24.5, 14.2.

(OAW2443) The bromofluoride was prepared as in the cases of olefins **3-5** and **3-6** (87% yield). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97-1.74 (m, 4H), 1.66-1.48 (m, 2H), 1.45-1.27 (m, 6H), 0.93 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.9, 95.7, 95.5, 94.2, 93.9, 93.7, 56.8, 56.5, 56.3, 56.1, 33.41, 33.36, 32.2, 32.0, 29.6, 27.3, 27.2, 22.7, 22.3, 14.1.

(OAW2449) The fluoroolefin was prepared as in the cases of olefins **3-5** and **3-6** (66% yield). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (dt, J = 23.2, 6.8 Hz, 2H), 1.92 (t, J = 6.4 Hz, 2H), 1.54-1.46 (m, 2H), 1.41-1.30 (m, 6H), 0.96-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 159.1, 105.7, 105.5, 105.3, 105.1, 32.5, 28.8 28.0, 27.7, 25.3, 25.2, 22.4, 22.3, 14.11, 14.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.2 (tt, J = 23.3, 3.0 Hz).

Characterization data of epoxides

Table 3.2, entries 1-3 (OAW2334-2, OAW1129-1, OAW2347-1)

***(Z)*-α-Fluoro-β-methylstyrene oxide.** Colorless oil; IR (film): 1453, 1247 cm^{-1}; $[\alpha]^{20}_D$ = +77.2 (*c* 0.71, $CHCl_3$, 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 5H),

3.23 (qd, J = 5.6, 2.4 Hz, 1H), 1.60 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 134.2, 129.7, 128.7, 125.8, 125.7, 98.2, 95.7, 62.3, 62.1, 13.42, 13.38; ^{19}F NMR (376 MHz, $CDCl_3$) δ –150.3 (s). HRMS calcd for C_9H_9FO (M^+) 152.0637, found 152.0634.

Table 3.2, entries 4-6 (OAW2334-1, OAW2341-2, OAW2341-1)

(*E*)-α-Fluoro-β-methylstyrene oxide. Colorless oil; $[\alpha]^{20}_D$ = -17.5 (*c* 0.46, $CHCl_3$, 74% ee); IR (film): 1450, 1338 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.47-7.44 (m, 3H), 3.75 (qd, J = 5.6, 1.6 Hz, 1H), 1.15 (dd, J = 5.6, 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 131.3, 130.0, 128.5, 127.40, 127.37, 99.2, 96.6, 61.1, 60.8, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –126.0 (s). HRMS calcd for C_9H_9FO (M^+) 152.0637, found 152.0633.

Table 3.2, entries 7-9 (OAW2335-2, OAW1347, OAW1119-1)

(*Z*)-Fluorostilbene oxide. White solid; mp 40-42 °C; $[\alpha]^{20}_D$ = +162.9 (*c* 0.85, $CHCl_3$, 91% ee); IR (film): 3066, 1451 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.34 (m, 10H), 4.06 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 133.6, 132.6, 132.5, 130.0, 129.0, 128.9, 128.5, 127.5, 125.92, 125.86, 98.6, 95.0, 66.6, 66.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –150.1 (s). HRMS calcd for $C_{14}H_{11}FO$ (M^+) 214.0794, found 214.0794.

Table 3.2, entries 10-12 (OAW2335-1, OAW1346-1, OAW1340-1)

(*E*)-Fluorostilbene oxide. Colorless oil; $[\alpha]^{20}_D$ = -5.3 (*c* 0.75, $CHCl_3$, 83% ee); IR (film): 3066, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.38-7.31 (m, 3H), 7.26-7.22 (m, 3H), 7.19-7.15 (m, 2H), 4.70 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.4, 130.1, 129.0, 128.9, 128.6, 128.5, 128.39, 128.35, 127.7,

127.6, 127.5, 126.7, 125.9, 99.3, 96.7, 64.6, 64.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.7 (s). HRMS calcd for $C_{14}H_{11}FO$ (M^+) 214.0794, found 214.0797.

Table 3.2, entries 13-15 (OAW2332-2, OAW2346-2, OAW2346-1)

(*E*)-5-Fluorodec-5-ene oxide. Colorless liquid; $[\alpha]^{20}_D$ = +18.2 (*c* 0.91, $CHCl_3$, 77% ee); IR (film): 2960, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (td, *J* = 6.0, 1.8 Hz, 1H), 2.06-1.58 (m, 4H), 1.53-1.28 (m, 8H), 0.94 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.4, 96.9, 62.5, 62.2, 34.3, 32.8, 32.4, 28.3, 27.0, 25.8, 22.6, 14.3, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –143.6 (t, *J* = 15.8 Hz). HRMS calcd for $C_{10}H_{19}FO$ (M^+) 174.1420, found 174.1423.

Table 3.2, entries 16-18 (OAW2333-1, OAW1105, OAW2347-2)

(*Z*)-5-Fluorodec-5-ene oxide. Colorless oil; IR (film): 2960, 1468 cm^{-1}; $[\alpha]^{20}_D$ = +12.8 (*c* 0.86, $CHCl_3$, 80% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23-3.20 (m, 1H), 1.91-1.73 (m, 2H), 1.67-1.26 (m, 10H), 0.96-0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.3, 96.9, 62.9, 62.6, 29.6, 29.2, 28.2, 28.0, 25.8, 22.7, 22.6, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –129.2 (t, *J* =19.9 Hz). Anal. Calcd for $C_{10}H_{19}FO$: C, 68.93; H, 10.99; Found: C, 68.69; H, 10.87.

Table 3.2, entries 19-21 (OAW2337-2, OAW1346-2, OAW1340-2)

2-Fluoro-3,3-dimethyl-2-phenyloxirane. Colorless oil; $[\alpha]^{20}_D$ = +31.6 (*c* 0.67, $CHCl_3$, 43% ee); IR (film): 2930, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.45-7.42 (m, 3H), 1.65 (s, 3H), 1.15 (d, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 132.4, 129.8, 128.4, 127.3, 102.3, 99.7, 66.9, 66.6, 19.6, 19.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –131.1 (s). HRMS calcd for $C_{10}H_{11}FO$ (M^+) 166.0794, found 166.0794.

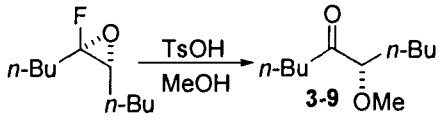
Table 3.2, entries 22-24 (OAW2337-1, OAW2340-2, OAW1114-1)

α-Fluorostyrene oxide. Colorless liquid; $[\alpha]^{20}_D$ = -4.9 (*c* 0.55, $CHCl_3$, 27 % ee); IR (film): 1475, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 5H), 3.51 (dd, *J* = 4.8, 2.4 Hz, 1H), 2.99 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 133.2, 130.0, 128.8, 125.91, 125.86, 95.3, 92.7, 54.8, 54.6; ^{19}F (376 MHz, $CDCl_3$) δ –140.4 (s). HRMS calcd for C_8H_7FO (M^+) 138.0481, found 138.0482.

Epoxide 3-14 in Scheme 3.10[31]

Colorless oil; $[\alpha]^{20}_D$ = +16.6 (*c* 0.69, $CHCl_3$, 91% ee); IR (film): 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94-1.76 (m, 2H), 1.66-1.26 (m, 10H), 0.97-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.9, 97.3, 62.8, 62.53, 62.50, 62.3, 62.2, 62.0, 29.6, 29.3, 28.2, 27.9, 25.8, 22.7, 22.6, 14.3, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –129.4 (t, *J* = 20.3 Hz). Anal. Calcd for $C_{10}H_{18}DFO$: C, 68.53; H, 10.91. Found: C, 68.38; H, 10.88.

Representative epoxide opening procedures (Schemes 3-6 and 3-8) (OAW2413, OAW2415, OAW2510)



To a solution of the epoxide (0.035 g, 0.2 mmol) in MeOH (0.2 mL) was added anhydrous *p*-TsOH (0.007 g, 0.04 mmol). The reaction mixture was stirred at rt for 2 h,

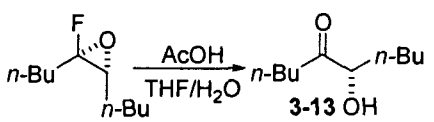
[31] The hydrogen content of a deuterated compound is calculated as follow:
[(# of H + # of D) (MW of H)] / (MW of the molecule)

concentrated, and purified by flash column chromatography (hexanes to hexanes:Et_2O 50:1, v/v) to give compound **3-9** as a colorless oil (0.023 g, 62% yield). $[\alpha]^{20}_D$ = -60.2 (*c* 1.13, $CHCl_3$); IR (film): 1716, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (t, *J* = 6.3 Hz, 1H), 3.34 (s, 3H), 2.50 (t, *J* = 7.2 Hz, 2H), 1.65-1.51 (m, 4H), 1.43-1.26 (m, 6H), 0.94-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 87.6, 58.4, 37.4, 31.9, 27.5, 25.5, 22.7, 22.6, 14.1. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.81; H, 11.79.

Compound 3-12 in Scheme 3.8[31]

Colorless oil; IR (film): 1716, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.61-1.52 (m, 4H), 1.36-1.27 (m, 6H), 0.93-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 87.3, 87.1, 86.9, 58.3, 37.3, 31.8, 27.5, 25.5, 22.7, 22.6, 14.1. Anal. Calcd for $C_{11}H_{21}DO_2$: C,70.54; H, 11.85. Found: C, 70.30; H, 11.61.

Representative epoxide opening procedures (Schemes 3.9 and 3.10) (OAW2836, OAW2832, OAW2839)



3-13

To a solution of the epoxide (0.017 g, 0.10 mmol, 91% ee) in THF (0.1 mL) and H_2O (0.1 mL) was added AcOH (5 drops). The reaction mixture was heated at 60 °C for 20 h. THF was evaporated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was then concentrated and purified by flash column chromatography (hexanes to hexanes:Et_2O = 8:1, v/v) to give compound **3-13** as a colorless oil (0.014 g, 81 % yield, 89 % ee). $[\alpha]^{20}_D$ = +9.0 (*c* 0.63, MeOH, 89% ee); IR (film): 3481, 1710 cm^{-}

[1]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (m, 1H), 3.49 (d, J = 4.8 Hz, 1H), 2.56-2.38 (m, 2H), 1.89-1.78 (m, 1H), 1.68-1.23 (m, 9H), 0.97-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 76.5, 37.7, 33.6, 27.1, 25.9, 22.7, 22.5, 14.0, 13.9. HRMS calcd for $C_{10}H_{20}O_2$ (M^+) 172.1463, found 172.1467.[22]

Compound 3-15 in Scheme 3.10[31]

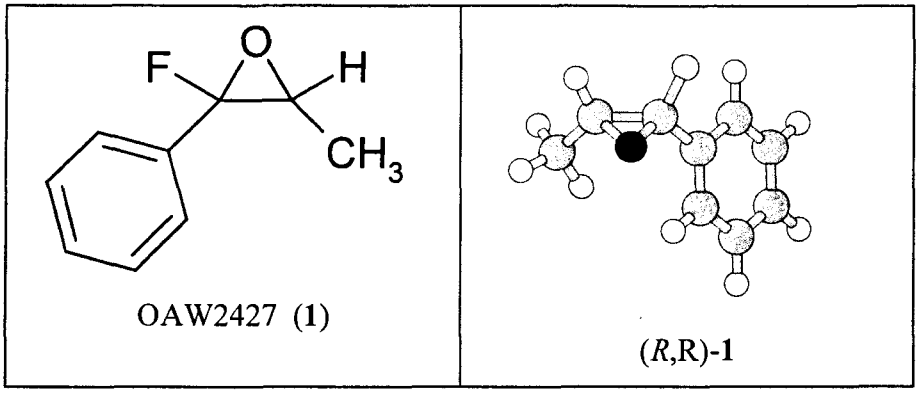
Colorless oil; $[\alpha]^{20}_D$ = +11.0 (*c* 0.62, MeOH, 89% ee); IR (film): 3483, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (brs, 1H), 2.53-2.39 (m, 2H), 1.85-1.78 (m, 1H), 1.65-1.27 (m, 9H), 0.92 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 76.4, 76.1, 75.9, 37.8, 33.6, 27.1, 25.9, 22.7, 22.6, 14.1, 14.0. Anal. Calcd for $C_{10}H_{19}DO_2$: C, 69.32; H, 11.63. Found: C, 69.33; H, 11.60.

3.5. VCD SPECTRA BY BIOTOOLS

VCD Spectra on Epoxides of 3-2 and 3-6 (using ketone 1-53) by BioTools

Report on OAW2427 (Epoxide of olefin **3-2**) and OAW2423 (Epoxide of **3-6**)

OAW2427 (Epoxide of olefin **3-2**)



OAW2427 (**1**)

(*R*,R)-**1**

Experimental Measurement: IR and VCD spectra of OAW2427 (**1**) were measured with a Chiral*IR* VCD spectrometer (BioTools, Inc, Jupiter, FL) for a sample dissolved in $CDCl_3$ (5 mg sample/100 μL $CDCl_3$) and placed in a 100-μm pathlength cell with BaF_2 windows. Spectra were recorded at 4 cm^{-1} resolution, with 6 h collection for sample and solvent. The experimental spectra are displayed in Figure 3.8, where the corresponding solvent spectra have been subtracted.

Calculations: Calculations of optimized geometries, vibrational frequencies and IR and VCD intensities were carried out with Gaussian 03 (Gaussian, Inc., Wallingford, CT) at the DFT level with B3LYP functional and 6-31G(d) basis set. Calculated frequencies were scaled by 0.97 and calculated intensities were converted into Lorentzian bands with 6-cm^{-1} bandwidth for comparison to experiment. Comparison of the experimental measurement with the calculations for the (*R*,*R*)-enantiomer shown above show excellent agreement (Figure 3.9), establishing assignment of the configuration of the sample OAW2427 to the (*R*,*R*)-configuration.

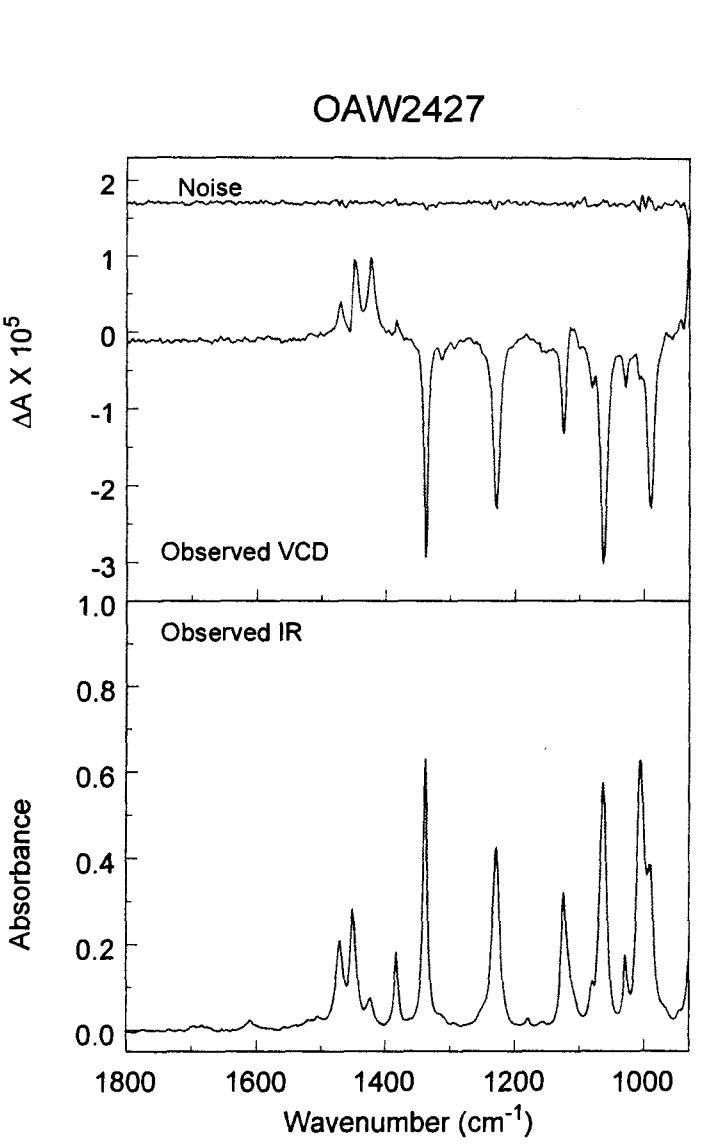


Figure 3.8 IR (lower frame) and VCD (upper frame) spectra measured for OAW2427, 5 mg sample/100 μL $CDCl_3$;100-μm pathlength cell with BaF_2 windows; 4 cm^{-1} resolution; 6 h collection for sample and solvent; instrument optimized at 1400 cm^{-1}. Spectra shown are solvent subtracted. Uppermost trace is the VCD noise.

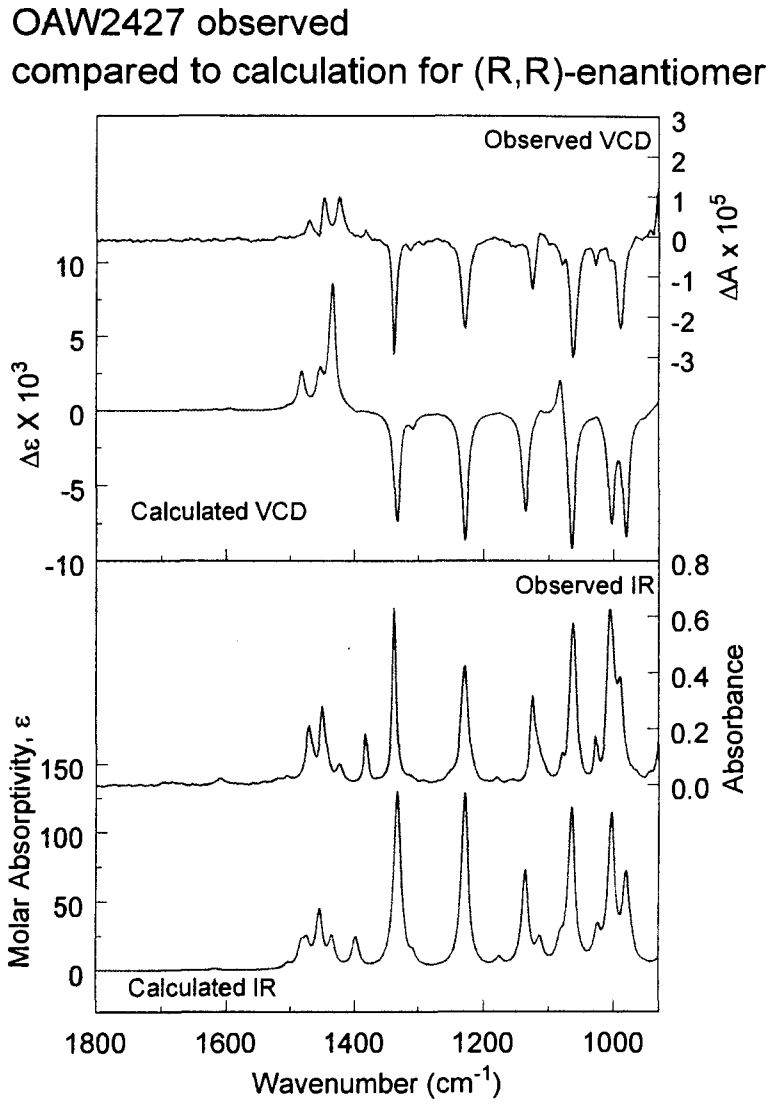
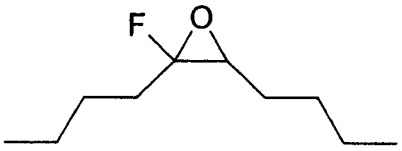


Figure 3.9. IR (lower frame) and VCD (upper frame) spectra observed for OAW2427 (right axes) compared to calculation (left axes) for the (*R*,*R*)-enantiomer.

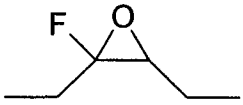
Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.955970	-0.243920	-1.062355
2	6	0	1.151973	0.542208	-0.238757
3	6	0	2.272889	-0.199001	0.365496
4	6	0	-0.304063	0.224361	-0.128283
5	9	0	1.356357	1.896646	-0.381353
6	6	0	2.147752	-1.479869	1.144212
7	1	0	3.161309	0.401147	0.568942
8	6	0	-1.160457	1.111421	0.536324
9	6	0	-2.516698	0.814390	0.657966
10	6	0	-3.029346	-0.364646	0.111336
11	6	0	-2.180120	-1.243880	-0.562134
12	6	0	-0.821017	-0.951136	-0.683972
13	1	0	1.179982	-1.960321	0.979455
14	1	0	2.938696	-2.179816	0.851588
15	1	0	2.256938	-1.276815	2.215883
16	1	0	-0.762474	2.033859	0.946856
17	1	0	-3.175334	1.506834	1.175162
18	1	0	-4.087609	-0.593123	0.205018
19	1	0	-2.575791	-2.155724	-1.001226
20	1	0	-0.156175	-1.617581	-1.223791

OAW2423 (Epoxide of Olefin **3-6**)



OAW2423



Fragment for calculaltion (**2**)

Experimental Measurement: IR and VCD spectra of OAW2423 (**2**) were measured with a Chiral*IR* VCD spectrometer (BioTools, Inc, Jupiter, FL) for a sample dissolved in $CDCl_3$ (5 mg sample/100 μL $CDCl_3$) and placed in a 100-μm pathlength cell with BaF_2 windows. Spectra were recorded at 4 cm^{-1} resolution, with 6 h collection for sample and solvent. The experimental spectra are displayed in Figure 3.10, where the corresponding solvent spectra have been subtracted.

Calculations: Because of the flexibility and numerous possible conformations of the n-butyl chains, calculations were carried out on the fragment shown above for ethyl substituents, which replicate the environment at the chiral centers, but with a reduced number of possible conformers. Calculations of optimized geometries, vibrational frequencies and IR and VCD intensities were carried out with Gaussian 03 (Gaussian, Inc., Wallingford, CT) at the DFT level with B3LYP functional and 6-31G(d) basis set. Calculated frequencies were scaled by 0.97 and calculated intensities were converted into Lorentzian bands with 6-cm^{-1} bandwidth for comparison to experiment. Eight conformers were identified, shown in Figure 3.11 in order of increasing relative energy (conformation numbers shown are for identification of the individual calculation files). Because of the small solution population at room temperature for the conformers lying >2.5 kcal/mol above C3, only the four lowest energy conformers were included in the comparison figures and the Boltzmann-population weighted sum. Comparison of the experimental measurement with the calculations for the (*R*,*R*)-enantiomer of the four low-energy conformers is shown in Figure 3.12, demonstrating the dependence of the VCD on conformation of the side-chains. In Figure 3.13, the experimental spectra are compared to the Boltzmann-population-weighted sum of the calculated spectra for

conformers 1 to 4 (31.8% C3 + 29.9% C1 + 20.4% C2 + 17.9% C4). The agreement in overall VCD pattern between experiment and calculation for (*R*,*R*)-fragment-**2** (Figure 3.13) provides assignment of the configuration of the sample OAW2423 to the (*R*,*R*)-configuration.

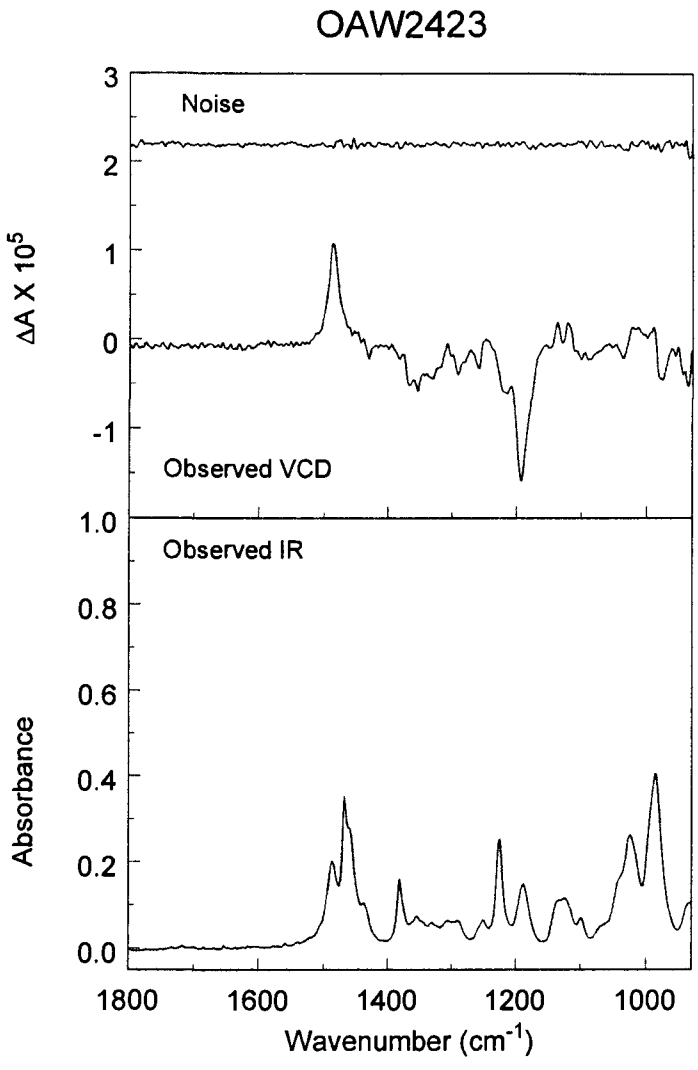


Figure 3.10 IR (lower frame) and VCD (upper frame) spectra measured for OAW2423, 5 mg sample/100 μL $CDCl_3$;100-μm pathlength cell with BaF_2 windows; 4 cm^{-1} resolution; 6 h collection for sample and solvent; instrument optimized at 1400 cm^{-1}. Spectra shown are solvent subtracted. Uppermost trace is the VCD noise.

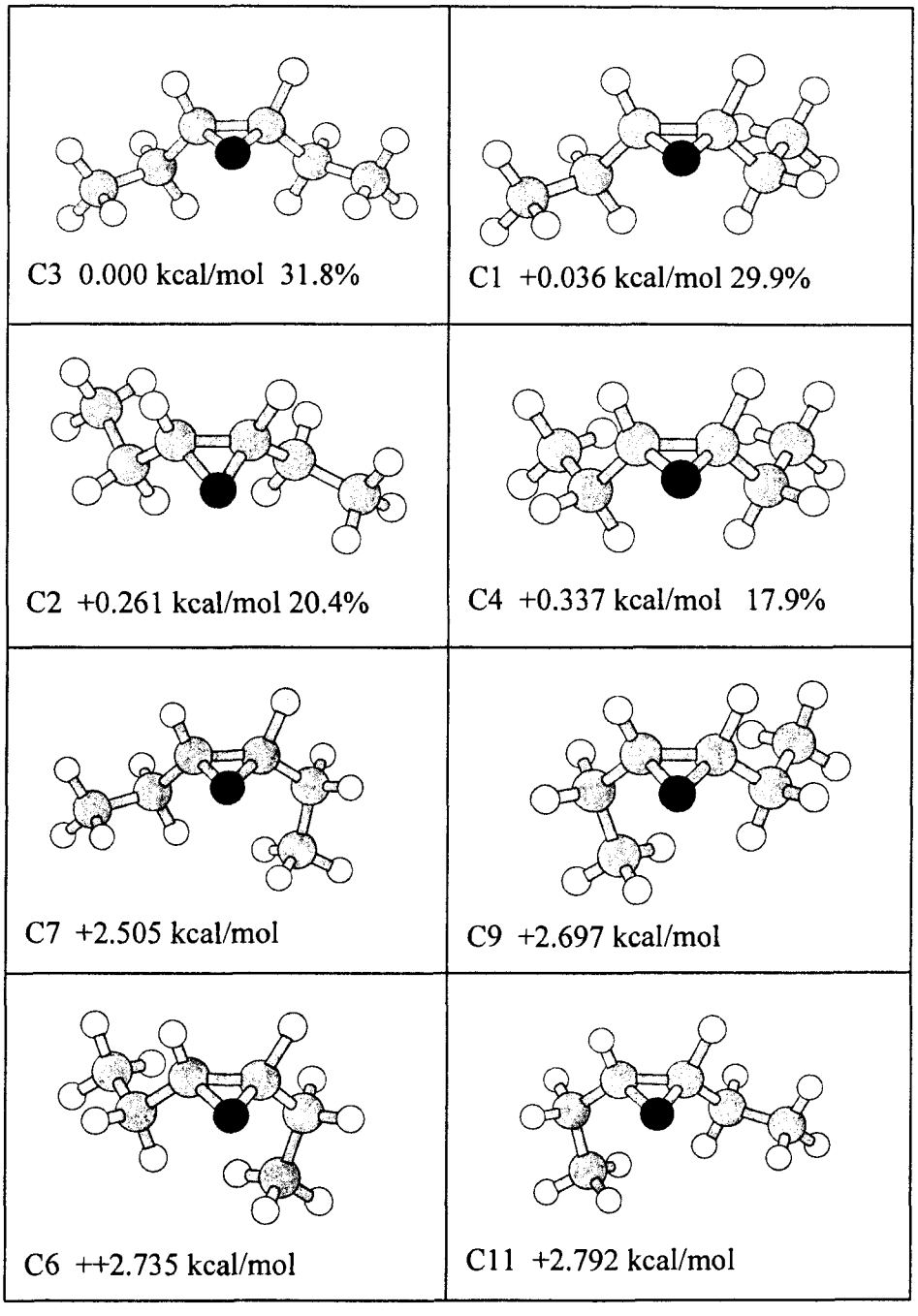


Figure 3.11 Optimized geometries and relative energies for the eight conformers identified for Fragment-**2**. Boltzmann populations at 23 °C are given for the four lower energy conformers.

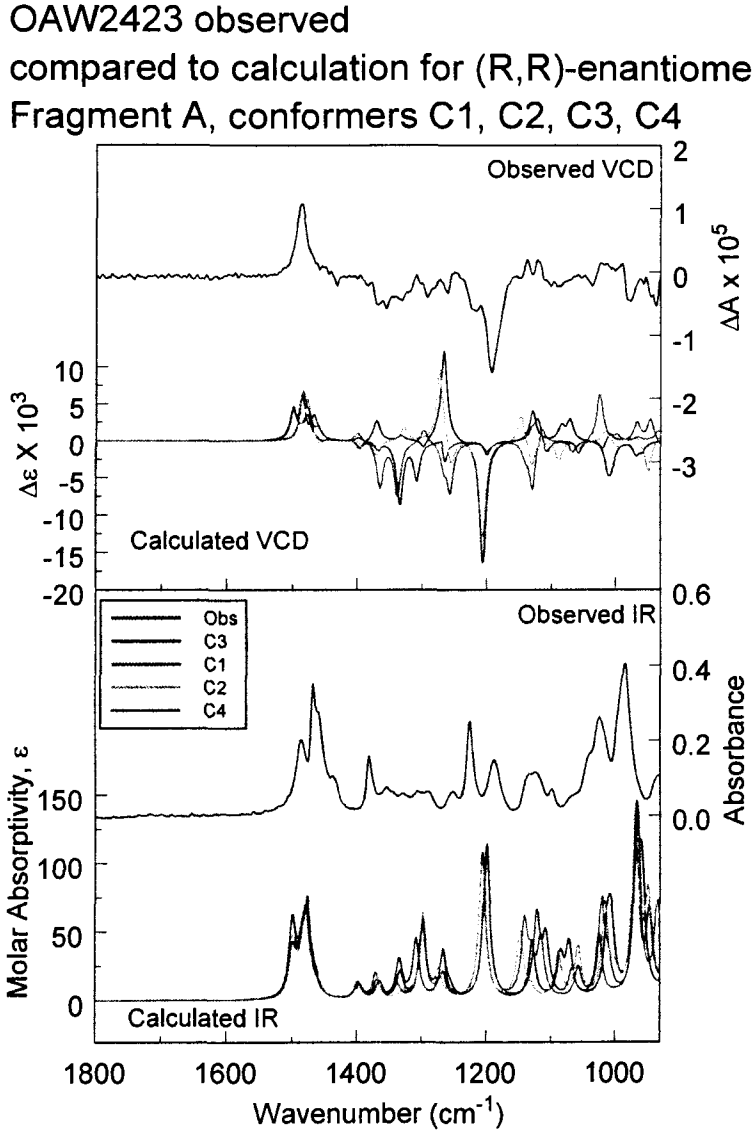


Figure 3.12 IR (lower frame) and VCD (upper frame) spectra observed for OAW2423 (right axes) compared to calculation (left axes) for the four lowest energy conformations of the (*R*,*R*)-enantiomer for fragment-**2** for OAW2423.

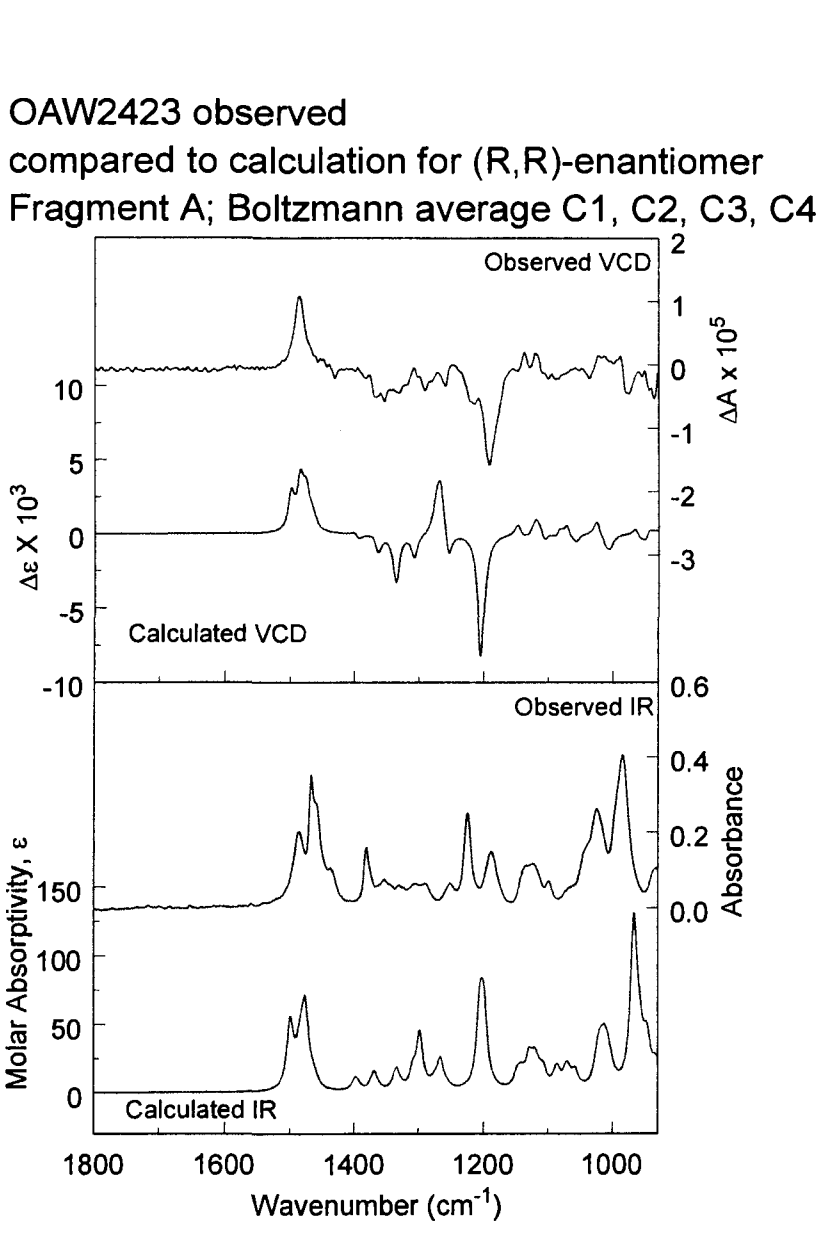


Figure 3.13 IR (lower frame) and VCD (upper frame) spectra observed for OAW2427 (right axes) compared to calculation (left axes) for the the Boltzmann-population-weighted sum for the (*R*,*R*)-enantiomer of fragment-**2** (31.8% C3 + 29.9% C1 + 20.4% C2 + 17.9% C4).

2423-C1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.394540	-1.091576	0.821044
2	6	0	0.741350	-0.401794	-0.426279
3	6	0	-0.631143	-0.500911	0.083671
4	6	0	1.653616	0.795180	-0.309022
5	1	0	0.989302	-1.102757	-1.226260
6	9	0	-1.438874	-1.415556	-0.559531
7	6	0	-1.472012	0.572445	0.728553
8	6	0	-2.356908	1.323644	-0.272834
9	6	0	3.093305	0.383620	0.027221
10	1	0	1.630852	1.340031	-1.263005
11	1	0	1.275272	1.479351	0.458493
12	1	0	-2.091961	0.081721	1.489801
13	1	0	-0.809913	1.262480	1.260130
14	1	0	-2.970041	2.071958	0.239652
15	1	0	-1.753275	1.842267	-1.026665
16	1	0	3.743737	1.261154	0.106238
17	1	0	3.126326	-0.154182	0.980379
18	1	0	-3.024931	0.631849	-0.794051
19	1	0	3.508921	-0.274368	-0.745150

2423-C2

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.239660	-0.848253	1.152441
2	6	0	0.875974	-0.690530	0.219207
3	6	0	-0.513179	-0.375774	-0.133655
4	6	0	1.947187	0.311696	0.579023
5	1	0	1.240603	-1.648707	-0.157836
6	9	0	-1.152599	-1.303409	-0.929246
7	6	0	-1.159896	0.977910	-0.288892
8	6	0	-2.613631	0.974547	0.202070
9	6	0	2.858479	0.635068	-0.612702
10	1	0	1.483625	1.225253	0.966953
11	1	0	2.542516	-0.105753	1.402049
12	1	0	-0.573544	1.715556	0.267628
13	1	0	-1.116619	1.257733	-1.348713
14	1	0	-3.068568	1.961451	0.069925
15	1	0	-3.208552	0.244537	-0.354907
16	1	0	3.650910	1.331118	-0.318817
17	1	0	3.338685	-0.269472	-1.004347
18	1	0	-2.662455	0.713987	1.264476
19	1	0	2.294468	1.093508	-1.433028

2423-C3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.125518	0.340389	1.058538
2	6	0	-0.855461	0.589236	-0.188710
3	6	0	0.598555	0.404608	-0.134332
4	6	0	-1.874330	-0.446327	-0.598884
5	1	0	-1.185796	1.627267	-0.269748
6	9	0	1.349525	1.555735	-0.252717
7	6	0	1.412996	-0.792525	-0.556692
8	6	0	2.618968	-1.014263	0.365629
9	6	0	-3.123515	-0.400599	0.291388
10	1	0	-2.150595	-0.261659	-1.646276
11	1	0	-1.427709	-1.445714	-0.557978
12	1	0	0.768230	-1.676623	-0.556444
13	1	0	1.746421	-0.631557	-1.589250
14	1	0	3.202817	-1.880011	0.036986
15	1	0	3.274059	-0.137932	0.365098
16	1	0	-3.853267	-1.156122	-0.018443
17	1	0	-2.857390	-0.589868	1.336503
18	1	0	2.290590	-1.192890	1.394831
19	1	0	-3.612213	0.579602	0.240483

2423-C4

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.068814	-1.607174	-0.673823
2	6	0	-0.776620	-0.784946	0.192403
3	6	0	0.660160	-0.542924	0.006220
4	6	0	-1.899029	-0.017056	-0.465021
5	1	0	-1.041457	-1.296268	1.120595
6	9	0	1.471110	-0.942710	1.047841
7	6	0	1.332586	0.546925	-0.790970
8	6	0	1.727321	1.760321	0.058729
9	6	0	-2.523073	1.020065	0.478321
10	1	0	-1.533587	0.465591	-1.378054
11	1	0	-2.663350	-0.738954	-0.782544
12	1	0	2.223408	0.103854	-1.254634
13	1	0	0.668082	0.842120	-1.608798
14	1	0	2.233212	2.512358	-0.555348
15	1	0	0.848304	2.232973	0.512361
16	1	0	-3.360398	1.532639	-0.006465
17	1	0	-2.905221	0.549072	1.391711
18	1	0	2.403857	1.464675	0.865716
19	1	0	-1.791427	1.779416	0.777374

CHAPTER FOUR

SUBSTRATE SCOPE EXPANSION FOR DIACETATE-CONTAINING KETONE **1-53**

4.1. INTRODUCTION

In 2002, our group reported that ketone **1-53** is effective toward the epoxidation of α,β-unsaturated esters (Scheme 4.1).[1] Optically active α,β-epoxy esters and ketones are useful intermediates for the synthesis of complex molecules and asymmetric epoxidation of prochiral α,β-unsaturated esters and ketones presents a convenient way to obtain this functionalilty.[2] Ketone **1-53** can be synthesized from ketone **1-41** in multigram scale in 62% overall yield (Scheme 4.1). The epoxidations of α,β-unsaturated esters with ketone **1-53** were carried out in MeCN and H_2O at 0 °C with the addition of a solid mixture of Oxone and $NaHCO_3$ over 4.5 h (Method A, Table 4.1). High ee's were obtained for various trans- and trisubstituted α,β-unsaturated esters (Table 4.1, entries 1-

[1] Wu, X-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.

[2] Porter, M.J.; Skidmore, J. *Chem. Commun.* **2000**, 1215.

8). Ketone **1-53** has also been shown to catalyze the epoxidation of an enone (Table 4.1, entry 9); however, it is generally a less effective catalyst for enones.

Scheme 4.1 Synthesis of Diacetate Ketone 1-53

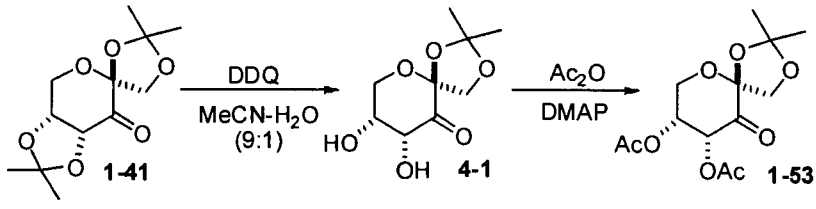
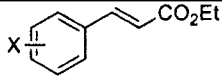
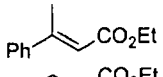
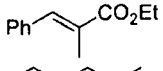
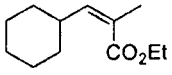
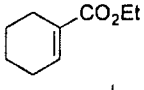
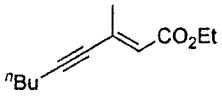
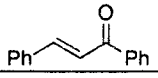


Table 4.1 Asymmetric Epoxidation of α,β-Unsaturated Esters and Enone Using Ketone **1-53**[a]

entry	substrate	yield (%)[b]	ee (%)	config.[j]
				
1[c]	X = H	73	96[f]	(+)-(2*S*,3*R*)[3,4]
2[d]	X = *p*-Me	91	97[g]	(+)
3[e]	X = *p*-OMe	57	90[h]	(+)-(2*S*,3*R*)[5]
4[d]		93	96[i]	(+)-(2*S*,3*R*)[6]
5[c]		45	86[g]	(+)
6[c]		77	89[f]	(+)
7[d]		77	93[f]	(+)
8[d]		74	98[h]	(+)
9[c]		42	82[i]	(+)-(2*S*,3*R*)[7]

[3] Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622.

[4] Cabon, O.; Buisson, D.; Larcheveque, M.; Azerad, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2211.

[5] Yamamoto, M.; Hayashi, M.; Masaki, M.; Nohira, H. *Tetrahedron: Asymmetry* **1991**, *2*, 403.

[6] Abidi, S.L.; Wolfhagen, J.L. *J. Org. Chem.* **1979**, *44*, 433.

[7] Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, 119, 2329.

[a] Method A: All reactions were carried out with substrate (0.50 mmol), ketone **1-53** (0.1-0.15 mmol), Bu_4NHSO_4 (0.03 mmol), Oxone (2.5 mmol), and $NaHCO_3$ (7.75 mmol) in CH_3CN-aq. $Na_2(EDTA)$ (4×10^{-4} M) (6.25 mL) (1.5/1, v/v). A mixture of Oxone and $NaHCO_3$ was added portionwise over 4.5 h at 0 °C and stirred for 7.5 h at 0 °C and for 12 h at rt. For entry 3 a mixture of Oxone and $NaHCO_3$ was added portionwise over 4.5 h at 0 °C and stirred for 7.5 h at 0 °C. [b] Isolated yields. [c] 0.15 mmol **1-53** used. [d] 0.125 mmol **1-53** used. [e] 0.10 mmol **1-53** used. [f] Determined by chiral GC (Chiraldex G-TA). [g] Determined by chiral HPLC (Chiralpak AD). [h] Determined by chiral HPLC (Chiralcel OD). [i] Determined by chiral HPLC (Chiralcel OB). [j] Determined by comparing the measured optical rotations with the reported ones.

The replacement of the fused ketal group of ketone **1-41** with more electron-withdrawing diacetate groups significantly enhanced the catalyst stability and reactivity. The Baeyer-Villiger oxidation of the catalyst under the epoxidation conditions, which leads to the decomposition of the catalyst, is reduced with the diacetate-containing ketone **1-53**. With the more robust ketone **1-53** in hand, we decided to expand the substrate scope beyond α,β-unsaturated esters.

4.2. RESULTS AND DISCUSSION

The synthesis of ketone **1-53** involves two chromatographic purifications, therefore is not ideal for large-scale production. Bin Wang had developed a one-pot procedure to synthesize the hydrate of ketone **1-53** (**1-53·H_2O**) with no purification necessary (Scheme 4.2). Compound **1-53·H_2O** is a powdery white solid, which makes it much easier to handle than thick oil ketone **1-53**. For the more reactive substrates, it was realized that less catalyst (9.2%) was required when the epoxidation was carried out at a slightly higher pH (around 8.75 to 9.50) with slow addition of Oxone and K_2CO_3 solutions. Consequently, the substrate scope investigation was carried out with 9.2% **1-53·H_2O** with slow addition of Oxone and K_2CO_3 solutions (Method B, Table 4.2).

Scheme 4.2 One-Pot Synthesis of Catalyst 1-53·H_2O

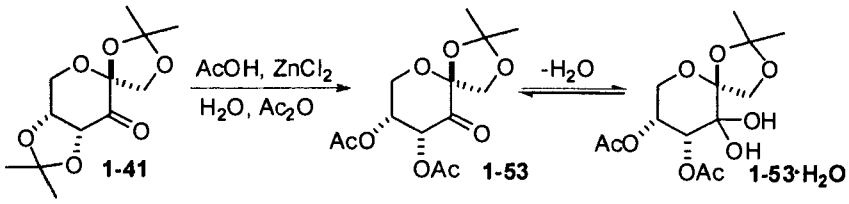
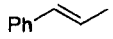
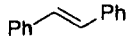
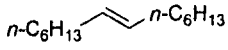
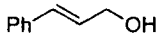
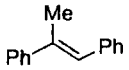
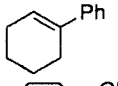
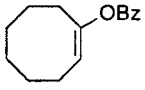
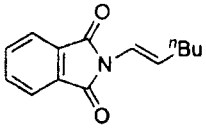
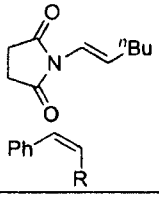


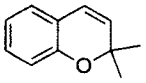
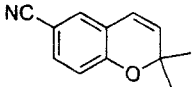
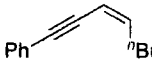
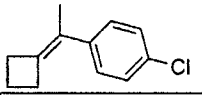
Table 4.2 Asymmetric Epoxidation of Olefins Catalyzed by **1-53** and **1-53·H_2O**[a,b]

entry	substrate	method (h)	yield[c] (ee) (%)	config.[d]
1		A (24) B (8)	75 (86[e]) 81 (86[e])	(+)-(*R*,*R*)[8]
2		A (24) B (16)	68 (92[f]) 63 (93[f])	(+)-(*R*,*R*)[8]
3		B (8)	53 (88[g])	(+)-(*R*,*R*)[8]
4		B (8)	73 (79[f])	(+)-(*R*,*R*)[9]
5		A (24) B (8)	93 (86[f]) 46 (88[f])	(+)-(*R*,*R*)[8]
6		A (24) B (8)	92 (92[e]) 82 (92[e])	(+)-(*R*,*R*)[8]
7		B (8)	97 (95[f])	(+)-(*R*,*R*)[10]
8[j]		A (14)	95 (75[h])	(+)
9[j]		A (14)	78 (86[e])	(+)

[8] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

[9] Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.

[10] Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

10	R = Me	B (8)	81 (49[e])	(+)-(1*S*,2*R*)[11]
11	R = CH_2OH	B (8)	85 (47[i])	(+)-(2*R*,3*S*)[12]
12	R = CH_2OTBS	B (8)	62 (70[e])	(+)
13	R = CH_2TMS	B (8)	81 (65[e])	(+)
14	R = TMS	B (8)	54 (80[e])	(+)
15	R = TBS	B (24)	60 (90[e])	(+)
16		B (8)	75 (88[f])	(-)-(*S*,*S*)[13]
17		B (8)	73 (90[f])	(-)-(*S*,*S*)[13]
18		B (8)	50 (62[e])	(+)-(2*R*,3*S*)[14]
19		B (8)	77 (27[e])	(-)-(*S*)[8]
20		B (8)	72 (6[f])	(+)-(*S*)[15]
21		B (8)	63 (67[e])	(-)-(*S*)[16]

[a] Method A: All reactions were carried out with olefin (0.5 mmol), ketone **1-53** (0.125 mmol), Bu_4NHSO_4 (0.03 mmol), Oxone (2.50 mmol), and $NaHCO_3$ (7.75 mmol) in CH_3CN-aq. $Na_2(EDTA)$ (4 x 10^{-4} M) (6.25 mL) (v/v, 1.5/1). For entries 1, 2, 5, and 6, a mixture of Oxone and $NaHCO_3$ was added portionwise over 4.5 h at 0 °C and stirred for 7.5 h at 0 °C and for 12 h at rt. For entries 8 and 9, a mixture of Oxone and $NaHCO_3$ was added portionwise over 3 h at 0 °C and stirred for another 11 h at 0 °C. [b] Method B: All epoxidations were carried out with substrate (0.5 mmol), ketone **1-53·H_2O** (0.046 mmol) (0.1 mmol for entries 14 and 15), Oxone (1.01 mmol), and K_2CO_3 (2.02 mmol) in CH_3CN-DMM (9 mL) (1/2, v/v), and buffer (0.05 M Na_2HPO_4/0.05 M KH_2PO_4, pH 7.0, 3 mL) at 0 °C for 8 h, 16 h, or 24 h. [c] Isolated yields. [d] Determined by comparing the measured optical rotations with the reported ones. [e] Determined by chiral GC (Chiraldex B-DM). [f] Determined by chiral HPLC (Chiralcel OD). [g] The epoxide was opened (NaOMe-MeOH), the resulting alcohol was converted to its benzoate, enantioselectivity was determined by chiral HPLC (Chiralcel OD-H). [h] Determined by chiral HPLC (Chiralpak AD-H). [i] Determined by chiral HPLC (Chiralcel OD-H). [j] Experiment carried out by Brian Nettles.

[11] Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435.

[12] Denis, J. N.; Greene, A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 46.

[13] Wong, O.A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973.

[14] Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093.

[15] Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.

[16] Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.

High ee's were obtained for the epoxidation of trans- and trisubstituted olefins, including less reactive trans-enimides (Table 4.2, entries 1-9). cis-Olefins with bulky R groups can also be epoxidized in high ee's (Table 4.2, entries 14-17). The enantioselectivities were low for terminal and tetrasubstituted olefins tested (Table 4.2, entries 19-21). The epoxidations of trans- and trisubstituted olefins using ketone **1-53** generally resulted in lower ee's compared to those using **1-41**. A possible reason is that the diacetate groups are not as effective as the fused ketal groups in blocking the bottom face of the dioxirane. As a result, it is possible for spiro transition state **B** to contribute to the production of the major enantiomer and spiro transition state **D** for the minor enantiomer (Figure 4.1). Based on the absolute configuration of the resulting epoxides, the epoxidation of trans- and trisubstituted olefins likely proceeds via spiro **A** with possible contribution from spiro **B** (Figure 4.1). For conjugated aromatic cis-olefins, the epoxidation appears to proceed via spiro **E** with possible contribution from spiro **F** (Figure 4.2). As discussed before, the R_π group of the olefin is proximal to the catalyst in the favored transition state when oxazolidinone-containing ketones, such as **1-104** and **1-111**, are used as epoxidation catalysts (Figure 1.20, page 52). On the other hand, when ketone **1-53** is used as the epoxidation catalyst, the R_π group is oriented away from the spiro ketal group of the catalyst in the favored transition state (Figure 4.2, spiro **E**). The optical rotation of the major epoxide enantiomer produced by ketone **1-53** is opposite to that produced by ketones **1-104** and **1-111**. Consequently, epoxidation with ketone **1-53** provides a complementary method to access the epoxide enantiomer that was otherwise difficult to obtain with glucose-derived ketone catalysts **1-104** and **1-111**.

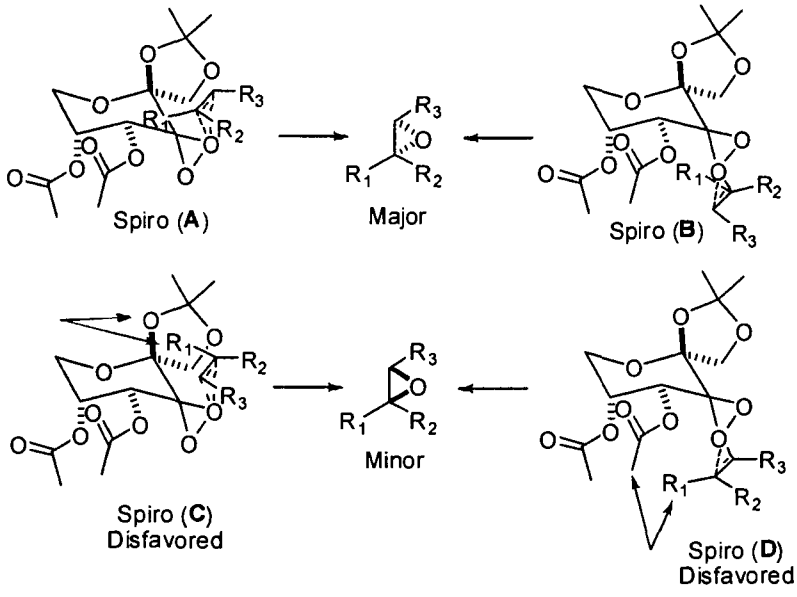


Figure 4.1 Possible Competing Spiro Transition States for the Epoxidation of trans- and Trisubstituted Olefins with Catalyst 1-53 or 1.53·H_2O

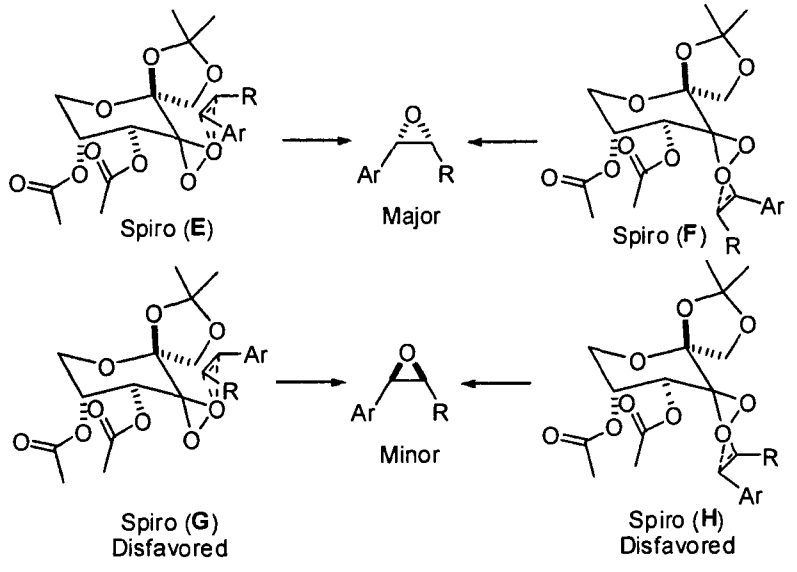


Figure 4.2 Possible Competing Spiro Transition States for the Epoxidation of cis-olefins with Catalyst 1-53 or 1.53·H_2O

4.3. CONCLUSIONS

In summary, the substrate scope of fructose-derived diacetate-containing ketone **1-53** was expanded to trans-, trisubstituted, and cis-olefins. High ee's were obtained for trans- and trisubstituted olefins although the ee's were generally lower than those obtained using ketone **1-41**. Moderate to good enantioselectivities were obtained for cis-olefins and it is worth pointing out that the optical rotations of the resulting epoxides are opposite to those obtained using ketones **1-104** and **1-111**.

4.4. EXPERIMENTAL

Representative Asymmetric Epoxidation Procedure using Oxone and $NaHCO_3$ (Method A) (Table 4.1, entry 3): Aqueous $Na_2(EDTA)$ (1×10^{-4} M, 2.5 mL) and a catalytic amount of tetrabutylammonium hydrogen sulfate (0.010 g, 0.03 mmol) were added to a solution of ethyl *trans*-4-methylcinnamate (0.095 g, 0.5 mmol) in CH_3CN (2.5 mL) with vigorous stirring at 0 °C. A mixture of Oxone (1.537 g, 2.5 mmol) and $NaHCO_3$ (0.651 g, 7.75 mmol) was pulverized, and a small portion of this mixture was added to the reaction mixture to bring pH to >7. Then a solution of ketone **1-53** (0.038 g, 0.125 mmol) in CH_3CN (1.25 mL) was added. The remainder of the Oxone and $NaHCO_3$ was added to the reaction mixture portionwise over a period of 4.5 h. Upon stirring for an additional 7.5 h at 0 °C and 12 h at rt, the resulting mixture was diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel,

hexane/EtOAc = 1/0 to 95/5) to give the epoxide as a colorless oil (0.094 g, 91% yield, 97% ee).

[For Table 4.1, entry 3, 7.5 mL of CH_3CN and 5.0 mL of Na_2(EDTA) were used due to the poorer solubility of the substrate. For Table 4.1 entries 3 and 8, the silica gel was buffered with 1% Et_3N in hexane.]

Representative Asymmetric Epoxidation Procedure using Oxone and K_2CO_3 (Method B) (Table 4.2, entry 1) (OAW2316-2): To a solution of *trans*-β-methylstyrene (0.059 g, 0.50 mmol), ketone **1-53·H_2O** (0.015 g, 0.046 mmol), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.03 mmol) in MeCN-DMM (v/v, 1/2) (9 mL) was added buffer (0.05 M aq Na_2HPO_4-0.05 M aq KH_2PO_4, pH 7.0) (3 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.212 M in 4 x 10^{-4} M aq EDTA, 4.8 mL) and a solution of K_2CO_3 (0.42 M in 4 x 10^{-4} M aq EDTA, 4.8 mL) were added dropwise simultaneously and separately over 8 h via syringe pump. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et_3N in organic solvent, first pentane, then pentane/Et_2O = 20/1) to give the epoxide as a colorless oil (0.054 g, 81% yield, 86% ee).

Table 4.2, entry 1 (OAW2316-2, b0805a, b1012e)

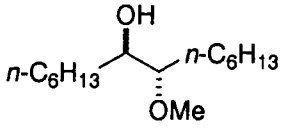
***trans*-β-Methylstyrene oxide.**[8,17] Colorless oil; $[\alpha]_D^{20}$ = +40.8 (*c* 0.92, $CHCl_3$) (86% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.59 (d, *J* = 2.1 Hz, 1H), 3.05 (qt, *J* = 5.1, 2.1 Hz, 1H), 1.70 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.6, 128.2, 125.7, 59.6, 59.2, 18.1.

Table 4.2, entry 2 (OAW2322-1, b0811c, b1012a)

***trans*-Stilbene oxide.**[8,18] White solid; $[\alpha]_D^{20}$ = +319.8 (*c* 0.80, Benzene) (93% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.24 (m, 10H), 3.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.0.

Table 4.2, entry 3 (OAW2318-1, b0811d)

***trans*-Tetradec-7-ene oxide.**[8] Colorless oil; $[\alpha]_D^{20}$ = +23.7 (*c* 0.90, $CHCl_3$) (88% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (t, *J* = 4.4 Hz, 2H), 1.56-1.23 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.1, 32.3, 32.0, 29.3, 26.2, 22.7, 14.2.



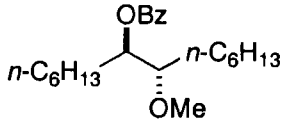
(OAW2319)

8-Methoxytetradecan-7-ol. To a solution of the above epoxide (0.056 g, 0.26 mmol) in MeOH (0.3 mL) was added NaOMe (0.07 g, 1.32 mmol) in a small screw cap vial equipped with a stir bar. The reaction was stirred at 100 °C for 2 d. The solvent was

[17] Witkop, B.; Foltz, C.M. *J. Am. Chem. Soc.* **1957**, *79*, 197.

[18] Chang, H-T.; Sharpless, K.B. *J. Org. Chem.* **1996**, *61*, 6456.

evaporated and the residue was purified by flash chromatography (silica gel, hexane/Et_2O = 3/1) to obtain a colorless oil (0.029 g, 46% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 3.78-3.70 (m, 1H), 3.40 (d, J = 1.2 Hz, 3H), 3.10-3.04 (m, 1H), 2.08-2.02 (m, 1H), 1.54-1.22 (m, 20H), 0.90-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.6, 71.5, 57.9, 32.1, 32.0, 29.7, 29.6, 28.7, 26.4, 26.0, 22.8, 14.3.



(OAW2321)

((8-methoxytetradecan-7-yloxy)methyl)benzene. To a solution of the above alcohol (0.029 g, 0.12 mmol) in benzene (1.2 mL) was added benzoyl chloride (0.017 g, 0.014 mL, 0.12 mmol) and pyridine (0.011 g, 0.011 mL, 0.14 mmol) in a small screw cap vial equipped with a stir bar. The reaction was heated at 60 °C overnight. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane/Et_2O = 16/1) to obtain a colorless oil (0.025 g, 60% yield). $[\alpha]_D^{20}$ = -4.1 (*c* 0.44, $CHCl_3$) (88% ee); IR (film): 1720, 1452, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.58-7.52 (m, 1H), 7.47-7.42 (m, 2H), 5.27 (dt, J = 9.6, 3.3 Hz, 1H), 3.45 (s, 3H), 3.81-3.22 (m, 1H), 1.87-1.48 (m, 5 H), 1.38-1.22 (m, 15 H), 0.91-0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 133.0, 130.7, 129.8, 128.5, 83.0, 75.9, 58.7, 32.0, 31.8, 31.0, 29.6, 29.44, 29.38, 26.1, 26.0, 22.7, 14.24, 14.20; HRMS calcd for $C_{22}H_{36}O_3$ (M) 348.2665; Found: 348.2667.

Table 4.2, entry 4 (OAW2314-2)

***trans*-Cinnamyl alcohol oxide.**[19] White solid; $[\alpha]_D^{20}$ = +35.5 (*c* 0.85, $CHCl_3$) (79% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 4.07 (dd, *J* = 12.6, 2.1 Hz, 1H), 3.95 (d, *J* = 2.1 Hz, 1H), 3.82 (dd, *J* = 12.6, 3.0 Hz, 1H), 3.24 (m, 1H), 1.81 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.6, 128.4, 125.9, 62.7, 61.5, 55.8.

Table 4.2, entry 5 (OAW2322-2, b1039, b1012b)

Methylstilbene oxide.[8,20] Colorless oil; $[\alpha]_D^{20}$ = +98.9 (*c* 0.98, EtOH) (88% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.46-7.40 (m, 6H), 7.39-7.33 (m, 2H), 4.02 (s, 1H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 136.1, 128.7, 128.4, 127.9, 126.7, 125.3, 67.3, 63.3, 16.9.

Table 4.2, entry 6 (OAW2316-1, b0805b, b1012c)

Phenylcyclohexene oxide.[8] Colorless oil; $[\alpha]_D^{20}$ = +86.0 (*c* 1.11, benzene) (92% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 3.09 (t, *J* = 1.8 Hz, 1H), 2.36-2.26 (m, 1H), 2.14 (dt, *J* = 15.0, 5.4 Hz, 1H), 2.04-1.98 (m, 2H), 1.70-1.45 (m, 3H), 1.41-1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 128.4, 127.3, 125.4, 62.0, 60.3, 29.0, 24.9, 20.3, 20.0.

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[19] Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.

[20] Brandes, B.D.; Jacobsen, E.N. *J. Org. Chem.* **1994**, *59*, 4378.

Table 4.2, entry 7 (OAW2314-1)

(*E*)-1-(Benzyloxy)cyclooct-1-ene oxide.[21] Colorless oil; $[\alpha]_D^{20}$ = +7.1 (*c* 1.09, $CHCl_3$) (95% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34-8.01 (m, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 3.22 (dd, *J* = 9.9, 4.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.29 (dq, *J* = 13.8, 4.5 Hz, 1H), 1.88-1.22 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 133.5, 130.2, 129.9, 128.6, 86.0, 60.5, 28.04, 28.99, 26.21, 26.17, 25.3, 24.9.

Table 4.2, entry 8 (BJN-II-25, OAW2304-3)

(*E*)-2-(Hex-1-enyl)isoindoline-1,3-dione oxide. White solid; mp 104-105 °C; $[\alpha]_D^{20}$ = +33.5 (*c* 1.04, $CHCl_3$) (75% ee); IR (film): 1778, 1729, 1394 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.77-7.75 (m, 2H), 4.66 (d, *J* = 1.6 Hz, 1H), 4.28 (td, *J* = 6.4, 1.6 Hz, 1H), 1.73-1.67 (m, 2H), 1.57-1.38 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 134.7, 131.8, 123.9, 59.3, 56.1, 31.1, 27.7, 22.6, 14.1; HRMS Calcd for $C_{14}H_{15}NO_3$ (M): 245.1052; Found: 245.1056.

Table 4.2, entry 9 (BJN-II-30, OAW2304-1)

(*E*)-1-(Hex-1-enyl)pyrrolidine-2,5-dione oxide. Pale yellow oil; $[\alpha]_D^{20}$ = +18.1 (*c* 1.01, $CHCl_3$) (86% ee); IR (film): 1784, 1712, 1395, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (d, *J* = 0.9 Hz, 1H), 4.03 (td, *J* = 5.4, 0.9 Hz, 1H), 2.68 (s, 4H), 1.65-1.28 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 59.3, 55.8, 30.8, 28.2, 27.5, 22.4, 14.0; HRMS Calcd for $C_{10}H_{15}NO_3$ (M): 197.1052; Found: 197.1057.

[21] Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

Table 4.2, entry 10 (OAW2309-1b)

***cis*-β-Methylstyrene oxide.**[11,17,22,23] Colorless oil; $[\alpha]_D^{20}$ = +17.7 (*c* 0.94, $CHCl_3$) (49% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.26 (m, 5H), 4.14 (d, *J* = 4.2 Hz, 1H), 3.38-3.31 (m, 1H), 1.15 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 128.2, 127.6, 126.7, 57.7, 55.3, 12.7.

Table 4.2, entry 11 (OAW2330-1)

***cis*-Cinnamyl alcohol oxide.**[24] Colorless oil; $[\alpha]_D^{25}$ = +25.2 (*c* 0.50, $CHCl_3$) (48% ee); IR (film): 3390, 1798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.17 (d, *J* = 4.2 Hz, 1H), 3.57-3.49 (m, 1H), 3.46-3.38 (m, 2H), 2.34 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 128.4, 128.0, 126.3, 60.5, 58.9, 57.2.

Table 4.2, entry 12 (OAW2330-2)

***(Z)-tert*-Butyldimethyl(3-phenylallyloxy)silane oxide.** Colorless oil; $[\alpha]_D^{25}$ = +14.7 (*c* 0.81, $CHCl_3$) (70% ee); IR (film): 1257, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 4.14 (d, *J* = 3.9 Hz, 1H), 3.57 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.46-3.35 (m, 2H), 0.83 (s, 9H), -0.06 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 128.3, 127.9, 126.5, 61.0, 59.1, 57.0, 26.0, 18.4, -5.25, -5.34; Anal. Calcd for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 68.19; H, 8.93.

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[22] Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

[23] Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

[24] Denis, J.-N.; Greene, A.E.; Serra, A.A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.

Table 4.2, entry 13 (OAW2315-2)

(*Z*)-*tert*-Butyldimethyl(3-phenylallyl)silane oxide. Colorless oil; $[\alpha]_D^{25}$ = +25.8 (*c* 0.91, $CHCl_3$) (65% ee); IR (film): 1496, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 4.08 (d, *J* = 4.2 Hz, 1H), 3.39-3.23 (m, 1H), 0.84 (dd, *J* = 14.1, 6.3 Hz, 1H), 0.56 (dd, *J* = 14.1, 7.2 Hz, 1H), -0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 128.1, 127.6, 126.9, 58.3, 58.1, 14.5, -1.0; Anal. Calcd. for $C_{12}H_{18}OSi$: C, 69.84; H, 8.79; Found: C, 70.03; H, 8.86.

Table 4.2, entry 14 (MXZ1230)

(*Z*)-*tert*-Butyldimethyl(styryl)silane oxide. Colorless oil; $[\alpha]_D^{25}$ = +49.7 (*c* 0.71, $CHCl_3$) (80% ee); IR (film): 1496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 4.27 (d, *J* = 5.4 Hz, 1H), 2.53 (d, *J* = 5.4 Hz, 1H), -0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.2, 127.6, 126.3, 57.3, 53.6, -2.0; Anal. Calcd for $C_{11}H_{16}OSi$: C, 68.69; H, 8.39. Found: C, 68.63; H, 8.25.

Table 4.2, entry 15 (MXZ1318)

(*Z*)-*tert*-butyldimethyl(styryl)silane oxide. Colorless oil; $[\alpha]_D^{25}$ = +51.4 (*c* 1.4, $CHCl_3$) (90% ee); IR (film): 1495, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.26 (d, *J* = 5.1 Hz, 1H), 2.63 (d, *J* = 5.1 Hz, 1H), 0.93 (s, 9H), -0.34 (s, 3H), -0.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.1, 127.6, 126.5, 56.9, 51.5, 26.7, 17.1, -6.6, -7.1; Anal. Calcd for $C_{14}H_{22}OSi$: C, 71.73; H, 9.46. Found: C, 71.85; H, 9.25.

Table 4.2, entry 16 (OAW2309-2b)

2,2-Dimethylchromene Oxide.[13,25,26] Pale yellow solid; $[\alpha]_D^{25}$ = -28.7 (*c* 1.06, THF) (88% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.23 (td, *J* = 7.8, 1.5 Hz, 1H), 6.92 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 3.90 (d, *J* = 4.5 Hz, 1H), 3.49 (d, *J* = 4.5 Hz, 1H), 1.58 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 130.4, 129.8, 121.2, 120.1, 118.1, 73.1, 63.0, 51.1, 25.8, 22.7.

Table 4.2, entry 17 (OAW2309-3b)

6-Cyano-2,2-dimethylchromene Oxide.[13,27,28] White solid; $[\alpha]_D^{25}$ = -70.6 (*c* 0.84, $CHCl_3$) (90% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 4.2 Hz, 1H), 3.54 (d, *J* = 4.2 Hz, 1H), 1.59 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 134.5, 133.9, 121.3, 119.1, 118.9, 104.4, 74.8, 62.4, 50.0, 25.6, 23.1.

Table 4.2, entry 18 (OAW2323-1)

(*Z*)-Oct-3-en-1-ynylbenzene oxide.[14] Colorless oil; $[\alpha]_D^{25}$ = +3.2 (*c* 0.90, $CHCl_3$) (62% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.35-7.29 (m, 3H), 3.65 (d, *J* = 3.9 Hz, 1H), 3.13 (td, *J* = 6.3, 3.9 Hz, 1H), 1.86-1.70 (m, 2H), 1.59-1.38 (m, 4H), 0.95 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 128.9, 128.5, 122.4, 85.4, 84.5, 58.8, 45.8, 29.3, 28.2, 22.7, 14.2.

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[26] Scheurer, A.; Mosset, P.; Spiegel, M.; Saalfrank, R.W. *Tetrahedron* **1999**, *55*, 1063.

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[28] Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541.

Table 4.2, entry 19 (OAW2320-2)

Styrene oxide.[8,11,29] Colorless oil; $[\alpha]_D^{25}$ = -8.7 (*c* 1.03, Benzene) (27% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 3.89 (dd, *J* = 4.2, 2.7 Hz, 1H), 3.17 (dd, *J* = 5.7, 4.2 Hz, 1H), 2.83 (dd, *J* = 5.7, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.6, 128.3, 125.6, 52.5, 51.4.

Table 4.2, entry 20 (OAW2324-1)

α-Methylstyrene oxide.[15] Colorless oil; $[\alpha]_D^{25}$ = +0.46 (*c* 1.02, $CHCl_3$) (6% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 2.99 (d, *J* = 5.1 Hz, 1H), 2.81 (d, *J* = 5.1 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 128.5, 127.6, 125.5, 57.2, 56.9, 22.0.

Table 4.2, entry 21 (OAW2315-1)

1-Chloro-4-(1-cyclobutylideneethyl)benzene oxide.[16] Colorless oil; $[\alpha]_D^{25}$ = -33.9 (*c* 0.95, $CHCl_3$) (67% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H), 7.18-7.15 (m, 2H), 2.49-2.25 (m, 3H), 1.86-1.71 (m, 2H), 1.62-1.51 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 133.0, 138.3, 127.5, 70.3, 63.4, 29.5, 29.1, 19.6, 12.4.

[29] Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112.

CHAPTER FIVE

ASYMMETRIC EPOXIDATION OF TRANS-, CIS- AND 1,1-DISUBSTITUTED OLEFINS BY MORPHOLINONE KETONES

5.1. ASYMMETRIC EPOXIDATION OF 1,1-DISUBSTITUTED OLEFINS BY MORPHOLINONE KETONE

5.1.1. Introduction

Among six classes of olefins, 1,1-disubstituted terminal olefins (**VI**) have been challenging substrates for asymmetric epoxidaiton (Figure 5.1).[1,2,3,4,5] In our earlier

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[1] For a leading review on asymmetric epoxidation, see: Xia, Q-H.; Ge, H-Q.; Ye, C-P.; Liu, Z-M.; Su, K-X. *Chem. Rev.* **2005**, *105*, 1603.

[2] For leading references on asymmetric epoxidation of 1,1-disubtituted terminal olefins directed by hydroxyl groups, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH: New York, 1993; Chapter 4.1. (b) Katsuki, T.; Martin, V.S. *Org. React.* **1996**, *48*, 1. (c) Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075.

[3] For examples of asymmetric epoxidation of 1,1-disubstituted terminal olefins with chiral metal catalysts, see: (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Halterman, R. L.; Jan, S.-T.; Nimmons, H. L.; Standlee, D. J.; Khan, M. A. *Tetrahedron* **1997**, *53*, 11257. (c) Kim, G.-J.; Shin, J.-H. *Catal. Lett.* **1999**, *63*, 83. (d) Tanaka, H.; Kuroboshi, M.; Takeda, H.; Kanda, H.; Torii, S. *J. Electroanal. Chem.* **2001**, *507*, 75. (e) Zhang, R.; Yu, W-Y.; Sun, H-Z.; Liu, W-S.; Che, C-M. *Chem. Eur. J.* **2002**, *8*, 2495. (f) Zhang, H.; Xiang, S.; Li, C. *Chem. Commun.* **2005**, 1209. (g) Fristrup, P.; Dideriksen, B. B.; Tanner, D.; Norrby, P. O. *J. Am. Chem. Soc.* **2005**, *127*, 13672. (h) Zhang, H.; Zhang, Y.; Li, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2417. (i) Yu, K.; Lou, L-L.; Ding, F.; Wang, S.;

studies with ketone **1-104**, it was found that (*S*)-α-methylstyrene oxide and α-isopropyl styrene oxide could be obtained in 30% ee and 58% ee respectively (Figure 5.2).[4f] Spiro transition states (**A-D**, Figure 5.3 and 5.4) are generally favored due to the stabilizing interaction between the oxygen non-bonding orbital and the olefin π* orbital (Figure 1.16, page 35). However, in the case of 1,1-disubstituted olefins, planar transition states **E** and **G** appear to be more sterically favored compared to spiro transition states (Figure 5.3 and 5.4). Planar **F** and **H** are both electronically and sterically unfavored, and thus are unlikely to be major contributors. As judged by the absolute configuration of the α-methylstyrene oxide, planar **E** appears to be favored over planar **G**. This is presumably due to the attraction between the oxazolidinone of the catalyst and the phenyl group of the substrate.

Wang, Z.; Liu, S. *Catal. Commun.* **2006**, *7*, 170. (j) Sun, Y.; Tang, N. *J. Mol. Catal. A: Chem.* **2006**, *255*, 171. (k) Lou, L-L.; Yu, K.; Ding, F.; Zhou, W.; Peng, X.; Liu, S. *Tetrahedron Lett.* **2006**, *47*, 6513.

[4] For examples of asymmetric epoxidation of 1,1-disubstituted terminal olefins with chiral dioxiranes, see: (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) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (d) 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. (e) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443. (f) Tian, H., She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (g) Armstrong, A.; Moss, W. O.; Reeves, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779. (h) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610. (i) Chan, W-K.; Yu, W-Y.; Che, C-M.; Wong, M-K. *J. Org. Chem.* **2003**, *68*, 6576. (j) Bez, G.; Zhao, C-G. *Tetrahedron Lett.* **2003**, *44*, 7403. (k) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Mari, L. *Tetrahedron: Asymmetry* **2004**, *15*, 3831. (l) Armstrong, A.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 257. (m) Armstrong, A.; Dominguez-Fernandez, B.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 6614

[5] For examples of asymmetric epoxidation of 1,1-disubstituted terminal olefins with oxaziridinium salts, see: (a) Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3325. (b) 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. (c) Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580. (d) Page, P. C. B.; Barros, D.; Buckley, B. R.; Ardakani, A.; Marples, B. A. *J. Org. Chem.* **2004**, *69*, 3595. (e) Page, P. C. B.; Buckley, B. R.; Rassias, G. A.; Blacker, A. J. *Eur. J. Org. Chem.* **2006**, 803.

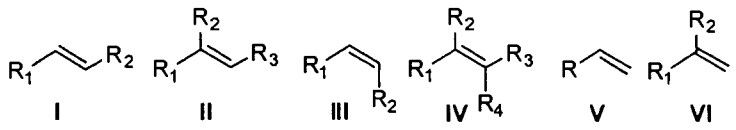
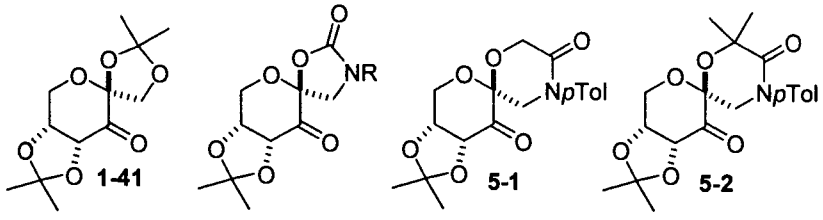


Figure 5.1



1-104, R = Boc
1-111b, R = *p*-PhMe
1-111c, R = *p*-PhEt

Figure 5.2

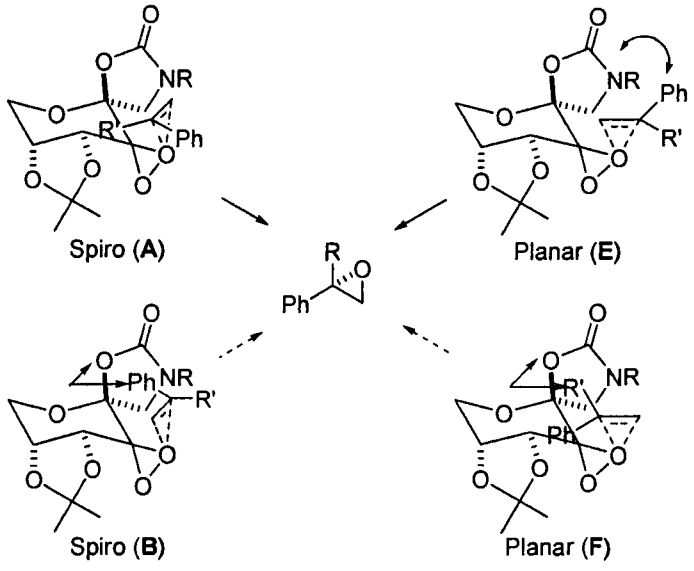


Figure 5.3

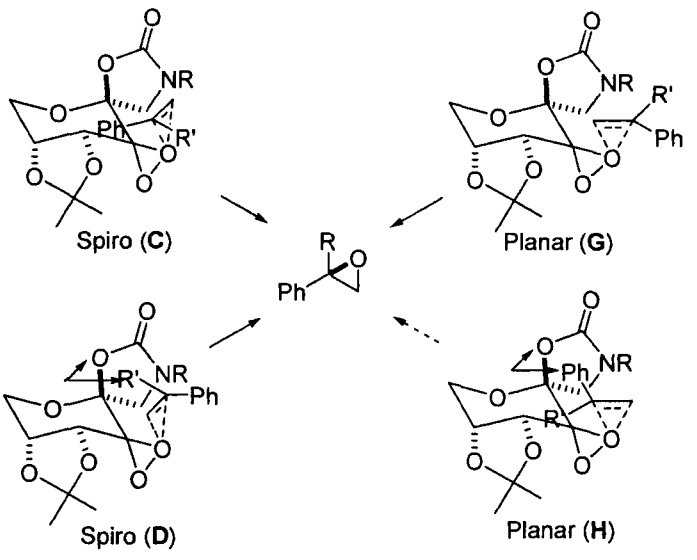
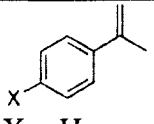
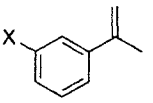
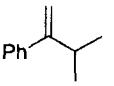
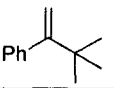


Figure 5.4

Initial studies of the epoxidation of 1,1-disubstituted olefins were performed using ketone **1-111c** (Figure 5.2). However, low ee's were obtained for the epoxidation of all the substrates studied (Table 5.1). With these results, it was realized that a new catalyst was needed for this class of substrate. The new catalyst (**5-1**, Figure 5.2) was designed to further favor planar **E**-like transition state based on the aforementioned observation with (*S*)-α-methylstyrene oxide and α-isopropyl styrene oxide (Figure 5.3 and 5.4).

Table 5.1 Early Studies of the Asymmetric Epoxidation of 1,1-Disubstituted Olefins[a,b]

entry	substrate	conv (%)	ee (%)
			
1	X = H	100	7
2	X = Cl	100	22
3	X = F	100	17

			
4	X = Me	81	29
5	X = OMe	100	14
6	X = NC	100	19
7		63	32
8		12	nd

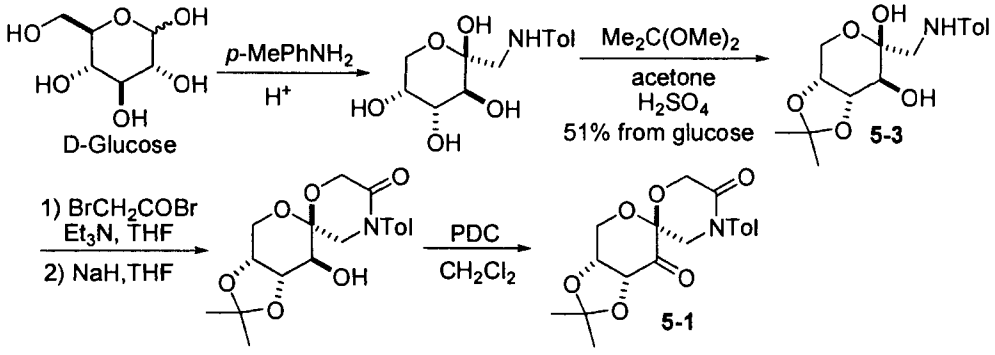
[a] All epoxidations were carried out with the olefin (0.2 mmol), ketone **1-111c** (0.04 mmol), Oxone (0.53 mmol), and K_2CO_3 (2.11 mmol) in DME/DMM (3/1, v/v, 3 mL), and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 2 mL) at 0 °C for 1.5 h. [b] Notebook pages: entry 1 OAW0816-1, entry 2 OAW0828-1, entry 3 OAW0827-2, entry 4 OAW0827-1, entry 5 OAW0817-1, entry 6 OAW0816-2, entry 7 OAW0843-1, entry 8 OAW0843-2.

5.1.2. Results and Discussion

Working alongside Bin Wang, the synthesis of ketone **5-1** is carried out as outlined in Scheme 5.1. Amino alcohol **5-3**, prepared from a previously reported procedure,[6] was treated with 2-bromoacetyl bromide in triethylamine and THF followed by NaH. The resulting alcohol was oxidized to ketone **5-1** using PDC in CH_2CH_2. The X-ray structure of ketone **5-1** is shown in figure 5.5. An overlay of ketone **5-1** (dashed line) and **1-111b** (solid line) indicated that, unlike ketone **1-111b**, the *N*-phenyl group and the lactam carbonyl group in ketone **5-1** are not coplanar (Figure 5.6).

[6] Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293.

Scheme 5.1 Synthesis of Ketone 5-1



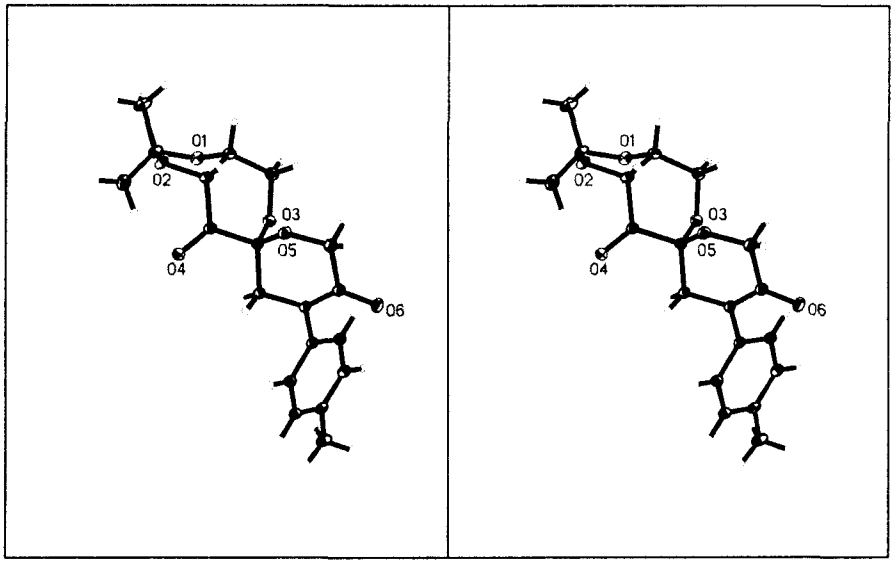


Figure 5.5 X-ray Sturcture of Ketone 5-1 (Stereoview)

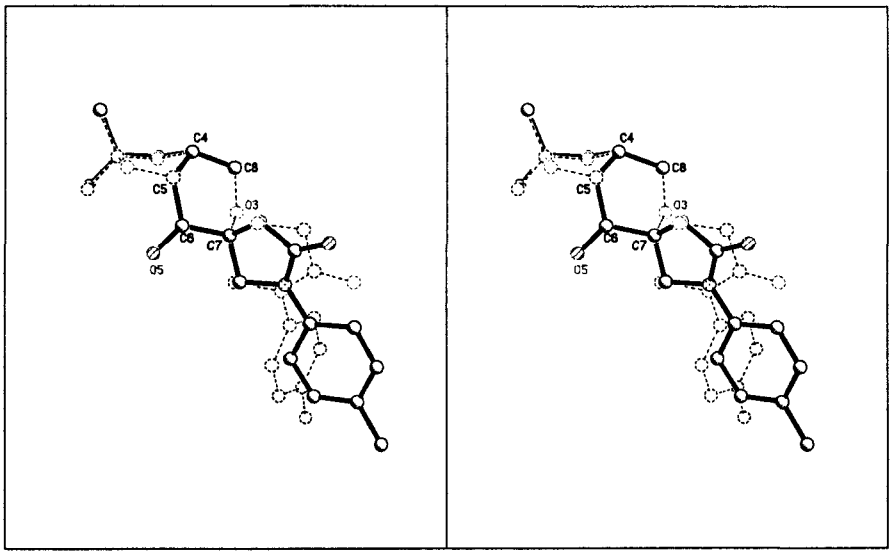


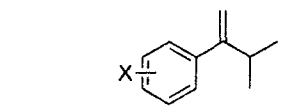
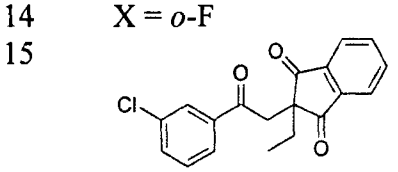
Figure 5.6 Crystal Structure Overlay of Ketones 1-111b and 5-1 (Stereoview)

As shown in Table 5.2, a variety of aromatic 1,1-disubstituted olefins could be epoxidized in good enantioselectivities (62-88% ee). Substrates with a bulky R group at the α-position generally produced epoxides with higher enantioselectivities than those with a small R group (Table 5.2, entries 1-6). The substitutions on the phenyl ring also affect enantioselectivity (Table 5.2, entries 7-14). Up to 88% ee was obtained for allylic, homoallylic and bishomoallylic alcohols (Table 5.2, entries 16-21). A non-aromatic substrate was also epoxidized in moderate ee (60% ee, Table 5.2, entry 22).

In addition to 1,1-disubstituted olefins, the epoxidations of cis- and trisubstituted olefins were also investigated with ketone **5-1**. Ketone **5-1** epoxidizes cis-olefins in similar enantioselectivities compared to ketone **1-111b** (Table 5.3, entries 1 and 2). This result indicated that there is a similar attraction between the morpholinone moiety of ketone **5-1** or the oxazolidinone moiety of ketone **1-111b** and the phenyl group of the

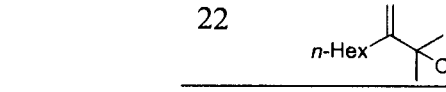
olefin in spiro transition state **I** (Figure 5.7). When 1-phenylcyclohexene was epoxidized with ketone **5-1**, 80% ee was obtained for the (*S*,*S*)-enantiomer presumably derived from planar transition state **L** (Figure 5.8, Table 5.3, entry 3). On the other hand, when ketones **1-111a** and **1-111b** were used as the catalyst, (*S*,*S*)-epoxide was obtained in 42% ee[4f] and (*R*,*R*)-epoxide was obtained in 25% ee[6] respectively. This result suggested that the morpholinone moiety of ketone **5-1** could accommodate a planar transition state better than the oxazolidinone of ketones **1-111a** and **1-111b**.

Table 5.2 Asymmetric Epoxidation of 1,1-Disubstituted Olefins with Ketone 5-1[a]

entry	substrate	yield (%)[b]	ee (%)	config.[c]
1	R = Me	60	62[c]	(+)-(*S*)[7]
2	R = Et	71	78[d]	(+)-(*S*)[7]
3	R = *n*-Pr	90	75[d]	(+)
4	R = *i*-Bu	54	74[d]	(+)
5	R = *c*-C_6H_{11}	62	77[c]	(+)
6	R = *t*-Bu	43	86[d]	(+)
				
7	X = H	71	84[d]	(+)
8	X = *p*-*i*-Pr	51	82[c]	(+)
9	X = *p*-OMe	94	84[c]	(+)
10	X = *p*-F	78	74[d]	(+)
11	X = *p*-Br	68	78[d]	(+)
12	X = *m*-Me	57	82[c]	(+)
13	X = *m*-F	74	81[d]	(+)
14	X = *o*-F	72	88[d]	(+)
15		51	66[c]	(-)-(*S*)[8]

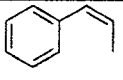
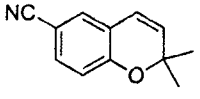
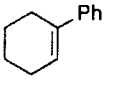
[7] Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.

[8] Tanaka, K.; Yoshida, K.; Sasaki, C.; Osano, Y. T. *J. Org. Chem.* **2002**, *67*, 3131.

				
16	n = 1	93	77[c]	(+)-(*R*)[9]
17	n = 2	47	72[c]	(+)
18	n = 3	62	74[c]	(+)
				
19	R = Me	76	87[c]	(+)-(*S*)[7]
20	R = Et	85	87[d]	(+)
21	R,R = $(CH_2)_4$	86	88[d]	(+)-(*S*)[7]
22		78	60[d]	(+)

[a] All epoxidations were carried out with the olefin (0.2 mmol), ketone **5-1** (0.06 mmol), Oxone (0.32 mmol), and K_2CO_3 (1.34 mmol) in 1,4-dioxane (3 mL), and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 2 mL) at -10 °C for 2 h (4 h for entries 6, 11, 13, and 14). [b] Isolated yield except entry 7 which is crude yield. [c] The ee was determined by chiral HPLC (Chiracel OD column). [d] The ee was determined by chiral GC (B-DM column). [e] The absolute configurations were determined by comparing the measured optical rotations with reported ones.

Table 5.3 Asymmetric Epoxidation of cis- and Trisubstituted Olefins by Ketone 5-1[a]

entry	substrate	conv. (yield) (%)[b]	ee (%)	config.[g]
1		100[c](60)	85[e]	(-)-(1*R*,2*S*)[10]
2		89[d](87)	84[f]	(+)-(3*R*,4*R*)[10]
3		99[c](89)	80[e]	(-)-(*S*,*S*)[4b,f,6]

[a] All reactions were carried out with substrate (0.2 mmol), ketone **5-1** (0.06 mmol for entry 1, 0.04 mmol for entries 2, 3, and 4), Oxone (0.32 mmol), and K_2CO_3 (1.344 mmol) in DME/DMM (3:1, v/v; 3.0 mL) and buffer (0.1 M K_2CO_3-AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3; 2 mL); For entries 1, 3, and 4, the reaction was carried out at -10 °C for 4 h; For entry 2, the reaction was carried out at 0 °C for 12 h. [b] Isolated yield. [c] The conversion

[9] Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Seebach, D.; Zhang, R. *Org. Lett.* **2003**, *5*, 725.

[10] Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

was determined by GC (B-DM column). [d] The conversion was determined by ^{1}H NMR. [e] The ee was determined by chiral GC (B-DM column). [f] The ee was determined by chiral HPLC (Chiracel OD column). [g] The absolute configurations were determined by comparing the measured optical rotations and GC trace with reported ones.

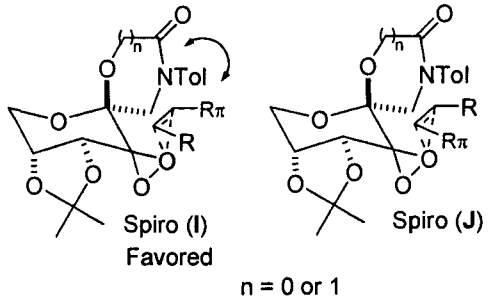


Figure 5.7 Proposed Competing Transition States for the Epoxidation of *cis*-Olefins with Ketone 5-1 and 1-111b

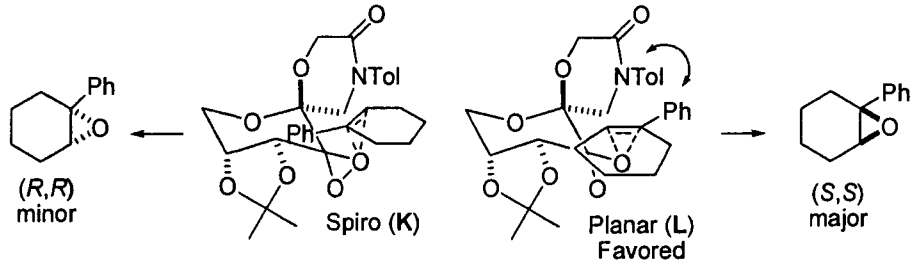


Figure 5.8 Proposed Competing Transition States for the Epoxidation of 1-Phenylcyclohexene with Ketone 5-1

The idea of planar transition state **M** (Figure 5.9) being the major transition state was further supported by the known absolute configuration of several epoxides (Table 5.2, entries 1, 2, 15, 16, 19, and 21). Bulky R groups at the α-position disfavor spiro transition state **P**, thus increasing the ee (e.g. Table 5.2, entry 1 vs 6).

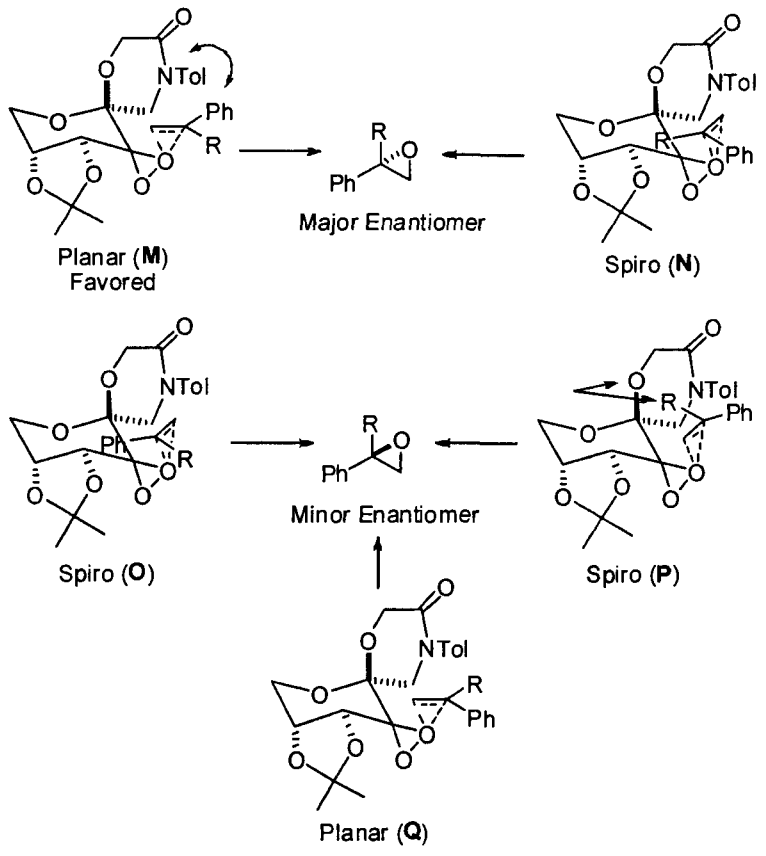


Figure 5.9 Proposed Competing Transition States for the Epoxidation of 1,1-Disubstituted Olefins with Ketone 5-1

5.2. ASYMMETRIC EPOXIDATION OF 1,1-DISUBSTITUTED OLEFINS BY 2,2-DIMETHYLMORPHOLIN-3-ONE KETONE

5.2.1. Introduction

Thus far, each of the ketone catalysts that are extensively studied in our laboratory has a unique feature and substrate scope. For instance, due to steric repulsion, many transition states are disfavored for the epoxidation of trans- and trisubstituted olefins with ketone **1-41**. Spiro **R** is the major transition state and competing transition states such as spiro **S** are disfavored by the steric interactions between the dimethyl ketone group on the

ketone and the R_l group on the olefin (Figure 5.10). For the epoxidation of conjugated cis-olefins with oxazolidinone-containing ketones such as **1-104** and **1-111** (Figure 5.2), the stereodifferentiation originates from the attraction between the oxazolidinone moiety of the ketone and the R_π group of the olefin, causing spiro **T** to be favored over spiro **U** (Figure 5.11). However, the enantioselectivity is lower for the epoxidation trans-olefins with ketone **1-104** and **1-111**.[4f,11] This is presumably due to the lack of steric repulsion by the dimethyl ketal group as in the case of ketone **1-41**, causing less stereodifferentiation between spiro transition states **V** and **W** (Figure 5.12). As discussed in section 5.1, the epoxidation of 1,1-disubstituted olefins with ketone **5-1** proceeds mainly via planar transition state **M** (Figure 5.9). The morpholinone moiety adopts a conformation that favors the planar transition state. Furthermore, ketone **5-1** provides a similar level of enantioselectivity compared to **1-111b**, which suggests that there exists an attraction between the morpholinone moiety and the R_π group of the olefin.

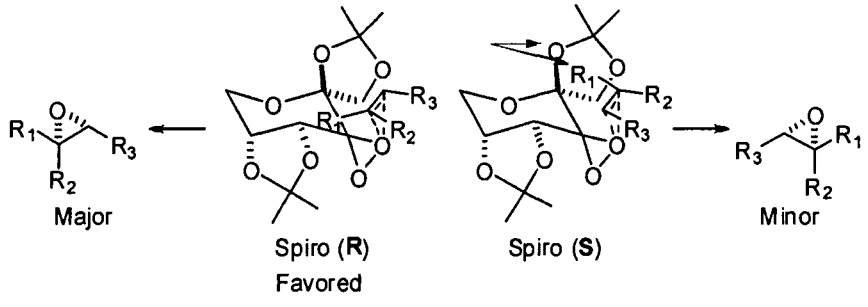


Figure 5.10 The Proposed Transition States for Asymmetric Epoxidations using Ketone 1-41

[11] *trans*-7-Tetradecene was epoxidized in 44% yield and 62% ee with ketone **1-111b**. (Reaction conditions: olefin (0.50 mmol), ketone (0.15 mmol), NBu_4HSO_4 (0.003 mmol), Oxone (1.32 mmol, 0.20 M), K_2CO_3 (5.29 mmol, 0.84 M) in CH_3CN-DMM (1:2, v/v, 7.5 mL) and buffer (0.1 M, K_2CO_3 – AcOH, pH 9.3) (5.0 mL) at 0 °C for 3.5 h). Notebook pages: OAW2815, OAW1816.

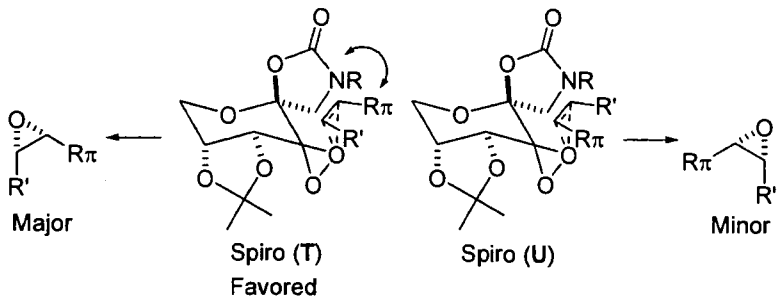


Figure 5.11 The Proposed Transition States for Asymmetric Epoxidations using Ketones 1-104 and 1-111

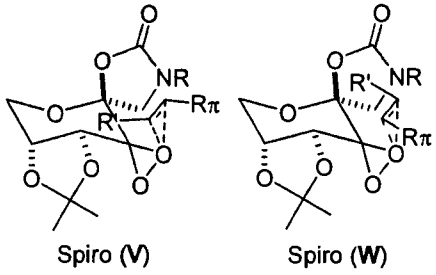


Figure 5.12 The Proposed Transition States for Asymmetric Epoxidations of trans-olefins using Ketones 1-104 and 1-111

With the information we have gained from the studies of ketones **1-41**, **1-104**, **1-111**, and **5-1**, ketone **5-2** was designed to combine the features of these catalysts with the hopes of creating a general catalyst for all classes of olefins (Figure 5.2). Ketone **5-2** possesses the dimethyl groups that are analogous to the dimethyl groups in ketone **1-41** which should cause steric repulsions between the substrate and the catalyst. Ketone **5-2** also has a morpholinone moiety, which should provide the attraction between the R_π group of the olefin and the catalyst.

5.2.2. Results and Discussion

Working alongside Bin Wang, ketone **5-2** was synthesized in good yield in two steps from previously reported aminoalcohol **5-3** (Scheme 5.2).[6,12] The X-ray crystal structure of ketone **5-2** is shown in figure 5.13.

Scheme 5.2 Synthesis of Ketone 5-2

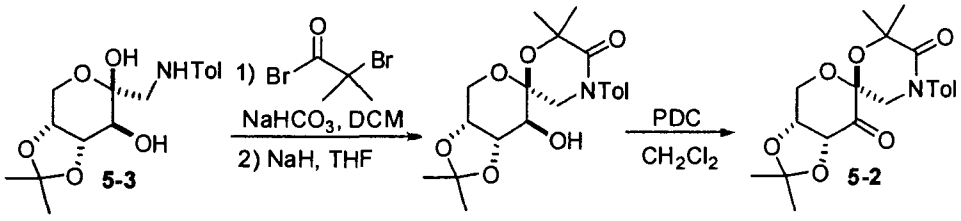


Table 5.4 Condition Screening for the Epoxidation of *trans*-β-Methylstyrene using Ketone 5-2[a]

entry	catalyst loading (%)	T (°C)	t (h)	buffer pH	conv (%)	ee (%)
1	30	-10	4	9.3	56	94
2	10	-10	4	9.3	21	86
3	30	0	4	9.3	98	92
4	10	0	4	9.3	59	88
5	**15**	**0**	**8**	**9.3**	**94**	**91**
6	10	0	8	9.3	82	87
7	15	0	8	8.0	84	86
8	15	0	8	10.0	88	87

[a] All reactions were carried out with substrate (0.2 mmol), ketone **5-2**, Oxone (0.35 mmol, 0.21M), and K_2CO_3 (0.81 mmol, 0.48M) in MeCN:DMM (1:2, v/v; 3.0 mL) and buffer (2 mL).

[12] Zhao, M-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.

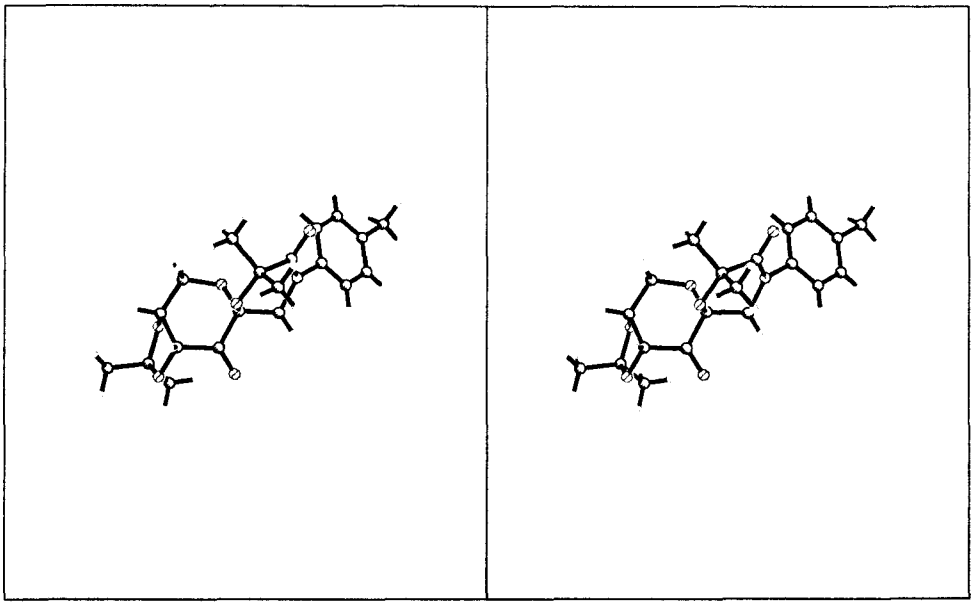
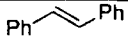
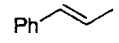
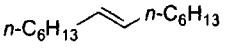
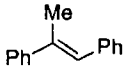
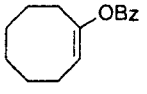
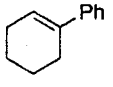
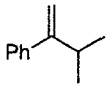
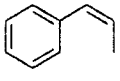
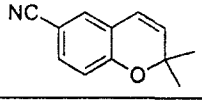


Figure 5.13 X-ray Sturcture of Ketone 5-2 (Stereoview)

The epoxidation conditions with ketone **5-2** were optimized using *trans*-β-methylstyrene as a substrate. Conducting the epoxidation at 0 °C, for 8 hours at pH 9.3 was found to be the best condition with a reasonable catalyst loading (15%) (Table 5.4, entry 5). Using this condition, the asymmetric epoxidation of various olefins was investigated. High enantioselectivities were obtained for the epoxidation of trans- and trisubstituted olefins with ketone **5-2** (Table 5.5, entries 2, 4, 6, 8, 10), which indicates that the catalyst is likely a general catalyst for these classes of olefins. It was also notable that the enantioselectivities of the epoxidation of trans- and trisubstituted olefins using ketone **5-2** were higher than the corresponding epoxidation with ketone **5-1** (Table 5.5, entries 1-10). To our surprise, the epoxidation of 1-phenylcyclohexene with ketone **5-2** produced the (+)-(*R*,*R*) epoxide in 87% ee (Table 5.5, entry 12). The configuration of the

resulting epoxide is opposite to that of the epoxide produced from the epoxidation with ketone **5-1** (Table 5.5, entry 11) but the same as that of the epoxide produced from the epoxidation with ketone **1-41** (Table 1.6, entry 11, page 23).[4b] The epoxidation of α-isopropyl styrene also results in the (+) and (-) epoxide with ketone **5-1** and **5-2**, respectively (Table 5.5, entries 13, 14). The epoxidation of cis-olefins with ketone **5-2** is slightly less enantioselective compared to that of ketone **5-1** (Table 5.5, entries 15-18).

Table 5.5. Asymmetric Epoxidation with Ketones 5-1 and 5-2[a]

entry	substrate	ketone (eq.)	T (°C)	t (h)	yield (%)[d]	ee (%)	config.[i]
1		**5-1** (0.30)	0	4	82	83[e]	(+)-(*R*,*R*)[4b]
2		**5-2** (0.30)	0	4	67	97[e]	(+)-(*R*,*R*)[4b]
3		**5-1** (0.15)	0	8	70	33[f]	(+)-(*R*,*R*)[4b]
4		**5-2** (0.15)	0	8	81	90[f]	(+)-(*R*,*R*)[4b]
5		**5-1** (0.15)	0	8	40	35[g]	(+)-(*R*,*R*)[4b]
6		**5-2** (0.15)	0	8	67	83[g]	(+)-(*R*,*R*)[4b]
7		**5-1** (0.15)	0	8	64	62[e]	(+)-(*R*,*R*)[4b]
8		**5-2** (0.15)	0	8	67	89[e]	(+)-(*R*,*R*)[4b]
9		**5-1** (0.15)	0	8	73	34[h]	(+)-(*R*,*R*)[13]
10		**5-2** (0.15)	0	8	83	90[h]	(+)-(*R*,*R*)[13]
11[b]		**5-1** (0.20)	-10	4	89	80[f]	(-)-(*S*,*S*)[j,4b]
12[b]		**5-2** (0.20)	-10	4	80	87[f]	(+)-(*R*,*R*)[4b]
13[c]		**5-1** (0.30)	-10	2	71	84[f]	(+)-(*S*)[j]
14[c]		**5-2** (0.30)	-10	2	89	45[f]	(-)-(*R*)[j]
15[b]		**5-1** (0.20)	-10	4	85	85[f]	(-)-(1*R*,2*S*)[4f]
16[b]		**5-2** (0.20)	-10	4	71	63[f]	(-)-(1*R*,2*S*)[4f]
17[b]		**5-1** (0.20)	0	12	87	84[e]	(+)-(3*R*,4*R*)[14]
18[b]		**5-2** (0.20)	0	12	61	81[e]	(+)-(3*R*,4*R*)[14]

[13] Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

[14] Wong, O.A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973.

[a] All reactions were carried out with olefin (0.2 mmol), ketone **5-1** or **5-2** (0.03-0.06 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.01 mmol), Oxone (0.26 mmol, 0.20 M), K_2CO_3 (1.16 mmol, 0.89 M) in CH_3CN-DMM (1:2 v/v) (3 mL) and buffer (0.1M K_2CO_3-AcOH, pH 9.3) (2 mL) for the indicated time and at the indicated temperature unless otherwise stated. [b] 0.32 mmol of Oxone (0.20 M) and 1.34 mmol of K_2CO_3 (0.84 M) were used, and DME-DMM (3:1) was used as the organic solvent. [c] 0.32 mmol of Oxone (0.20 M) and 1.34 mmol of K_2CO_3 (0.84 M) were used, and 1,4-dioxane was used as the organic solvent. [d] Isolated yield. [e] The ee was determined by chiral HPLC (Chiralcel OD column). [f] The ee was determined by GC (Chiraldex B-DM). [g] The epoxide was opened with NaOMe-MeOH, the resulting alcohol was converted to its benzoate, and the ee was determined by chiral HPLC (Chiralcel OD-H). [h] The ee was determined by chiral HPLC (Chiralpak AD-H column). [i] The absolute configurations were determined by comparing the measured optical rotations, GC trace, and HPLC trace with reported ones. [j] The configuration was assigned by analogy based on the mechanistic model described in section 5.1.

A structure overlay of ketones **1-41** (dashed line) and **5-2** (solid line) indicates that the ketones share similar steric features in the spiro ring (Figure 5.14). The dimethyl group on the six-membered morpholinone of **5-2** (R = Me, Figure 5.15) thus reduces the competition from transition states such as spiro **Y** via the greater steric repulsion as compared to ketone **5-1** (R = H, Figure 5.15). As a result, the enantioselectivities for trans- and trisubstituted olefins using ketone **5-2** are much higher than those using **5-1**.

In the case of 1-phenylcyclohexene, the attraction between the morpholinone of the catalyst and the phenyl group of the substrate causes planar **BB** to be the favored transition state (Figure 5.16). As a result, the (*S*,*S*) epoxide is obtained in 80% ee (Table 5.5, entry 11). However, the dimethyl group on the morpholinone of ketone **5-2** disfavors the corresponding planar transition state **DD**, thus giving the (*R*,*R*) epoxide in 87% ee (Figure 5.16, Table 5.5, entry 12).

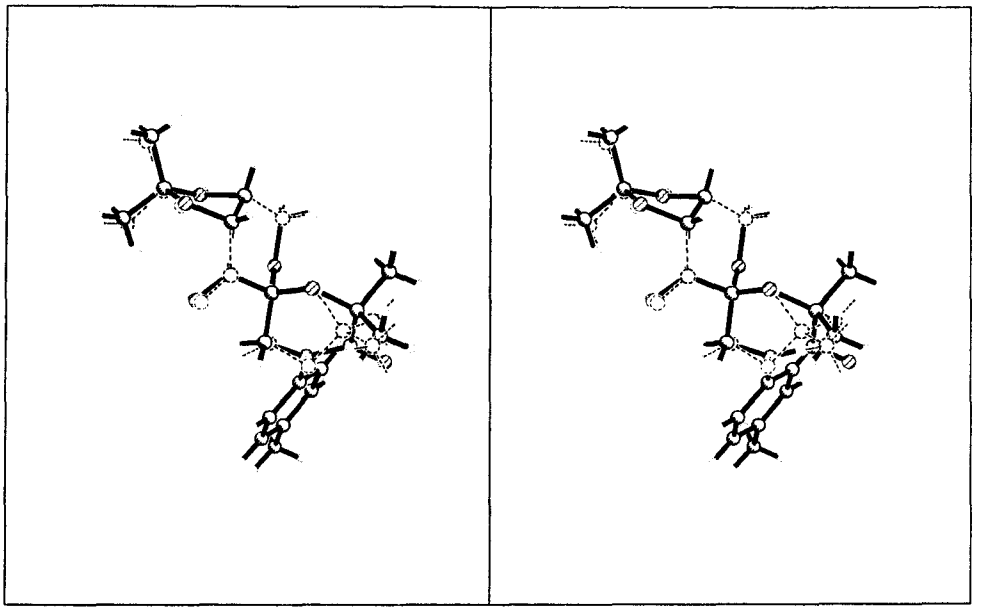


Figure 5.14 The Stereoview of the Structure Overlay of Ketones 1-41 and 5-2

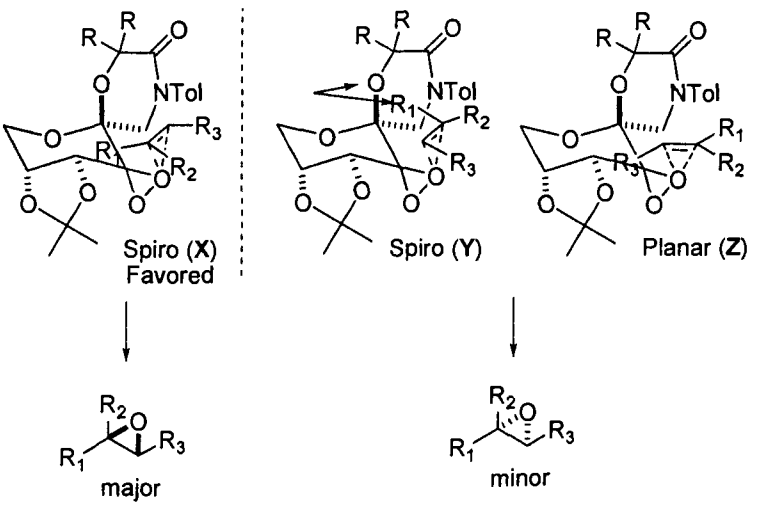


Figure 5.15 Proposed Competing Transition States for the Epoxidation of *trans*- and Trisubstituted Olefins with Ketones 5-1 and 5-2

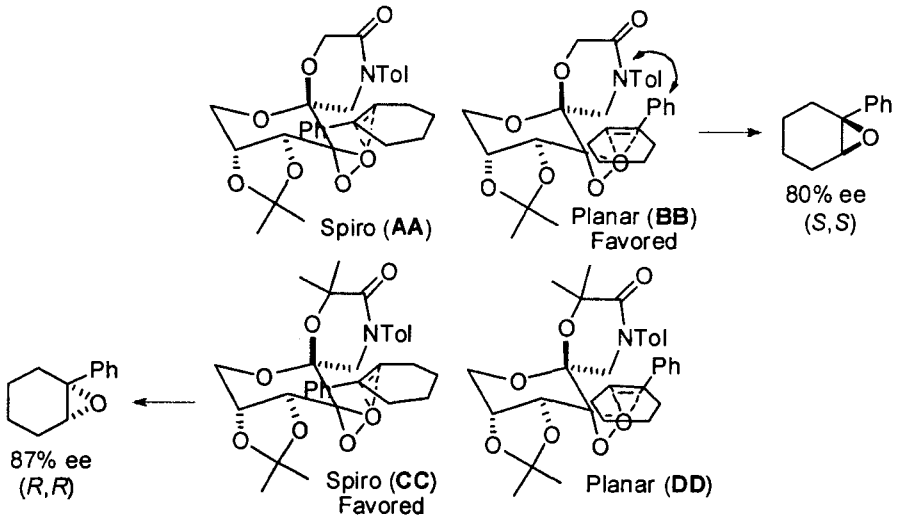


Figure 5.16 Proposed Competing Transition States for the Epoxidation of 1-Phenylcyclohexene with Ketones 5-1 and 5-2

α-Isopropyl styrene is another case where the dimethyl group in ketone **5-2** disfavors the planar transition state. Planar **FF** is favored when ketone **5-1** is used for the epoxidation, resulting in the (+) epoxide in 84% ee (Figure 5.17, Table 5.5, entry 13). However, when ketone **5-2** was used as the catalyst, spiro **KK** may become the major transition state, providing the (-) epoxide in 45% ee (Figure 5.18, Table 5.5, entry 14).

The epoxidation of cis-olefins with ketones **5-1** and **5-2** both provided the same enantiomer for both *cis*-β-methylstyrene (Table 5.5, entries 15 and 16) and 6-cyano-2,2-dimethylchromene (Table 5.5, entries 17 and 18), indicating there also exists an attraction between the morpholinone moiety of ketone **5-2** and the aromatic substituent of the olefin in spiro transition state **MM** (Figure 5.19). The attraction in spiro **MM** may have been weakened by the dimethyl group as compared to spiro **I** (Figure 5.7, n = 1), thus giving lower enantioselectivity for the epoxidation compared to that of ketone **5-1**.

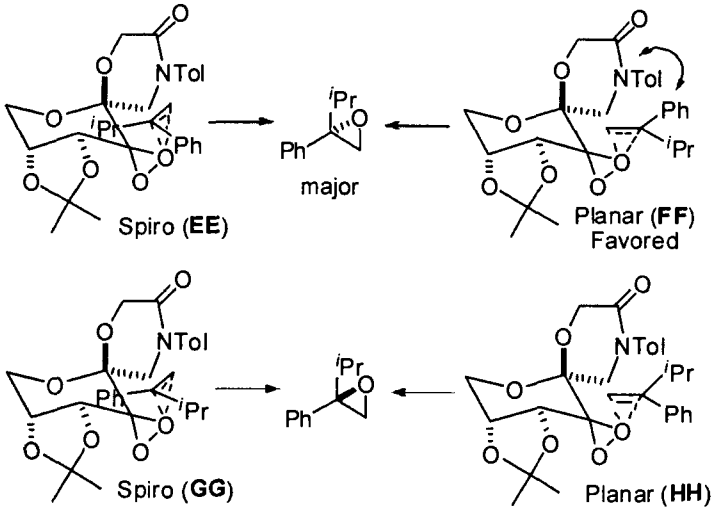


Figure 5.17 Proposed Competing Transition States for the Epoxidation of α-Isopropyl Styrene with Ketones 5-1

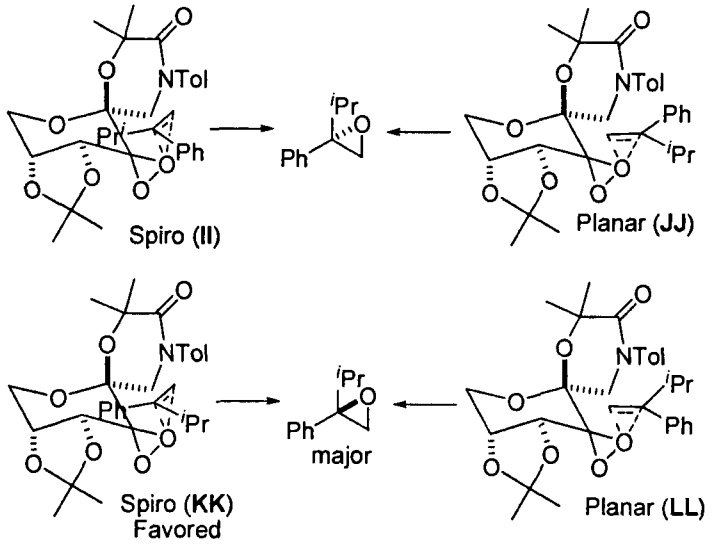


Figure 5.18 Proposed Competing Transition States for the Epoxidation of α-Isopropyl Styrene with Ketones 5-2

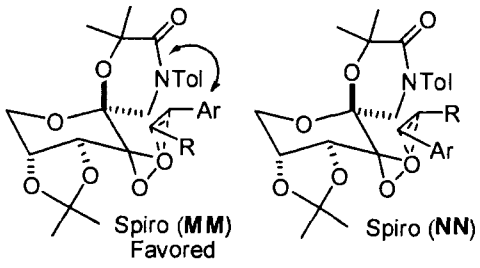


Figure 5.19 Proposed Competing Transition States for the Epoxidation of *cis*-Olefins with Ketone 5-2

5.3. CONCLUSIONS

In summary, a variety of 1,1-disubstituted olefins were epoxidized using ketone **5-1** as the catalyst and up to 88% ee was obtained. Transition state analysis and absolute configuration of the resulting epoxides suggested that the epoxidation of 1,1-disubstituted olefins with ketone **5-1** mainly proceeds via a planar transition state. Ketone **5-1** also provided good enantioselectivities for the epoxidation of cis-olefins, indicating that there exist an attraction between the morpholinone moiety of the catalyst and the aromatic substituent of the substrate. Furthermore, the epoxidation of trans-, cis-, 1,1-disubstituted, and trisubstituted olefins was investigated using ketones **5-1** and **5-2**. Ketone **5-2**, possessing the features of ketones **1-41**, **1-111**, and **5-1**, epoxidizes trans- and trisubstituted olefins in much higher enantioselectivities compared to ketone **5-1**. However, the dimethyl group in ketone **5-2** decreased the enantioselectivity of 1,1-disubstituted and cis-olefins. The attraction between the morpholinone moiety and the aromatic group of the substrate was weakened by the steric repulsion of the dimethyl

groups particularly in the planar transition states, thus reducing the enantioselectivity or even providing the opposite enantiomer in some cases.

5.4. EXPERIMENTAL

Representative Epoxidation Procedure using Ketone 5-1 (Table 5.2, entry 6). 2-*tert*-Butyl-2-phenyloxirane (OAW1933). To a solution of the □-*tert*-butylstyrene (0.032 g, 0.20 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.010 mmol), and ketone **5-1** (0.0208 g, 0.06 mmol) in dioxane (3 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous Na_2(EDTA), pH = 9.3) (2 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature), a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous Na_2(EDTA), 1.60 mL) (0.197 g, 0.32 mmol) and a solution of K_2CO_3 (0.84 M in 4 x 10^{-4} M aqueous EDTA, 1.60 mL) (0.186 g, 1.34 mmol) were added separately and simultaneously via syringe pump over a period of 2 h. The reaction mixture was quenched with hexanes, extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et_3N in organic solvent; hexanes/Et_2O=5/1 as eluent) to give the epoxide as a white solid (0.010 g, 43% yield, 86% ee).

Table 5.2, entry 6 (OAW1933)

2-*tert*-Butyl-2-phenyloxirane.[15] Colorless oil; $[\alpha]^{20}_D$ = +53.3 (*c* 0.90, $CHCl_3$) (86% ee); IR (film): 1480, 1462, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H),

[15] Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

3.12 (d, J = 5.2 Hz, 1H), 2.66 (d, J = 5.2 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 129.0, 127.5, 127.4, 67.0, 51.0, 34.0, 26.5; Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.53; H, 9.10.

Table 5.2, entry 9 (OAW1934-2)

2-Isopropyl-2-(4-methoxyphenyl)oxirane. Colorless oil; $[\alpha]^{20}_D$ = +22.2 (*c* 1.1, $CHCl_3$) (84% ee); IR (film): 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.88-6.86 (m, 2H), 3.81 (s, 3H), 2.97 (d, J = 5.2 Hz, 1H), 2.71 (d, J = 5.2 Hz, 1H), 2.03 (septet, J = 6.8 Hz, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 131.6, 128.7, 113.5, 64.4, 55.5, 53.5, 33.6, 18.8, 18.1; Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.78; H, 8.22.

Table 5.2, entry 21 (OAW1934-1)

1-(2-Phenyloxiran-2-yl)cyclopentanol.[7] Colorless oil; $[\alpha]^{20}_D$ = +48.6 (*c* 1.0, $CHCl_3$) (88% ee); IR (film): 3465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.37-7.29 (m, 3H), 3.30 (d, J = 5.6 Hz, 1H), 2.78 (d, J = 5.6 Hz, 1H), 1.92-1.70 (m, 4H), 1.65-1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 128.7, 128.1, 82.5, 64.5, 51.4, 36.30, 36.27, 23.6, 23.5; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.33; H, 7.76.

Procedure for the Synthesis of Ketone 5-2 (b1248). To a slurry of **5-3** (3.09 g, 10.0 mmol) (prepared from *D*-glucose in two steps)[6,12] and $NaHCO_3$ (1.68 g, 20.0 mmol) in CH_2Cl_2 (400 mL), 2-bromo-2-methylpropanoyl bromide (2.76 g, 1.48 mL, 12.0 mmol)

was added dropwise at rt. The resulting mixture was stirred at rt for 16 h to form a brown slurry (monitored by TLC until no starting material remained, the product and the starting material have similar R_f values, but can be differentiated by color with anisaldehyde stain). The reaction was quenched by addition of 0.1 M aqueous K_2CO_3 solution (50 mL), and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, concentrated, and dried under vacuum for 3 h to give crude brown syrup (this intermediate is unstable and should be used without delay), which was dissolved in THF (200 mL). Upon addition of NaH (60%, 0.8 g, 20.0 mmol), the resulting mixture was stirred at rt for 0.5 h, quenched with water (0.2 mL), filtered, concentrated, and purified by flash chromatography (silica gel, hexanes/EtOAc = 1/1) to give the product as a light yellow syrup (1.70 g, 45% yield). $[\alpha]_D^{25}$ = -54.4 (*c* 1.0, $CHCl_3$); IR (film): 3431, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.16 (m, 4H), 4.30-4.23 (m, 2H), 4.19 (d, *J* = 12.9 Hz, 1H), 4.13 (dd, *J* = 13.2, 1.8 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 12.9 Hz, 1H), 3.63-3.61 (m, 1H), 2.34 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 139.6, 137.0, 130.0, 125.8, 109.7, 95.7, 77.3, 76.0, 73.3, 71.7, 60.7, 55.8, 28.3, 27.8, 27.0, 25.9, 21.3; HRMS Calcd. for $C_{20}H_{28}NO_6$ (M+1): 378.1917; Found: 378.1907.

To a slurry of the above alcohol (1.70 g, 4.5 mmol), PDC (5.12 g, 13.6 mmol), and 3Å MS (3.3 g) in DCM (50 mL), 2 drops of AcOH was added. The resulting mixture was stirred at rt for 3 d (monitored by TLC until no alcohol remained), filtered through a pad of silica gel, washed with EtOAc, concentrated, and purified by flash chromatography (silica gel, hexanes/EtOAc = 2/1) to give ketone **5-2** as a white solid (1.60 g, 95% yield).

mp = 118-119 °C; $[\alpha]_D^{25}$ = -96.9 (*c* 1.2, $CHCl_3$); IR (film): 1751, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23-7.17 (m, 4H), 4.86 (d, *J* = 5.7 Hz, 1H), 4.61 (dd, *J* = 5.7, 1.5 Hz, 1H), 4.46 (dd, *J* = 13.5, 2.4 Hz, 1H), 4.39 (d, *J* = 13.8 Hz, 1H), 4.18 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 13.8 Hz, 1H), 2.35 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 170.8, 139.2, 137.1, 129.9, 125.7, 110.8, 96.5, 78.6, 78.4, 75.7, 59.6, 52.0, 27.7, 27.3, 26.6, 26.3, 21.3; Anal. Calcd. for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.75; H, 6.89.

Representative Epoxidation Procedure using Ketones 5-1 or 5-2 (Table 5.5, entry 4). ***trans*-β-Methylstyrene oxide (OAW2350-1).** To a solution of *trans*-β-methylstyrene (0.024 g, 0.026 mL, 0.20 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.012 mmol), and ketone **5-2** (0.011 g, 0.03 mmol) in CH_3CN-DMM (v/v, 1:2) (3.0 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 x 10^{-4} M aqueous EDTA, pH = 9.3) (2.0 mL) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.20 M, in 4 × 10^{-4} M aqueous Na_2(EDTA), 1.3 mL) and a solution of K_2CO_3 (0.89 M in 4 × 10^{-4} M aqueous Na_2(EDTA), 1.3 mL) were added separately and simultaneously with a syringe pump over a period of 8 h at 0 °C. The reaction mixture was quenched with hexanes, extracted with hexanes, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; hexanes/Et_2O = 50/1 was used as eluent] to give the epoxide as a colorless oil (0.022 g, 82% yield, 90% ee).

Table 5.5, entries 1 and 2 (OAW2725-1, OAW2434-1)

***trans*-Stilbene oxide.**[4b,16] White solid; $[\alpha]_D^{20}$ = +334.6 (*c* 0.73, benzene) (97 % ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.34 (m, 10H), 3.90 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 128.8, 128.5, 125.7, 63.1.

Table 5.5, entries 3 and 4 (OAW2434-2, OAW2350-1)

***trans*-β-Methylstyrene oxide.**[4b,17] Colorless oil; $[\alpha]_D^{20}$ = +44.3 (*c* 0.32, $CHCl_3$) (90 % ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.60 (d, *J* = 2.1 Hz, 1H), 3.06 (qd, *J* = 5.1, 2.1 Hz, 1H), 1.48 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.6, 128.2, 125.8, 59.7, 59.2, 18.1.

Table 5.5, entries 5 and 6 (OAW2436-1, OAW2411-2)

***trans*-Tetradecene oxide.**[4b] Colorless oil; $[\alpha]_D^{20}$ = +22.8 (*c* 0.65, $CHCl_3$) (83% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (t, *J* = 4.5 Hz, 2H), 1.56-1.23 (m, 20H), 0.89 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.2, 32.4, 32.0, 29.3, 26.2, 22.8, 14.3.

Table 5.5, entries 7 and 8 (OAW2436-2, OAW2412-2)

(*E*)-Methylstilbene oxide.[4b,18] White solid; $[\alpha]_D^{20}$ = +98.8 (*c* 0.72, EtOH) (89 % ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.34 (m, 10H), 4.02 (s, 1H), 1.51 (s, 3H); ^{13}C NMR

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[16] Chang, H-T.; Sharpless, K.B. *J. Org. Chem.* **1996**, *61*, 6456.

[17] Witkop, B.; Foltz, C.M. *J. Am. Chem. Soc.* **1957**, *79*, 197.

[18] Brandes, B.D.; Jacobsen, E.N. *J. Org. Chem.* **1994**, *59*, 4378.

(100 MHz, $CDCl_3$) δ 142.5, 136.1, 128.7, 128.4, 127.9, 127.7, 126.7, 125.3, 67.3, 63.3, 16.9.

Table 5.5, entries 9 and 10 (2437-1, 2412-1)

(*E*)-1-(Benzyloxy)cyclooct-1-ene oxide.[13] Colorless oil; $[\alpha]_D^{20}$ = +7.3 (*c* 0.62, $CHCl_3$) (90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.00 (m, 2H), 7.57 (tt, *J* = 7.2, 1.5 Hz, 1H), 7.46-7.41 (m, 2H), 3.21 (dd, *J* = 10.2, 4.5 Hz, 1H), 2.91-2.86 (m, 1H), 2.27 (ddd, *J* = 13.8, 7.8, 4.5 Hz, 1H), 1.88-1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 133.5, 130.1, 129.9, 128.6, 85.9, 60.4, 28.0, 26.2, 26.1, 25.2, 24.9.

Table 5.5, entries 11 and 12 (OAW2725-2, 2724)

Phenylcyclohexene oxide.[4b] Colorless oil; $[\alpha]_D^{20}$ = -92.0 (*c* 0.64, benzene) (80% ee); $[\alpha]_D^{25}$ = +102.4 (*c* 0.54, benzene) (87% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 3.10 (s, 1H), 2.36-2.26 (m, 1H), 2.12 (dt, *J* = 14.7, 5.1 Hz, 1H), 2.03-1.99 (m, 2H), 1.69-1.46 (m, 3H), 1.41-1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.4, 127.4, 125.5, 62.1, 60.4, 29.0, 24.9, 20.3, 20.0.

Table 5.5, entries 13 and 14 (OAW2726-1)

2-Isopropyl-2-phenyloxirane. Colorless oil; $[\alpha]_D^{20}$ = +33.5 (*c* 1.10, $CHCl_3$) (84% ee); $[\alpha]_D^{25}$ = -19.4 (*c* 0.51, $CHCl_3$) (45% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.00 (d, *J* = 5.4 Hz, 1H), 2.73 (d, *J* = 5.4 Hz, 1H), 2.10 (septet, *J* = 6.9 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 128.1, 127.6, 127.5, 64.7, 53.4, 33.3, 18.7, 18.0.

Table 5.5, entries 15 and 16 (OAW2437-2, OAW2729)

***cis*-β-Methylstyrene oxide.**[4f] Colorless oil; $[\alpha]_D^{20}$ = -37.8 (*c* 0.49, $CHCl_3$) (85% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 4.08 (d, *J* = 4.5 Hz, 1H), 3.36 (qd, *J* = 5.4, 4.5 Hz, 1H), 1.10 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 128.2, 127.7, 126.8, 57.7, 55.4, 12.7.

Table 5.5, entries 17 and 18 (OAW2438)

6-Cyano-2,2-dimethylchromene.[14] White solid; $[\alpha]_D^{20}$ = +59.8 (*c*, 1.20, $CHCl_3$) (81% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.92 (d, *J* = 4.5 Hz, 1H), 3.55 (d, *J* = 4.5 Hz, 1H), 1.60, (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 134.6, 134.0, 121.3, 119.2, 118.9, 104.4, 74.8, 62.5, 50.1, 25.7, 23.2.

CHAPTER SIX

^{18}O-LABELING STUDIES OF ASYMMETRIC EPOXIDATION CATALYZED BY CHIRAL DIOXIRANE

6.1. INTRODUCTION

^{18}O-labeling studies have been employed by several research groups to provide evidence for the involvement of dioxirane intermediates in the ketone-catalyzed epoxidation.[1] In our laboratory, chiral dioxirane epoxidation transition state models, such as those in Figure 1.17 (page 36), have provided accurate predictions of the stereochemical outcome of the resulting epoxides.[2,3] It has been proposed that the equatorial oxygen is the oxygen that gets transferred to the carbon-carbon double bond during the epoxidation with fructose or glucose-derived ketones such as **1-41** and **1-111**

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[1] (a) Montgomery, R.E. *J. Am. Chem. Soc.* **1974**, *96*, 7820. (b) Edwards, J.O.; Pater, R.H.; Curci, R.; Di Furia, F. *Photochem. Photobio.* **1979**, *30*, 63. (c) Camporeale, M.; Fiorani, T.; Troisi, L.; Adam, W.; Curci, R.; Edwards, J.O. *J. Org. Chem.* **1990**, *55*, 93. (d) Denmark, S.E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964. (e) Schulz, M.; Liebsch, S.; Kluge, R. *J. Org. Chem.* **1997**, *62*, 188. (f) Denmark, S.E.; Wu, Z. *Synlett* **1999**, 847. (g) Yang, D.; Yip, Y.C.; Tang, M.W.; Wong, M.K.; Cheung, K.K. *J. Am. Chem. Soc.* **1998**, *120*, 5943.

[2] Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

[3] For a transition state calculation on the epoxidation with ketones **1-41** and **1-111a**, see: Singleton, D.A.; Wang, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6679.

(Figure 6.1). Nevertheless, we are interested in obtaining further evidence through ^{18}O-labeling studies to support the currently accepted epoxidation transition state hypothesis.

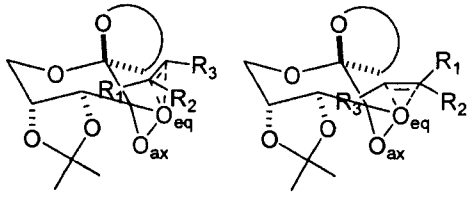


Figure 6.1

6.2. RESULTS AND DISCUSSION

When an ^{18}O-labeled catalyst is used in the epoxidation of olefins, there are four possible outcomes. The peroxymonosulfate anion from Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) can attack the ketone on either the less sterically hindered face of the ketone (path **a**) or the more sterically hindered face (path **b**) (Figure 6.2). Epoxidation of olefins can then occur on either face of the resulting dioxiranes (**6-1** and **6-2**). The formation of non-^{18}O-labeled epoxide can be formed via paths **ac** (the olefin approaches from the less hindered face of the dioxirane **6-1**) and path **bf** (the olefin approaches from the more hindered face of the dioxirane **6-2**). Likewise, the formation of ^{18}O-labeled epoxide can be formed via paths **ad** (the olefin approaches from the more hindered face of the dioxirane **6-1**) and path **be** (the olefin approaches from the less hindered fase of the dioxirane **6-2**).

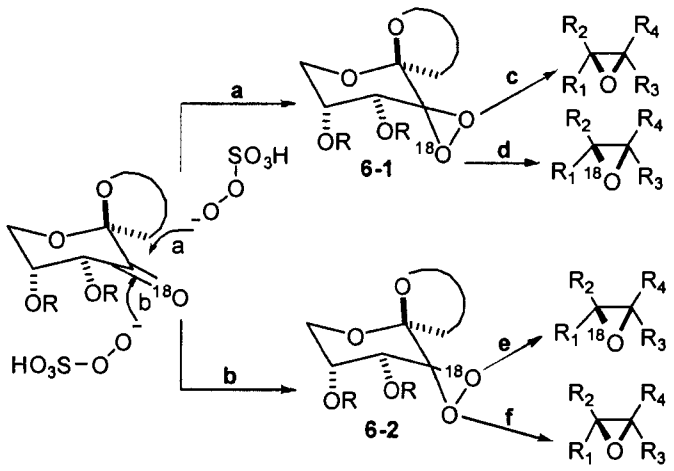


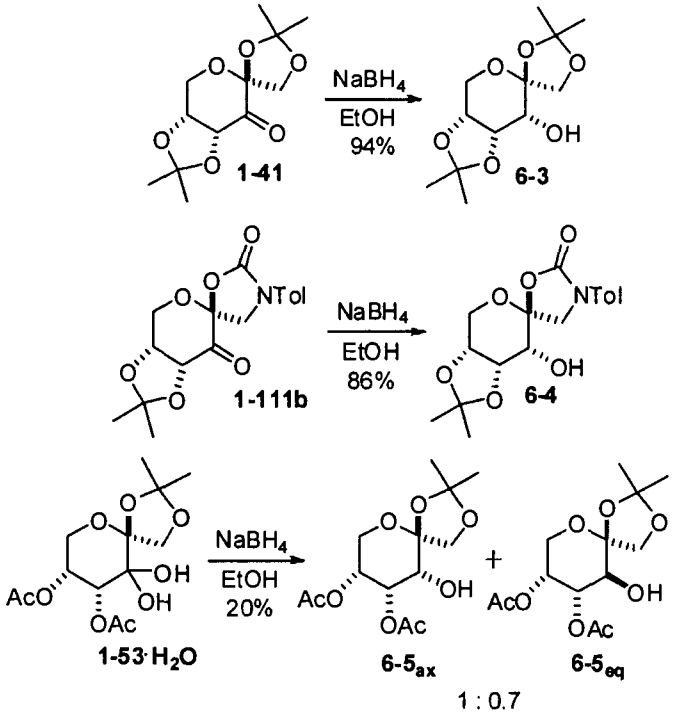
Figure 6.2

Catalysts **1-41**, **1-111b**, and **1-53·H$_2$O** were reduced with $NaBH_4$ with hopes that the stereochemistry of the resulting alcohol would provide information as to which face the peroxymonosulfate anion would attack the ketone to form dioxiranes **6-1** or **6-2** (Figure 6.2). It has been reported that the reduction of ketone **1-41** is highly stereoselective and alcohol **6-3** can be obtained in 94% yield (Scheme 6.1).[4] Ketone **1-111b** was subjected to the same reaction conditions and alcohol **6-4** was obtained in 86% yield (Scheme 6.1). **1-53·H$_2$O** was also subjected to the reduction conditions and alcohols **6-5$_{ax}$** and **6-5$_{eq}$** were obtained in 1:0.7 ratio (Scheme 6.1). The results from these reduction reactions indicates that the nucleophilic attack of BH_4^- on ketones **1-41** and **1-111b** occurs exclusively on the face opposite the fused ketal, forming the axial alcohol product. The reduction of **1-53·H$_2$O** suggests that the acetate groups do not block nucleophilic attack as well as the fused ketal group. Nonetheless, the major alcohol product (**6-5$_{ax}$**) still results from nucleophilic attack on the face opposite the acetates. These ketone reduction results suggest that during dioxirane formation the peroxymonosulfate anion would also largely

[4] Prisbe, E.J.; Smejkal, J.; Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.* **1976**, *41*, 1836.

attack the face opposite the ketal or the acetates. Therefore, dioxirane **6-1** should be the major dioxirane formed when an ^{18}O-labeled ketone is treated with Oxone (Figure 6.2).

Scheme 6.1 Reduction of Catalysts 1-41, 1-111b, and 1-53·H_2O



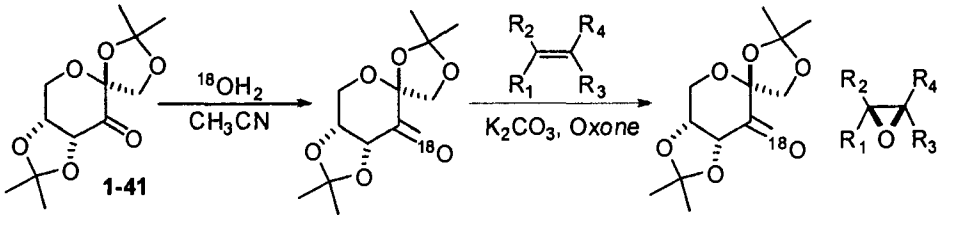
In order to distinguish between paths **ac** and **ad** (Figure 6.2), the ^{18}O content in an epoxide synthesized using an ^{18}O-labeled ketone and Oxone were studied. To carry out the epoxidation with ^{18}O-labeled ketones, the unlabeled ketones (1.0 or 2.0 equiv.) were first stirred at ambient temperature in $^{18}OH_2$ and organic solvent to achieve >90% ^{18}O-labeled ketone as determined by GCMS or Electrospray/Atomospheric Pressure Chemical Ionization.[5] To the ketone solution was added an olefin (1.0 equiv.), and tetrabutylammonium sulfate (0.04 equiv.). Solutions of Oxone (1.2 equiv.) and K_2CO_3 (5.0 equiv.) in $^{18}OH_2$ were then added simultaneously and separately to the reaction vial

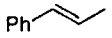
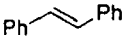
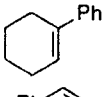
[5] Water (^{18}O, 97%) purchased from Cambridge Isotope Laboratories, Inc.

at the reaction temperature over the required reaction time. An aliquot (about 0.1 mL) of the crude reaction mixture was then diluted with EtOAc for GCMS analysis of ^{18}O content. The remainder of the reaction solution was extracted with hexanes for GC or HPLC analysis of conversion and ee.

The epoxidations of trans-, cis-, trisubstituted, and terminal olefins carried out with ^{18}O labeled ketones **1-41** and **1-111b** resulted in moderate to good conversions, while the enantioselectivity and configuration of the epoxides were in agreement with the results of previous studies (Tables 6.1 and 6.2).[6] The ^{18}O content in the epoxides was on average only about 5%, which indicates that path **ac** is the major pathway (Figure 6.2).

Table 6.1 Asymmetric Epoxidation of Olefins using ^{18}O-Labeled Ketone 1-41[a,b]



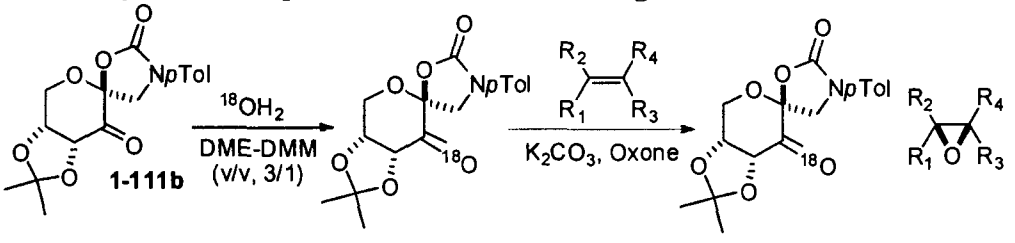
entry	substrate	conv.[c] (%)	ee[c] (%)	^{18}O in ketone (%)[d]		^{18}O in epoxide (%)[d]	config.[f]
				before reaction[e]	after reaction		
1		55	89	95	93	5	(*R*,*R*)
2		70	94	97	93	4	(*R*,*R*)
3		59	94	96	94	4	(*R*,*R*)
4		66	7	94	96	6	(1*R*,2*S*)
5		84	17	95	93	4	(*R*)

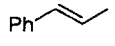
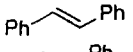
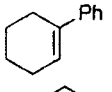
[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled ketone solution (0.05 mmol, 0.013 g) in MeCN:$^{18}OH_2$ (0.63 mL, v/v 3:2), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath

[6] See Chapter 1.2.6. for previous epoxidation results with ketones **1-41** and **1-111b**.

temperature) for 2 h. For entry 2, an additional 0.50 mL MeCN was used to dissolve the olefin before mixing with the ketone solution and the reaction was run at rt for 4 h. [b] Notebook pages: entry 1 OAW2626, entry 2 OAW2635, entry 3 OAW2631, entry 4 OAW2627, entry 5 OAW2632. [c] The conversions and ees were determined by GC (Chiraldex B-DM), except for entry 2 which was determined by ^{1}H NMR (conversion) and HPLC (ee, Chiralcel OD). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm). [e] The ketone (0.05 mmol, 0.013 g) was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and MeCN (0.38 mL) at rt overnight (ca. 16 h). For entry 2, 0.25 mL $^{18}OH_2$ (97% ^{18}O) and 0.25 mL MeCN was used. [f] Configuration was determined by comparing the GC/HPLC trace with epoxides of known configurations.

Table 6.2 Asymmetric Epoxidation of Olefins using ^{18}O-Labeled Ketone 1-111b[a,b]

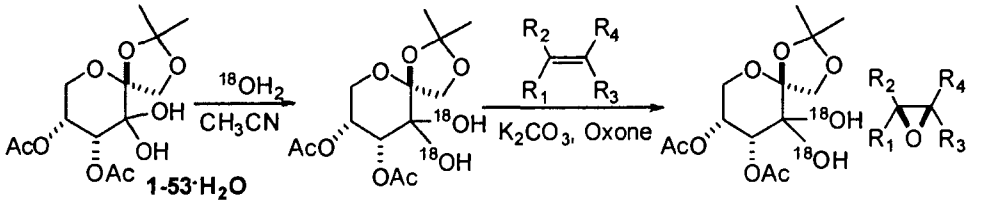


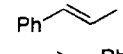
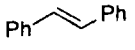
entry	substrate	conv.[c] (%)	ee[c] (%)	^{18}O in ketone (%)[d]		^{18}O in epoxide (%)[d]	config.[f]
				before reaction[e]	after reaction		
1		91	80	97	74	2	(*R*,*R*)
2		78	93	98	87	3	(*R*,*R*)
3		75	27	97	94	3	(*R*,*R*)
4		63	82	97	88	4	(1*R*,2*S*)
5		99	79	98	96	3	(*R*)

[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled ketone solution (0.05 mmol, 0.017 g) in DME:DMM:$^{18}OH_2$ (v/v/v 3:1:2.6, 0.63 mL), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 2 h. For entry 2, an additional 0.50 mL DME:DMM (v/v 3:1) was used to dissolve the olefin before mixing with the ketone solution and the reaction was ran at rt for 4 h. [b] Notebook pages: entry 1 OAW2639, entry 2 OAW2635, entry 3 OAW2649, entry 4 OAW2640, entry 5 OAW2650. [c] The conversions and ees were determined by GC (Chiraldex B-DM), except for entry 2 which were determined by ^{1}H NMR (conversion) and HPLC (ee, Chiralcel OD). [d] The ^{18}O contents were determined by flow injection (ESI/APCI). [e] The ketone (0.05 mmol, 0.013 g) was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and DME:DMM (v/v 3:1) (0.38 mL) at rt overnight (ca. 16 h). For entry 2, 0.25 mL $^{18}OH_2$ (97% ^{18}O) and 0.25 mL DME:DMM (v/v 3:1) was used. [f] Configuration was determined by comparing the GC/HPLC trace with the epoxides of known configurations.

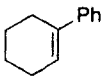
The epoxidations of various olefins were carried out with ^{18}O-labeled **1-53·H_2O** and generally resulted in good conversions (Table 6.3). The ees and configurations of the epoxides are also in agreement with previous studies.[7] The ^{18}O content is below 5% for trans- and trisubstituted olefins, which indicates that pathway **ac** is the major pathway in these cases (Figure 6.2). However, for the epoxidation of cis- and terminal olefins, the ^{18}O content in the resulting epoxides is as high as 12% (Table 6.3, entries 4 and 5). In these cases, it is possible for pathway **ad**, **be**, and **bf** to contribute in the epoxidation process in addition to pathway **ac**. The higher ^{18}O content of *cis*-β-methylstyrene oxide and styrene oxide (Table 6.3, entries 4 and 5) is in agreement with the fact that two alcohol products, **6-5$_{ax}$** and **6-5$_{eq}$**, were formed from the reduction of **1-53·H_2O** (Scheme 6.1). Both sets of data indicate that the acetate groups in **1-53·H_2O** is less effective than the fused ketal group in ketones **1-41** and **1-111b** in preventing nucleophilic attack and epoxidation from occurring on the same faces.

Table 6.3 Asymmetric Epoxidation of Olefins using ^{18}O-Labeled 1-53·H_2O[a,b]



entry	substrate	conv.[c] (%)	ee[c] (%)	^{18}O in hydrate (%)[d]		^{18}O in epoxide (%)[d]	config.[f]
				before reaction[e]	after reaction		
1		96	85	95	94	4	(*R*,*R*)
2		24	90	94	92	4	(*R*,*R*)

[7] See Chapter 4 for previous epoxidation results with ketone **1-53**.

3		100	93	94	93	3	(*R*,*R*)
4		81	17	94	91	12	(1*S*,2*R*)
5		80	2	94	93	11	(*R*)

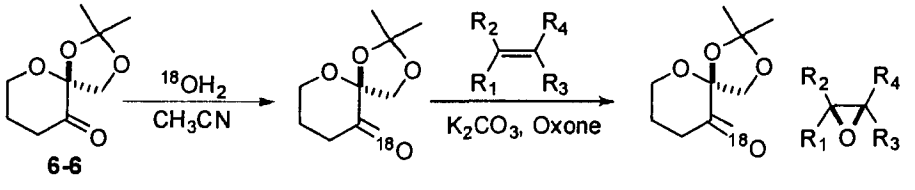
[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled hydrate solution (0.05 mmol, 0.016 g) in MeCN:$^{18}OH_2$ (v/v 3:2, 0.63 mL), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 2 h. For entry 2, The reaction was carried out with olefin (0.05 mmol), ^{18}O-labeled hydrate solution (0.10 mmol, 0.032 g) in MeCN:$^{18}OH_2$ (v/v 1:1, 0.50 mL), MeCN (used to dissolve the olefin, 0.50 mL), Oxone (0.12 mmol, 0.36 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.50 mmol, 1.52 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at rt for 4 h. [b] Notebook pages: entry 1 OAW2705, entry 2 OAW2720, entry 3 OAW2712, entry 4 OAW2706, entry 5 OAW2713. [c] The conversions and ees were determined by GC (Chiraldex B-DM), except for entry 2 which were determined by ^1H NMR (conversion) and HPLC (ee, Chiralcel OD). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm). [e] The hydrate (0.05 mmol, 0.013 g) was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and MeCN (0.38 mL) at rt overnight (ca. 16 h). For entry 2, 0.10 mmol of ketone, 0.25 mL $^{18}OH_2$ (97% ^{18}O) and 0.25 mL MeCN was used. [f] Configuration was determined by comparing the GC/HPLC trace with the epoxides with known configurations.

In order to investigate the effect of the fused ketal group in ketones **1-41** and **1-111b** on ^{18}O content of the resulting epoxides, epoxidation using ^{18}O-labeled ketone **6-6** was carried out (Table 6.4).[8] The epoxidations using ketone **6-6** generally resulted in good conversion, while the enantioselectivities for trans- and trisubstituted olefins were lower than those obtained with ketone **1-41**. The ^{18}O content for the resulting epoxides ranges from 40% to 47%, a significant increase from the epoxides obtained with ^{18}O-labeled ketone **1-41**, which indicates that the contribution from pathways **ad** and **be** almost equals that from pathways **ac** and **bf** (Figure 6.2). The lack of obstruction from the fused ketal allows the peroxymonosulfate anion to attack freely on either face of the ketone and also allows the transfer of either oxygen from the resulting dioxirane to the olefin. The epoxidation with ^{18}O-labeled *tert*-butylcyclohexanone (**6-7**) was also studied and generally resulted in moderate conversions for various olefins (Table 6.5).

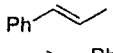
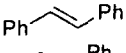
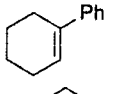
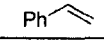
[8] Tu, Y.; Wang, Z-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475.

Surprisingly, the ^{18}O content of the resulting epoxides was very low (ca. 5%). It is possible that the conformation of 4-*tert*-butylcyclohexanone disfavors paths **ad** and **be** (Figure 6.3). In order to determine if the catalyst loading and solvent affect the ^{18}O content of the epoxide, the epoxidation of *cis*-β-methylstyrene was carried out with differing catalytic amounts of catalyst **1-53·H$_2$O** (0.25, 0.50, and 0.75 equiv.) and solvent mixtures [DME:DMM (3:1)]. As shown in table 6.6, the ^{18}O content did not change significantly with the variation of catalyst loading and solvent. Background reaction (epoxidation reaction without a ketone as the catalyst) of the epoxidation was investigated (Table 6.7). It is currently unclear how up to 20% of ^{18}O become incorporated into the epoxide for the background reaction.

Table 6.4 Asymmetric Epoxidation of Olefins using ^{18}O-Labeled Ketone 6-6[a,b]



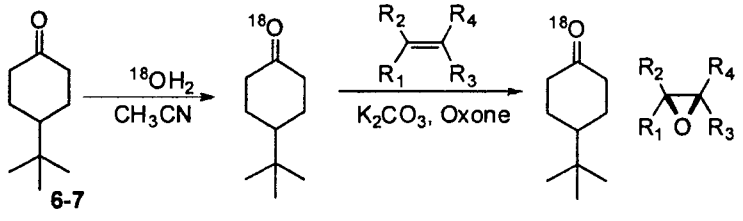
6-6

entry	substrate	conv.[c] (%)	ee[c] (%)	^{18}O in ketone (%)[d]		^{18}O in epoxide (%)[d]	config.[f]
				before reaction[e]	after reaction		
1		70	69	97	97	41	(*R*,*R*)
2		100	74	97	93	47	(*R*,*R*)
3		100	84	96	92	42	(*R*,*R*)
4		91	17	97	96	40	(1*S*,2*R*)
5		100	7	98	88	40	(*R*)

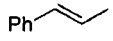
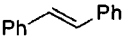
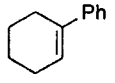
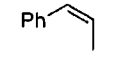
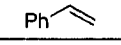
[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled ketone solution (0.05 mmol, 0.009 g) in MeCN:$^{18}OH_2$ (v/v 3:2, 0.63 mL), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 2 h. For entry 2, The reaction was carried out with olefin (0.05 mmol), ^{18}O-labeled

ketone solution (0.10 mmol, 0.018 g) in MeCN:$^{18}OH_2$ (v/v 1:1, 0.50 mL), MeCN (used to dissolve the olefin, 0.50 mL), Oxone (0.12 mmol, 0.36 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.50 mmol, 1.52 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at rt for 4 h. [b] Notebook pages: entry 1 OAW2732, entry 2 OAW2737, entry 3 OAW2735, entry 4 OAW2733, entry 5 OAW2736. [c] The conversions and ees were determined by GC (Chiraldex B-DM), except for entry 2 which were determined by ^1H NMR (conversion) and HPLC (ee, Chiralcel OD). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm). [e] The ketone (0.05 mmol, 0.018 g) was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and MeCN (0.38 mL) at rt overnight (ca. 16 h). For entry 2, 0.10 mmol of ketone, 0.25 mL $^{18}OH_2$ (97% ^{18}O) and 0.25 mL MeCN was used. [f] Configuration was determined by comparing the GC/HPLC trace with the epoxides with known configurations.

Table 6.5 Asymmetric Epoxidation of Olefins using ^{18}O-Labeled Ketone 6-7[a,b]



6-7

entry	substrate	conv.[c] (%)	ee[c] (%)	^{18}O in ketone (%)[d]		^{18}O in epoxide (%)[d]	config.
				before reaction[e]	after reaction		
1		38	0	94	93	4	-
2		79	0	94	93	4	-
3		41	0	94	92	4	-
4		41	0	94	91	6	-
5		45	0	94	93	3	-

[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled ketone (0.10 mmol, 0.015 g)/K_2CO_3 (0.02 mmol, 0.003 g) solution in DME:DMM:$^{18}OH_2$ (v/v/v 3:1:2.6, 0.63 mL), Oxone (0.12 mmol, 0.36 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.50 mmol, 1.52 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 4 h. For entry 2, The reaction was carried out with olefin (0.05 mmol), ^{18}O-labeled ketone solution (0.10 mmol, 0.018 g) in DME:DMM:$^{18}OH_2$ (v/v/v 3:1:4, 0.50 mL), DME:DMM (v/v 3:1, used to dissolve the olefin, 0.50 mL), Oxone (0.12 mmol, 0.36 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.50 mmol, 1.52 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at rt for 4 h. [b] Notebook pages: entry 1 OAW2540, entry 2 OAW2544, entry 3 OAW2542, entry 4 OAW2541, entry 5 OAW2543. [c] The conversions and ees were determined by GC (Chiraldex B-DM), except for entry 2 which were determined by ^1H NMR (conversion) and HPLC (ee, Chiralcel OD). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm). [e] The ketone (0.10 mmol, 0.015 g) was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and DME:DMM (v/v, 3:1, 0.38 mL) with K_2CO_3 (0.02 mmol, 0.003 g) at rt for 21 days. For entry 2, 0.25 mL $^{18}OH_2$ (97% ^{18}O) and 0.25 mL DME:DMM (v/v 3:1) was used.

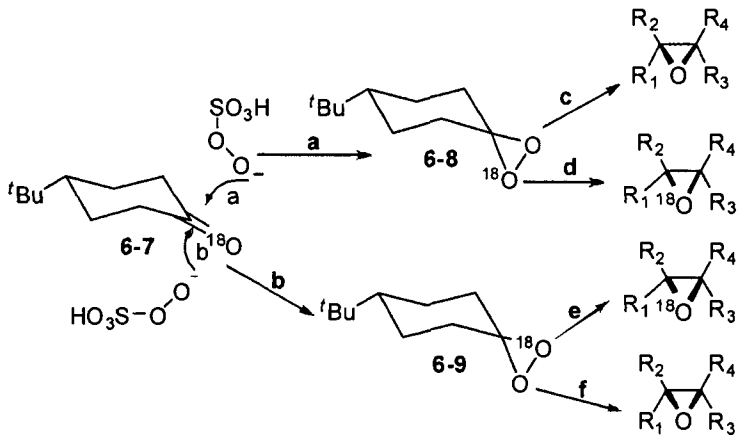
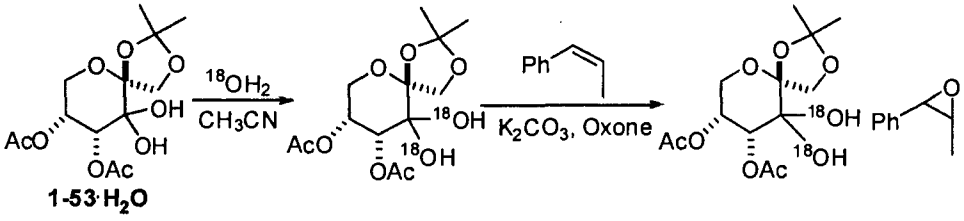


Figure 6.3

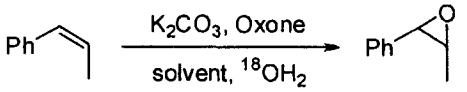
Table 6.6 Asymmetric Epoxidation of Olefins using Various Loading of ^{18}O-Labeled 1-53·H_2O [a,b]



entry	catalyst loading (eq)	solv.	conv.[c] (%)	ee[c] (%)	^{18}O in hydrate (%)[d]		^{18}O in epoxide (%)[d]
					before reaction[e]	after reaction	
1	0.25	MeCN	14	15	95	nd	13
2	0.50	MeCN	86	14	96	nd	10
3	0.75	MeCN	81	15	95	nd	11
4	1.00	MeCN	81	17	94	91	12
5	1.00	DME: DMM (3:1)	95	30	96	92	11

[a] The reactions were carried out with olefin (0.05 mmol), ^{18}O-labeled hydrate solution in MeCN:$^{18}OH_2$ (v/v 3:2, 0.63 mL), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 2 h. [b] Notebook pages: entry 1 OAW2805, entry 2 OAW2806, entry 3 OAW2807, entry 4 OAW2706, entry 5 OAW2734. [c] The conversions and ees were determined by GC (Chiraldex B-DM). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm). [e] The hydrate was labeled by stirring in $^{18}OH_2$ (97% ^{18}O, 0.25 mL) and MeCN (0.38 mL) at rt overnight (ca. 16 h).

Table 6.7 Background Reaction Studies with *cis*-β-Methylstyrene[a,b]



entry	solvent	conv. (%)[c]	ee (%)[c]	^{18}O in epoxide (%)[d]
1	MeCN	4	0	20
2	DME:DMM 3:1	8	0	12

[a] The reactions were carried out with olefin (0.05 mmol), Oxone (0.06 mmol, 0.18 M in $^{18}OH_2$, 0.33 mL), K_2CO_3 (0.25 mmol, 0.77 M in $^{18}OH_2$, 0.33 mL), and Bu_4NHSO_4 (0.0002 mmol, 0.0007 g) at 0 °C (bath temperature) for 2 h. [b] Notebook pages: entry 1 OAW2714-2, entry 2 OAW2727. [c] The conversions and ees were determined by GC (Chiraldex B-DM). [d] The ^{18}O contents were determined by GCMS (ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm).

6.3. CONCLUSION

In conclusion, the results from the epoxidation of olefins using ^{18}O-labeled catalysts support the proposed epoxidation transition state model. The monoperoxysulfate anion exclusively attacks ketones **1-41** and **1-111b** on the face opposite of the fused ketal, and the equatorial oxygen of the resulting dioxirane is subsequently transferred to the olefin. The acetate groups in **1-53·H_2O** does not hinder nucleophilic attack or epoxidation as well as the ketal group; thus some of the monoperoxysulfate addition and epoxidation may occur on the same face as the acetate groups. When no obstruction is present such as in ketone **6-6**, both the monoperoxysulfate addition and epoxidation almost occur equally on both faces.

6.4. EXPERIMENTAL

Epoxidation Procedure for the Asymmetric Epoxidation of *trans*-β-Methylstyrene, 1-Phenylcyclohexene, *cis*-β-Methylstyrene, and Styrene using ^{18}O-Labeled Ketones 1-41, 1-111b, 1-53, 6-6, 6-7 (Table 6.1 – Table 6.5, entries 1, 3-5).

(Table 6.1, entry 1). To a solution of ketone **1-41** (0.013 g, 0.05 mmol) in MeCN (0.38 mL) was added $^{18}OH_2$ (97% ^{18}O, 0.28 g, 0.25 mL). The solution was allowed to stir at rt overnight. To the ketone solution was added *trans*-β-methylstyrene (0.006 g, 0.0065 mL, 0.05 mmol), Bu_4NHSO_4 (0.0007 g, 0.0002 mmol) and one drop of K_2CO_3 solution (0.77 M in $^{18}OH_2$). After being cooled by an ice bath (0 °C), Oxone (0.33 mL, 0.18 M in $^{18}OH_2$, 0.06 mmol) and K_2CO_3 (0.33 mL, 0.77 M in $^{18}OH_2$, 0.25 mmol) were added simultaneously and separately via syringe pump over 2 h. A small amount of crude reaction mixture was taken for GCMS analysis. The remainder of the reaction mixture was extracted with hexanes (0.5 mL x 2). The combined organic layers were dried with Na_2SO_4 for GC analysis (Chiraldex B-DM).

GCMS conditions

Column: ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm; inlet temperature 275 °C; split ratio 50:1; oven temperature program: 60 °C held for 2 min, then 10 °C min^{-1} ramp to 250 °C and held for 5 min; GC carrier gas: He. Retention time for Ketone **1-41**: 14.1 min; Ketone **1-53**: 15.9 min; Ketone **6-6**: 9.6 min; Ketone **6-7**: 10.0 min; *trans*-β-Methylstyrene oxide: 8.3 min; 1-Phenylcyclohexene oxide: 13.1 min; *cis*-β-Methylstyrene oxide: 8.1 min; Styrene oxide: 7.5 min.

Flow injection conditions (For ^{18}O-content analysis of ketone 1-111b)

Electrospray / Atomospheric Pressure Chemical Ionization (ESI/APCI); Gas Temp: 310 °C, Vaporizer: 200 °C; Gas Flow: 8 L/min; Nebulizer 45 psi; Charging voltage: 2000 V; Solvent: MeOH; Solvent flow: 0.3 mL/min.

Epoxidation Procedure for the Asymmetric Epoxidation of *trans*-Stilbene using ^{18}O-Labeled Ketones 1-41, 1-111b, 1-53, 6-6, 6-7 (Table 6.1 – Table 6.5, entry 2)

(Table 6.1, entry 2) To a solution of ketone **1-41** (0.013 g, 0.05 mmol) in MeCN (0.25 mL) was added $^{18}OH_2$ (97% ^{18}O, 0.28 g, 0.25 mL). The solution was allowed to stir at rt overnight. To the ketone solution was added a solution of *trans*-stilbene (0.006 g, 0.0065 mL, 0.05 mmol) in MeCN (0.50 mL), Bu_4NHSO_4 (0.0007 g, 0.0002 mmol), and one drop of K_2CO_3 solution (0.77 M in $^{18}OH_2$). Oxone (0.33 mL, 0.18 M in $^{18}OH_2$, 0.06 mmol) and K_2CO_3 (0.33 mL, 0.77 M in $^{18}OH_2$, 0.25 mmol) were added simultaneously and separately via syringe pump over 4 h at rt. A small amount of crude reaction mixture was taken for GCMS analysis. The remainder of the reaction mixture was extracted with hexanes (0.5 mL x 2). The combined organic layers were dried over Na_2SO_4 for GC analysis (Chiraldex B-DM).

GCMS conditions

Column: ZB-5HT Inferno, 30m x 0.25 mm x 0.25 μm; inlet temperature 275 °C; split ratio 50:1; oven temperature program: 60 °C held for 2 min, then 10 °C min^{-1} ramp to 250

°C and held for 5 min; GC carrier gas: He. Retention times for ketones: same as above; Stilbene oxide: 16.3 min.

Flow injection conditions (For ^{18}O-content analysis of ketone 1-111b)

Electrospray / Atomospheric Pressure Chemical Ionization (ESI/APCI); Gas Temp: 310 °C, Vaporizer: 200 °C; Gas Flow: 8 L/min; Nebulizer 45 psi; Charging voltage: 2000 V; Solvent: MeOH; Solvent flow: 0.3 mL/min

Scheme 6.1 (b2431)

Alcohol 6-4. White solid; $[\alpha]^{20}_D$ = -118.5 (*c* 1.15, $CHCl_3$); IR (film): 3408, 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4, 2H), 4.60 (dd, *J* = 7.6, 3.2 Hz, 1H), 4.56 (d, *J* = 10.4 Hz, 1H), 4.37 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.20 (dd, *J* = 6.0, 2.8 Hz, 1H), 4.16 (d, *J* = 5.2 Hz, 1H), 3.99 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 2.31 (s, 3H), 1.55 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 135.2, 134.3, 129.7, 119.0, 110.3, 102.9, 73.3, 73.2, 68.0, 63.4, 53.7, 26.4, 24.9, 21.0. HRMS calcd for $C_{17}H_{21}NO_6$ (M) 335.1369, found 335.1362.

Scheme 6.1 (b2427A)

Alcohol 6-5_{ax} and 6-5_{eq}. White solid; $[\alpha]^{20}_D$ = -114.0 (*c* 1.20, $CHCl_3$); IR (film): 3483, 1747 cm^{-1}; **6-5_{ax}** ^1H NMR (400 MHz, $CDCl_3$) δ 5.27-5.23 (m, 2H), 4.18 (d, *J* = 9.6, 1H), 4.12 (dd, *J* = 13.2, 1.2 Hz, 1H), 4.10 (d, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.76 (dd, *J* = 13.2, 2.0 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H); **6-**

5$_{eq}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29-5.28 (m, 1H), 5.12 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 4.05-4.02 (m, 2H), 3.87 (t, *J* = 10.5, 1H), 3.74 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H); **6-5$_{ax}$** and **6-5$_{eq}$** ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.6, 170.2, 169.7, 113.1, 112.6, 106.1, 105.8, 73.9, 72.2, 71.8, 71.7, 69.7, 69.1, 67.5, 67.4, 62.7, 62.6, 26.9, 26.6, 26.5, 21.3, 21.2, 21.12, 21.08. Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.55; H, 6.84.