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DISSERTATION

SYNTHETIC AND MECHANISTIC STUDIES OF NOVEL DIOXIRANES

Submitted by

Michael John Frohn

Department of Chemistry

In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 2000

COLORADO STATE UNIVERSITY

May 4, 2000

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY MICHAEL JOHN FROHN ENTITLED SYNTHETIC AND MECHANISTIC STUDIES OF NOVEL DIOXIRANES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION

SYNTHETIC AND MECHANISTIC STUDIES OF NOVEL DIOXIRANES

Epoxides are versatile synthetic intermediates. The epoxidation of olefins via dioxiranes provides a particularly efficient route towards their synthesis, and studies into an asymmetric version have received great interest recently. Our group has been active in this area, and we have found an efficient asymmetric epoxidation method for simple unfunctionalized olefins using a fructose-derived ketone as catalyst and Oxone as oxidant.

The asymmetric monoepoxidation of unsymmetrical conjugated dienes has been studied using the fructose-derived ketone. The regio- and enantioselectivities have been found to be very high in most cases. As a result, a variety of synthetically useful vinyl epoxides can be readily produced in optically enriched form. The method is complementary to the selective epoxidation of conjugated dienes catalyzed by chiral (salen)Mn complexes, in which the *cis*-olefins are preferentially epoxidized. It is also complementary to the Sharpless asymmetric epoxidation of dienyl alcohols, which gives complete regioselective epoxidation at the epoxide proximal to the alcohol.

The kinetic resolution of racemic olefins using this asymmetric epoxidation strategy has also been studied intensively. Very high levels of resolution efficiency have been observed with both 1,6- and 1,3-disubstituted cyclohexenes. Exocyclic cyclohexenes and acyclic olefins are resolved less efficiently. The method can be viewed as a valuable alternative to some of the existing kinetic resolutions since it does not involve transition metals and the experimental procedure is simple.

Finally, in conjunction with these asymmetric studies, the efficient racemic epoxidation of olefins using dimethyldioxirane at high pH has also been discovered.

Nearly every class of olefins can be efficiently epoxidized using the general procedure that has been developed. In addition, it is highly practical, as epoxidations of 0.1 mol can be undertaken without complications. Further advantages include a simple workup procedure and the use of environmentally benign ingredients.

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I have been blessed to have met a number of fascinating people while I have been in Colorado. Two in particular are Graham Abramo and Tom Wynn. They both have been fantastic colleagues and friends, and I am looking forward to the many backpacking trips I will be venturing into with them in the future. Rhonda Critchlow is my soul mate in every sense of the word, and I can only say that my life has been enriched exponentially with her in it. I am looking forward to spending the rest of my life with her. Furthermore, "the gang" is a group of incredible people with whom I have had immeasurable numbers of good times and laughs.

To all of these people I am eternally greatful, for my life is better that I have met and spent time with them. Thank you.

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CHAPTER ONE

CHIRAL KETONE-CATALYZED ASYMMETRIC EPOXIDATION OF OLEFINS

1.A. INTRODUCTION

Dioxiranes are remarkably versatile oxidizing agents that show encouraging potential for asymmetric synthesis, particularly asymmetric epoxidation of unfunctionalized olefins. Dioxiranes can be generated *in situ* from Oxone (potassium peroxomonosulfate) and ketones (Scheme 1.1).[1,2] The ketone is regenerated upon epoxidation. Therefore, in principle, only a catalytic amount of ketone is required. If the ketone is chiral, there exists the opportunity for catalytic asymmetric epoxidation.[3] Since the pioneering work reported

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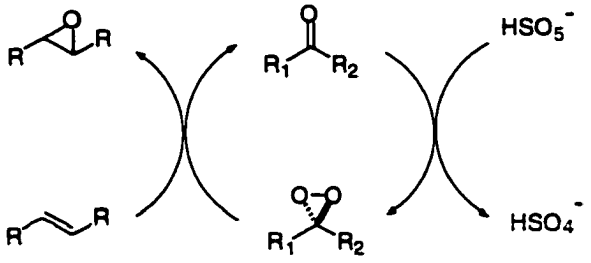
[1] For general leading references on dioxiranes see: (a) Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R.W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R.; Dinoi, A.; Rubino, M.F. *Pure & Appl. Chem.* **1995**, *67*, 811. (d) Clennan, E.L. *Trends in Organic Chemistry* **1995**, *5*, 231. (e) Adam, W.; Smerz, A.K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581. (f) Denmark, S.E.; Wu, Z. *Synlett* **1999**, 847.

[2] For some leading references, see: (a) Denmark, S.E.; Forbes, D.C.; Hays, D.S.; DePue, J.S.; Wilde, R.G. *J. Org. Chem.* **1995**, *60*, 1391. (b) Yang, D.; Wong, M.K.; Yip, Y.C. *J. Org. Chem.* **1995**, *60*, 3887. (c) Denmark, S.E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964. (d) Boehlow, T.R.; Buxton, P.C.; Grocock, E.L.; Marples, B.A.; Waddington, V.L. *Tetrahedron Lett.* **1998**, *39*, 1839. (e) Denmark, S.E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (f) Frohn, M.; Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. (g) Yang, D.; Yip, Y-C.; Jiao, G-S.; Wong, M-K. *J. Org. Chem.* **1998**, *63*, 8952. (h) Yang, D.; Yip, Y-C.; Tang, M-W.; Wong, M-K.; Cheung, K-K. *J. Org. Chem.* **1998**, *63*, 9888.

[3] For a recent account on this subject see: ref. 1f.

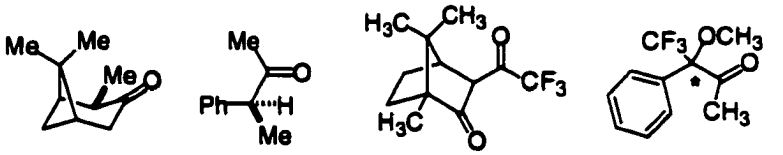
by Curci in 1984,[4] this area has received intensive interest, and this review will summarize some of the recent progress in this area.



Scheme 1.1

1.B. Early Ketones

The first chiral ketone-catalyzed asymmetric epoxidation was reported by Curci and coworkers in 1984.[4] The epoxidation was studied using (+)-isopinocamphone (**1-1**) or (*S*)-(+)-3-phenylbutan-2-one (**1-2**) as catalyst and (*E*)-β-methylstyrene or 1-methylcyclohexene as substrate in a biphasic mixture of CH_2Cl_2 - H_2O buffered to a pH of 7-8, with Bu_4NHSO_4 as phase transfer catalyst (Figure 1.1). Some of the results are shown in Table 1.1. Although long reaction times were needed, the amount of ketone could be reduced to as little as 20 mol% without reducing conversions and ee's compared to the cases where stoichiometric amounts of ketones were used. Up to 12.5% ee was obtained, demonstrating for the first time that chiral epoxides can be obtained if chiral ketones are used.



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

Figure 1.1 Early ketones

[4] Curci, R.; Fiorentino, M.; Serio, M.R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.

Table 1.1. Asymmetric Epoxidation of Olefins with Ketones **1-1** and **1-2**

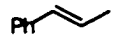
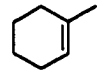
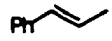
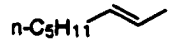
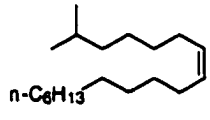
Entry	Substrate	Ketone (eq.)	Yield (%)	ee (%)	Configuration
1		**1-1** (2.0)	60	11	(+)-(1*R*,2*R*)
2		**1-1** (1.0)	60	12.5	(+)-(1*R*,2*R*)
3		**1-1** (0.2)	68	11.2	(+)-(1*R*,2*R*)
4		**1-2** (1.0)	85	9.5	(+)-(1*R*,2*R*)
5		**1-1** (1.0)	90	10.4	(+)-(1*S*,2*R*)
6		**1-1** (0.2)	85	10.2	(+)-(1*S*,2*R*)
7		**1-2** (0.5)	92	12	(+)-(1*S*,2*R*)

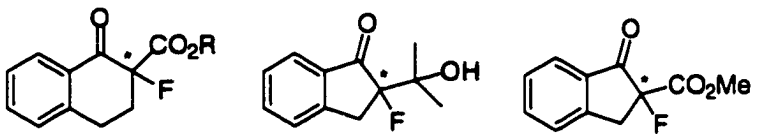
Table 1.2. Asymmetric Epoxidation of Olefins with Ketones **1-3** and **1-4** (0.8 - 1.2 eq.)

Entry	Substrate	Ketone	Yield (%)	ee (%)	Configuration
1		**1-3**	82	13	(+)-(1*R*,2*R*)
2		(*S*)**1-4**	77	18	(+)-(1*R*,2*R*)
3		(*S*)**1-4**	80	20	(+)-(2*S*,3*S*)
4		(*S*)**1-4**	80	16	(+)-(7*R*,8*S*)

Ketones **1-1** and **1-2** reacted sluggishly, and somewhat high catalyst loadings were required to give high conversion in reasonable times at 5 °C. Since electron-deficient ketones are generally more reactive for epoxidation,[1] a trifluoromethyl group was incorporated into the ketones. The resulting ketones **1-3** and **1-4** were subsequently investigated under similar biphasic reaction conditions, and were found to be much more

active (Table 1.2).[5] High conversions could be achieved within 17-48 hours with 0.8 – 1.2 eq. ketone at 2-5 °C. It was shown that the ketones could be recovered from the reaction with only minor (2-5%) loss.

In 1995, Marples and coworkers reported a class of 1-tetralone and 1-indanone based chiral ketones substituted at the C-2 position with a fluorine and either an alkoxycarbonyl or a 2-hydroxyisopropyl group (**1-5** - **1-8**) (Figure 1.2).[6] These ketones were designed as the cyclic equivalents of trifluoroacetophenone and related ring fluorinated acetophenones, which had been shown to generate reactive dioxiranes. Although none of these ketones provided optically active epoxides, the concept of carbonyl activation with electron withdrawing groups was further illustrated.



1-5 R = Me
1-6 R = (-)-menthyl

1-7

1-8

Figure 1.2 1-Indanone and 1-tetralone based ketones

1.C. Binaphthyl-Based and Related Ketones

In 1996, Yang and coworkers reported a C_2 symmetric, 11-membered ring chiral ketone (**1-9a**) derived from 1,1'-binaphthyl-2,2'-dicarboxylic acid (Figure 1.3).[7,8,9] In such ketones, a remote binaphthalene unit was used as the chiral control element. This ketone

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[5] Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.
[6] Brown, D.S.; Marples, B.A.; Smith, P.; Walton, L *Tetrahedron* **1995**, *51*, 3587.
[7] Yang, D.; Yip, Y.C.; Tang, M.W.; Wong, M.K.; Zheng, J.H.; Cheung, K.K. *J. Am. Chem. Soc.* **1996**, *118*, 491.
[8] Yang, D.; Wang, X-C.; Wong, M-K.; Yip, Y-C.; Tang, M-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311.
[9] 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.

was designed based on the following considerations: (a) The C_2 symmetry was introduced to limit the competing reaction modes of attack on the dioxirane, which has two faces for oxygen transfer; (b) The chiral element was placed away from the catalytic center (the carbonyl group) with the intention of avoiding any substituents at the α carbon since these are prone to racemization, and steric hindrance at the α carbon decreases catalyst activity; (c) Two electron withdrawing ester groups were introduced to activate the carbonyl.

The combination of unhindered carbonyl and electron withdrawing groups proved to be powerful. Ketone **1-9a** is very reactive, with the ability to give high conversion with as little as 10 mol% catalyst in a few hours at pH 7-7.5 (Table 1.3). Another aspect that may help in regard to its high reactivity is that the reaction is run in a homogeneous solvent system (CH_3CN-H_2O),[2b] which increases dioxirane-olefin interaction. The ketones are stable, and can be recovered in high yield. Up to 87% ee was obtained for 4,4'-*trans*-disubstituted stilbenes (Table 3, Entry 6).

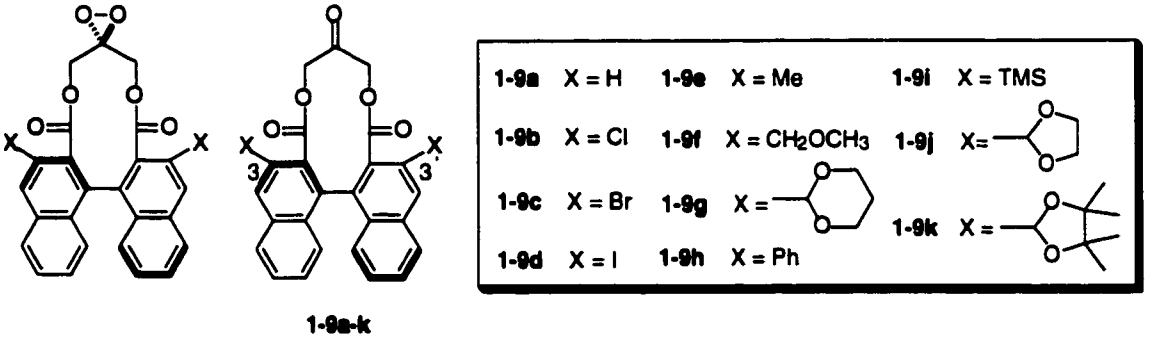
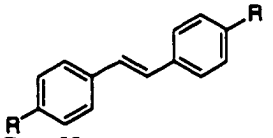
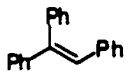
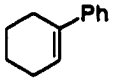
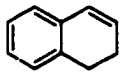
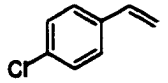


Figure1.3 Yang's binaphthyl-based ketones

The X-ray structure of ketone **1-9a** reveals that the two naphthalene rings are located on the opposite faces of the keto group.[8,9] H-3 and H-3' are closer to the putative dioxirane than other atoms on the chiral binaphthyl unit and may therefore be viewed as the steric sensors in the oxygen transfer process. It was therefore expected that higher enantioselectivity could be obtained by increasing the steric bulk at the 3 and 3' positions.

Ketones **1-9b** - **1-9k** were thus designed and investigated.[8,9] As shown in Table 1.4, the enantioselectivity was indeed affected by the substituents at the 3 and 3' positions. As the size of the steric sensor became larger (e.g. from H to Cl to Br to I) (Table 1.4, Entries 1-4), enantioselectivity first increased and then decreased, indicating optimal results require the appropriate size of steric sensor. Among these ketones the most reactive is **1-9g**, which has two ketal rings, and thus four additional inductively withdrawing oxygen atoms. Apparently, the electronic nature of the groups on the binaphthyl ring are transmitted rather well to the carbonyl in this case, providing even further activation.

Table 1.3. Asymmetric Epoxidation of Olefines with Ketone **1-9a**

Entry	Substrate	Yield (%)	ee (%)	Configuration
				
1	R = H	99	47	(-)-(*S,S*)
2	R = Me	99	50	(-)-(*S,S*)
3	R = Et	96	60	(-)-(*S,S*)
4	R = *i*-Pr	98	71	(-)-(*S,S*)
5	R = *t*-Bu	95	76	(-)-(*S,S*)
6	R = Ph	82	87	(-)-(*S,S*)
7		97	48	(+)-(*S*)
8		83	33	(-)-(*S,S*)
9		70	18	
10		85	<5	
11		83	18	(-)-(*S*)

As shown in Table 1.5, *para* substituted *trans*-stilbenes proved to be very good substrates for ketone **1-9**, and the size of the substituents on the phenyl rings of the olefin strongly influenced the enantioselectivity of the epoxidation. As the substituents became larger (from H to Me to Et to *i*-Pr to *t*-Bu), higher ee's were obtained (84 to 95% ee for **1-9g**) (Table 1.5, Entries 1-5).

Table 1.4. Asymmetric Epoxidation of *trans*-Stilbene with Ketone **1-9a - 1-9k** (0.1 eq.)

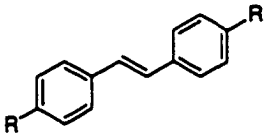
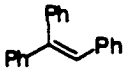
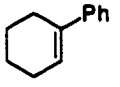
Entry	Ketone	Yield (%)	ee (%)	Configuration
1	**1-9a**	91	47	(-)-(*S,S*)
2	**1-9b**	95	76	(-)-(*S,S*)
3	**1-9c**	92	75	(-)-(*S,S*)
4	**1-9d**	90	32	(-)-(*S,S*)
5	**1-9e**	93	56	(+)-(*R,R*)
6	**1-9f**	92	66	(-)-(*S,S*)
7	**1-9g**	95	71	(-)-(*S,S*)
8	**1-9g** (0 °C)	93	84	(-)-(*S,S*)
9	**1-9h**	50	55	(-)-(*S,S*)
10	**1-9i**	--	44	(+)-(*R,R*)
11	**1-9j**	90	77	(-)-(*S,S*)
12	**1-9k**	91	75	(-)-(*S,S*)

Several other ketones with oxygens at the β-position to the carbonyl were also prepared and tested for their epoxidation effectiveness. In 1997, Song and coworkers reported ketones **1-10** and **1-11**, which replace the ester groups of **1-9** with ethers to bring the carbonyl closer to the chiral element (Figure 1.4).[10,11] Ketone **1-11** also changed the

[10] Song, C.E.; Kim, Y.H.; Lee, K.C.; Lee, S.G.; Jin, B.W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921.
[11] Adam, W.; Zhao, C-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995.

chiral element to simple phenyl groups. Results with *trans*-stilbene and *trans*-β-methylstyrene are given in Table 1.6. A full equivalent of these ketones was required to reach high conversions. As the reaction temperature was reduced to 0 °C the reaction became much slower, but the enantioselectivity increased up to 59% (Table 1.6, Entries 1 and 3 vs. Entries 2 and 4).

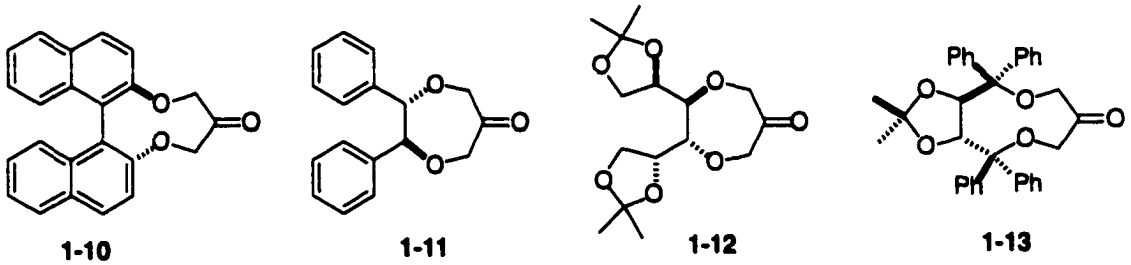
Table 1.5. Asymmetric Epoxidation of Olefins with Ketones **1-9b**, **1-9c**, & **1-9g** (0.1 eq.)

		Epoxide ee (%)				
Entry	Substrate	**1-9b** (RT)	**1-9c** (RT)	**1-9c** (0 °C)	**1-9g** (RT)	**1-9g** (0 °C)
						
1	R = H	76	75	80	71	84
2	R = Me	80	85	88	84	88
3	R = Et	85	88	92	82	91
4	R = *i*-Pr	85	90	92	88	91
5	R = *t*-Bu	91	93	95	90	95
6		76	81		73	
7		65	64		71	

The lower reactivity of these ketones compared to ketone **1-9** could be due to the fact that an ether group is a weaker electron withdrawing group than an ester group.

In 1997, another variation was reported by Adam and coworkers, using mannitol (**1-12**) and tartaric acid (**1-13**) as the chiral backbones (Figure 1.4).[11] The reactivity of these

ketones is similar to **1-10** and **1-11**. Based on the earier reported pH effect for the fructose-derived ketone **1-28** (*vide infra*), the reactivity and selectivity of **1-10** and **1-11** increased when the reaction is run at higher pH (Table 1.7, Entries 5, 7, 8, 10-12).



1-10 **1-11** **1-12** **1-13**

Figure 1.4 Ketones with oxygen atoms β to the carbonyl

Table 1.6. Asymmetric Epoxidation with Ketones **1-10** & **1-11** (1.0 eq.)[10]

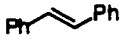
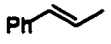
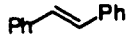
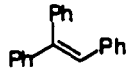
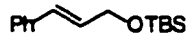
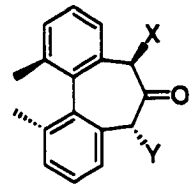
Entry	Substrate	Ketone	Temp.	Time (h)	Yield (%)	ee (%)	Configuration
1		**1-10**	rt	1	90	20	(*S,S*)
2		**1-10**	0 °C	5	79	26	(*S,S*)
3		**1-11**	rt	1	73	30	(*S,S*)
4		**1-11**	0 °C	5	72	59	(*S,S*)
5		**1-10**	rt	1	95	29	(*S,S*)
6		**1-11**	rt	1	61	20	(*S,S*)

Table 1.7. Epoxidation of Olefins with Ketones **1-12** & **1-13**

Entry	Substrate	Ketone (eq.)	pH	Time (h)	Conv. (%)	ee (%)	Configuration
1		**1-12** (2.0)	8.0	0.4	39	38.9	(+)-(*R*,*R*)
2		**1-12** (2.0)	8.0	24	72	38.3	(+)-(*R*,*R*)
3		**1-12** (2.0)	8.0	1.5	37	39.0	(+)-(*R*,*R*)
4		**1-13** (1.0)	8.0	168	54	32.6	(+)-(*R*,*R*)
5		**1-13** (1.0)	10.5	5	67	64.8	(+)-(*R*,*R*)
6		**1-13** (1.0)	8.0	84	55	66.0	(-)-(*R*)
7		**1-13** (1.0)	10.5	5	70	80.5	(-)-(*R*)
8		**1-13** (0.1)	10.5	5	12	78.7	(-)-(*R*)
9		**1-13** (1.0)	8.0	240	40	14.2	(+)-(*R*,*R*)
10		**1-13** (1.0)	10.5	5	51	79.7	(+)-(*R*,*R*)
11		**1-13** (1.0)	10.5	5	78	77.0	(+)-(*R*,*R*)
12		**1-13** (0.5)	10.5	5	80	78.8	(+)-(*R*,*R*)

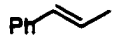
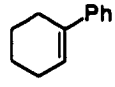
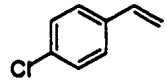
In 1999, Denmark and coworkers reported a highly active and selective carbocyclic 7-membered chiral ketone (**1-14**) (Figure 1.5).[1f] The ketone was designed to bring the chirality closer to the carbonyl, and it was found that fluorine substitution at the α-carbon had a dramatic influence on the epoxidation rate. One equivalent of the nonfluorinated ketone **1-14a** afforded only 5% conversion for *trans*-β-methystyrene, whereas monofluoroketone **1-14b** gave 24% conversion and difluoro ketone **1-14c** gave a quantitative transformation. A change to pH 10.0 by the addition of K_2CO_3 to the reaction mixture increased catalyst activity, resulting in a catalytic system that gave high yields of epoxide product with high ee's (Table 1.8).



1-14a, X = Y = H
1-14b, X = H, Y = F
1-14c, X = Y = F

Figure 1.5 Denmark's axially chiral ketones

Table 1.8. Asymmetric Epoxidation of Olefins with Ketone **1-14c** (0.1 - 0.3 eq.)

Entry	Substrate	Time (h)	Yield (%)	ee (%)
1		10	80	88
2		72	46	94
3		7	93	89
4		11	72	68
5		4	78	59
6		30	55	43

1.D. Ammonium Salts and Related Ketones

A ketone-catalyzed epoxidation usually involves using a biphasic solvent system. Effective partitioning of the ketone and its dioxirane between both the organic and aqueous phase is extremely important for epoxidation efficiency. During elegant and detailed studies of various reaction parameters, Denmark and coworkers revealed that 4-oxopiperidinium salts (**1-15**), which unite the dioxirane precursor (carbonyl group) with the

phase transfer catalyst, provided an efficient class of catalysts (Figure 1.6).[2a] The phase transfer ability of **1-15** can be regulated by controlling the chain length of the alkyl groups on the nitrogen. In addition, the inductive effect of the ammonium substituents activates the ketone and suppresses the Baeyer-Villiger oxidation. Building on this work, a number of chiral ammonium salts were investigated (Figure 1.6).[12] Initially, ammonium ketones **1-16** and **1-17** were prepared and tested.[2a,12] Both ketones were found to have low reactivity, probably due to the extra crowding imposed by the chiral centers adjacent to the carbonyl. Ketone **1-17** gave 58% ee for 1-phenylcyclohexene and 34% ee for *trans*-β-methylstyrene (Table 1.9, Entries 1 and 9).

To achieve greater activation of the carbonyl center and greater suppression of Baeyer-Villiger oxidation, dicationic ketones **1-18** - **1-22** were investigated. Up to 40% ee was obtained with ketone **1-20** (Table 1.9, Entry 4). The low ee's obtained with these ketones could be due to the distance between the chiral unit and the carbonyl. To draw the chiral environment closer to the reaction center, ketones **1-21** and **1-22** were prepared from chiral pyrrolidines. Both ketones were very active catalysts, although the ee did not improve (Table 1.9, Entries 5 and 6).

The low enantioselectivities obtained with the above bis(ammonium) ketones (**1-18** - **1-22**) could be attributed to the high flexibility of the 7-membered ring. Therefore, a tropinone-based rigid ammonium ketone **1-23** was then explored (Figure 1.6).[13,1f] In this ketone, fluorine was used as a second activating group, and it was highly reactive. High conversion was obtained for *trans*-β-methylstyrene (Table 1.9, Entry 7), and a 58% ee was obtained for *trans*-stilbene (Table 1.9, Entry 8).

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[12] For a detailed discussion on this class of ketones see: ref. 1f.
[13] Denmark, S.E.; Wu, Z.; Crudden, C.M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288.

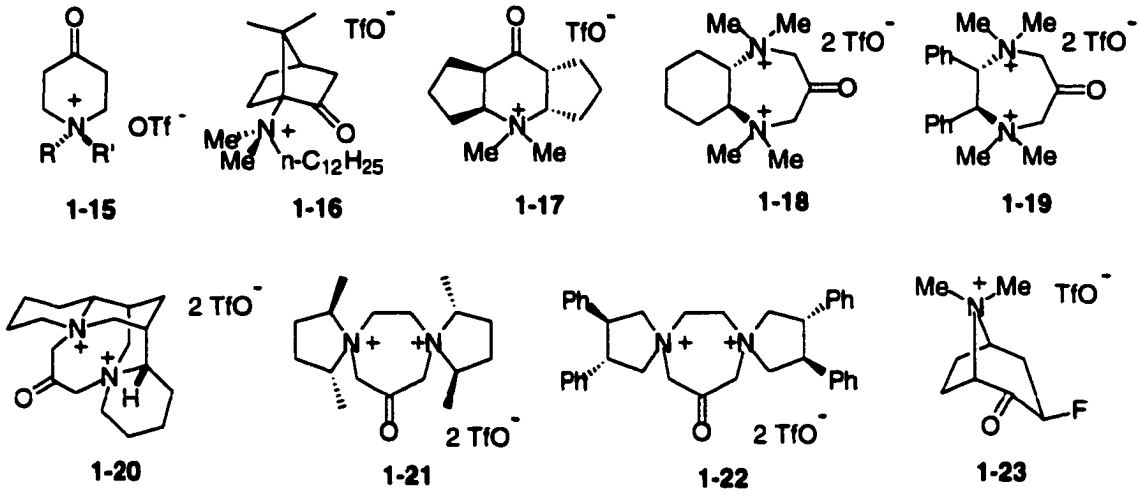
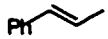
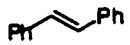
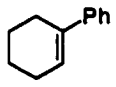


Figure 1.6 Ketones with β or γ nitrogens

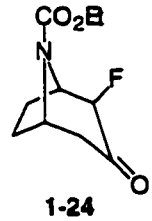
Table 1.9. Asymmetric Epoxidation of Olefins with Ammonium Ketones **1-17** - **1-23**

Entry	Substrate	Ketone (eq.)	Conv. (%)	ee (%)
1		**1-17**	--	34
2		**1-18** (cat.)	100	9
3		**1-19**	NR	
4		**1-20**	54	40
5		**1-21** (cat.)	100	<10
6		**1-22** (cat.)	100	<10
7		**1-23** (0.1)	100	35
8		**1-23**	--	58
9		**1-17**	--	58

In 1998, Armstrong and coworkers reported the uncharged tropinone-derived ketone **1-24** (Figure 1.7) (Table 1.10).[14] Placement of a carbamate on the bridgehead nitrogen in

[14] Armstrong, A.; Hayter, B.R. *J. Chem. Soc., Chem. Commun.* **1998**, 621.

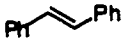
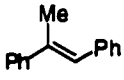
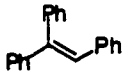
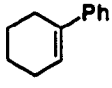
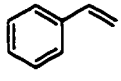
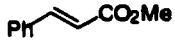
combination with the fluorine atom created a highly reactive catalyst, with up to 83% ee obtained for phenylstilbene (Table 1.10, Entry 3).



1-24

Figure 1.7 Armstrong's tropinone-based ketone

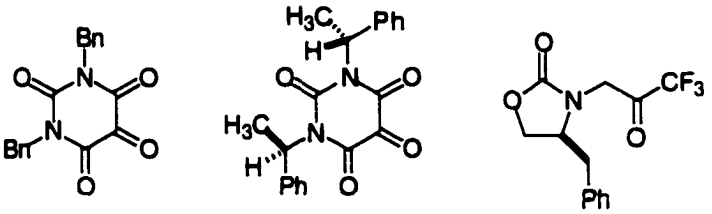
Table 1.10. Asymmetric Epoxidation of Olefins with Ketone **1-24**

Entry	Substrate	Cat. (eq.)	Yield (%)	ee (%)	Configuration
1		0.1	88	76	(*R,R*)
2		0.1	100	73	(*R,R*)
3		0.1	100	83	(*R*)
4		0.1	97	69	(*R*)
5		0.1	33	29	(*R*)
6		0.25	33	64	

Recently, Carnell and coworkers found that N,N-dialkylalloxans such as **1-25** were very reactive epoxidation catalysts (Figure 1.8).[15] Placement of carbonyls on either side of the dioxirane precursor suppressed Baeyer-Villiger oxidation and ketone **1-25** could be recovered without decomposition. Unfortunately, no asymmetric induction was achieved on

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

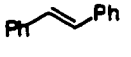
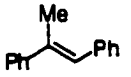
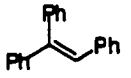
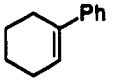
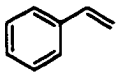
epoxidation of *trans*-stilbene when chiral ketone **1-26** was used, presumably because the chiral center was not close to the reaction center.



1-25 **1-26** **1-27**

Figure 1.8 Additional nitrogen containing ketones

Table 1.11. Asymmetric Epoxidation of Olefins with Ketone **1-27**

Entry	Substrate	Conv. (%)	Yield (%)	ee (%)	Configuration
1		75	69	25	(*R,R*)
2		65	52	31	(*R,R*)
3		33	26	33	(*R*)
4		100	67	34	(*R,R*)
5		64	18	<5	

Although ketones **1-15** - **1-26** have nitrogens at β-positions of carbonyl groups, an oxazolidinone-derived trifluoromethyl ketone **1-27** containing the nitrogen at the α-position was investigated by Armstrong and coworkers (Figure 1.7).[16] Unfortunately, ketone **1-27** decomposed via Baeyer-Villiger oxidation at pH 7-8. However, good conversions could be achieved using 3 equivalents of the ketone, with up to 34 % ee obtained (Table 1.11).

1.E. Carbohydrate-Based and Related Ketones

In 1996, a fructose-derived ketone **1-28** was developed as a highly effective epoxidation catalyst (Figure 1.9).[17] Ketone **1-28** can be synthesized in two steps from D-fructose by ketalization and oxidation (Scheme 1.2).[17,18,19] The enantiomer of ketone catalyst **1-28** (ketone **ent 1-28**) can be prepared in the same way from L-fructose, which can be prepared from readily available L-sorbose following a literature procedure.[20,21] Ketone **ent 1-28** prepared this way showed the same enantioselectivity in the opposite sense for the epoxidation.

Ketone **1-28** is a member of a class of ketones designed to contain the following general features (Figure 1.9): (1) the stereogenic centers are close to the reacting center, resulting in efficient stereochemical communication between substrate and catalyst; (2) the presence of fused ring(s) or a quaternary center α to the carbonyl group minimizes the epimerization of the stereogenic centers; (3) approach of an olefin to the reacting dioxirane can be controlled by sterically blocking one face or using a C_2 or pseudo C_2 symmetric element; (4) inductively withdrawing substitutents are introduced to activate the carbonyl.

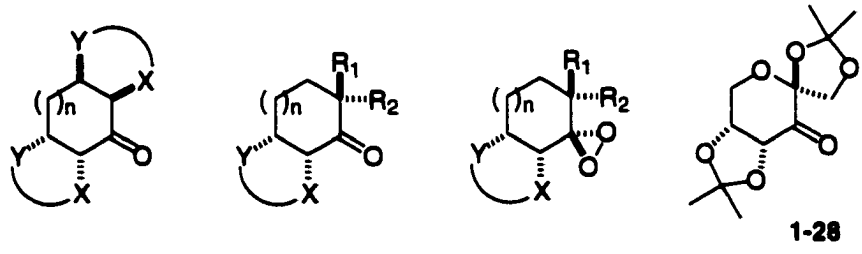


Figure 1.9 General design for carbohydrate-based ketones

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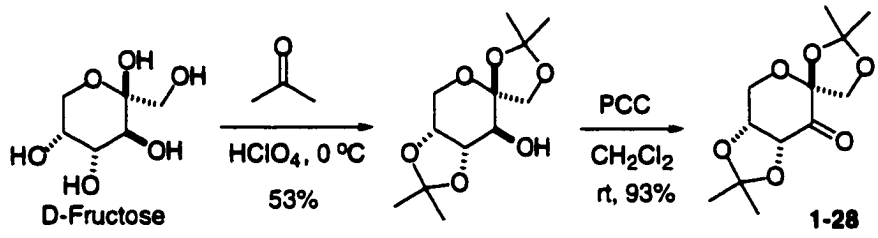
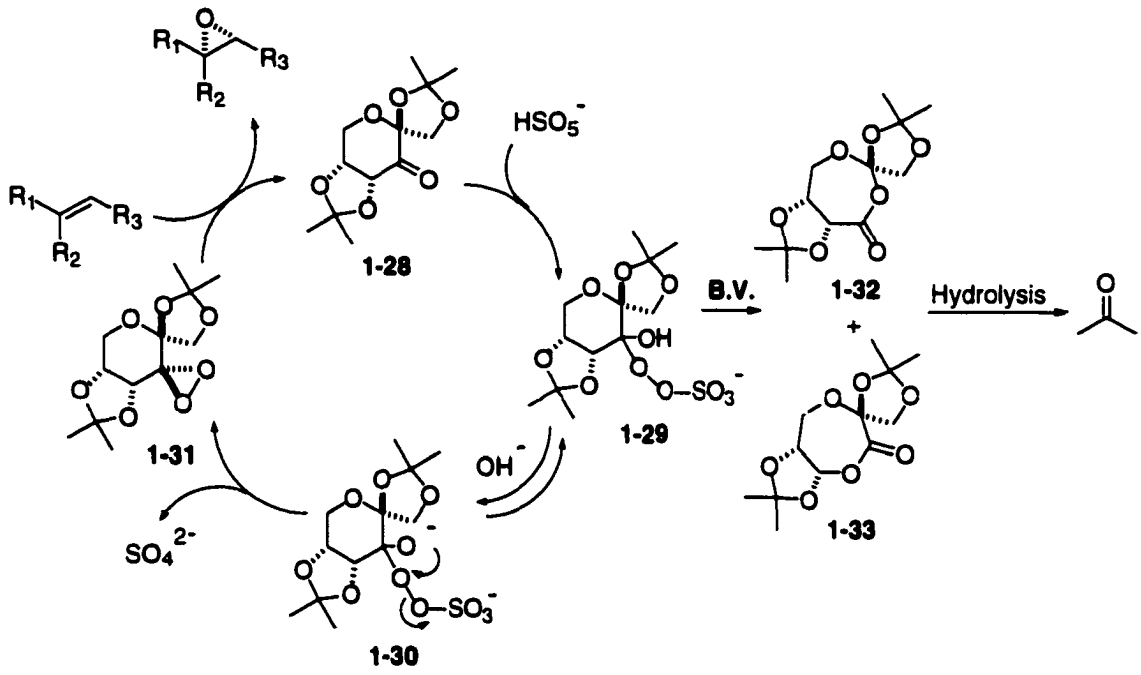
[16] Armstrong, A.; Hayter, B.R. *Tetrahedron* **1999**, *55*, 11119.
[17] Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
[18] Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.
[19] Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.
[20] Chen, C-C.; Whistler, R.L. *Carbohydr. Res.* **1988**, *175*, 265.
[21] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.



Scheme 1.2

The pH of the reaction mixture is a very important factor for epoxidation with dioxiranes generated *in situ*.[2] High pH results in the rapid autodecomposition of Oxone,[22,23] thus leading to a decrease in epoxidation efficiency. For this reason, ketone-mediated epoxidations are usually carried out at pH 7.[2,4-11,13-16] Initial studies with ketone **1-28** were therefore carried out at pH 7-8, and high enantioselectivies (>90% ee) were obtained for a variety of *trans*-disubstituted and trisubstituted olefins.[17] However, at this pH, ketone **1-28** decomposed very rapidly, and a large amount of ketone was required to achieve good conversion of substrate. It was subsequently envisioned that a possible decomposition pathway could involve the Baeyer-Villiger reaction resulting from intermediate **1-29** (Scheme 1.3). Although the corresponding lactone had not been isolated, it was surmised that this competing reaction (B.V.) could be suppressed by raising the pH, since at a higher pH intermediate **1-30** would be favored, leading to more efficient formation of dioxirane **1-31**. It was also envisioned that the autodecomposition of Oxone at high pH could possibly be overridden if the ketone **1-28** was sufficiently reactive.

[22] Ball, D.L.; Edwards, J.O. *J. Am. Chem. Soc.* **1956**, *78*, 1125.
[23] Montgomery, R.E. *J. Am. Chem. Soc.* **1974**, *96*, 7820.



Scheme 1.3

Based on these considerations, a systematic investigation of the pH effect on the epoxidation of *trans*-β-methylstyrene was then carried out.[19,21] The pH had a profound effect on the substrate conversion and the higher pH was indeed beneficial to the catalyst efficiency (Figure 1.10). The conversion of *trans*-β-methylstyrene to its epoxide increased more than 10 fold on going from pH 7-8 to pH >10, and the enantioselectivity remained high at high pH (90-92% ee). In addition, the amount of Oxone used in this catalytic procedure was reduced significantly, suggesting that ketone **1-28** was indeed reactive enough to compete with the autodecomposition of Oxone. This dramatic pH effect lead to a catalytic asymmetric epoxidation process, which significantly enhanced the potential of the current epoxidation for practical use. The optimal pH range is broad, which simplifies the experimental operation. The epoxidation is typically carried out at pH around 10.5, which can be conveniently achieved by adding either K_2CO_3 or KOH as the reaction proceeds. Furthermore, epoxides are usually more stable under these basic conditions.

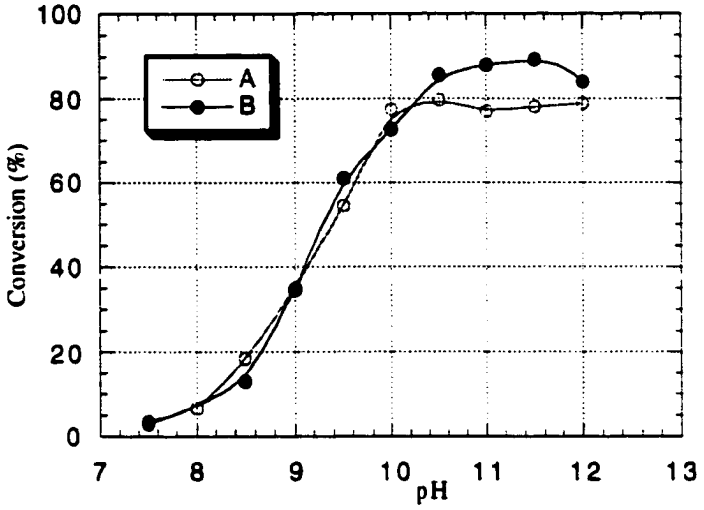


Figure 1.10. Plot of the conversion of *trans*-β-methylstyrene against pH using ketone **1-28** (0.2 eq.) as catalyst in two solvent systems, H_2O-CH_3CN (1 : 1.5, V/V) (**A**), H_2O-CH_3CN-DMM (2 : 1 : 2, V/V) (**B**) (for details see ref. 21).

For comparison, the pH effect on the epoxidation of *trans*-β-methylstyrene using acetone as catalyst was also studied. The results in Figure 1.11 show that the efficiency of the acetone catalyzed epoxidation is generally enhanced as well at higher pH.[21,2f] This could be due to the enhanced nucleophilicity of Oxone, which increases the reactivity towards acetone (It is noteworthy that the epoxidation by Oxone itself under these conditions is negligible and the epoxidation is solely due to acetone catalysis). Therefore the enhanced epoxidation efficiency at higher pH for ketone catalyst **1-28** is not only due to a decrease of the Baeyer-Villiger reaction, but also a result of increased nucleophilicity of Oxone (the enhanced nucleophilicity would suppress additional competing side reactions of the catalyst). A clearer understanding of the mechanistic consequence awaits further studies.

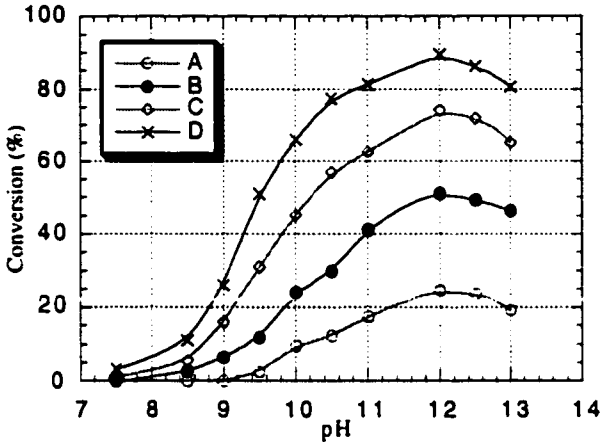


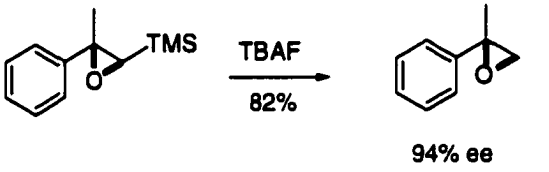
Figure 1.11. Plot of the conversion of *trans*-β-methylstyrene against pH using acetone (3 eq.) as catalyst in H_2O-CH_3CN (1 : 1.5, V/V). Samples were taken at different reaction times for the determination of conversion, 0.5 h (**A**), 1.0 h (**B**), 1.5 h (**C**), 2.0 h (**D**) (for details see ref. 21).

To test the generality of this epoxidation, a variety of olefins were investigated with a catalytic amount of ketone **1-28** (typically 20-30 mol%). The results are summarized in Tables 1.12-1.19. High enantioselectivities can be obtained for a variety of unfunctionalized *trans*- and trisubstituted olefins (Tables 12 & 13). However, this ketone catalyst currently gives relatively low ee's for *cis*-disubstituted and terminal olefins (Table 1.14).[21]

Among other olefins, hydroxyalkenes can also be expoxidized nicely (Table 1.15).[24] This method is complementary to the Sharpless Asymmetric Epoxidation since homoallylic and bishomoallylic alcohols can be epoxidized with high ee's. Conjugated dienes can be regio- and enantioselectively epoxidized to provide vinyl epoxides with high ee's (Table 1.16).[25] For unsymmetrical dienes, the regioselectivity can be regulated by using both steric or electronic control. Conjugated enynes can be highly chemo- and enantioselectively epoxidized to produce chiral propargyl epoxides (Table 1.17).[26,27] Enol silyl ethers and

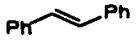
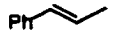
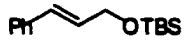
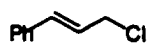
[24] Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.
[25] Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.
[26] Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425.
[27] Wang, Z-X.; Cao, G-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

esters can also be enantioselectively epoxidized to produce optically active α-hydroxy ketones[28,29] and enol ester epoxides,[29] respectively (Table 1.18). The resulting chiral enol ester epoxides are versatile synthetic intermediates, which can be converted into optically active α-hydroxy or α-acyloxy ketones by hydrolysis or stereospecific rearrangement.[29,30,31] A variety of 2,2-disubstituted vinyl silanes can also be enantioselectively epoxidized (Table 1.19).[32] Subsequent desilylation of the resulting epoxysilanes using TBAF provides easy access to 1,1-disubstituted terminal epoxides with high enantioselectivity (eq. **1.1**).

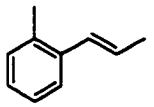
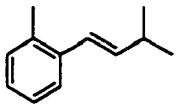
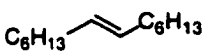
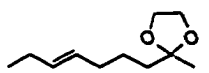
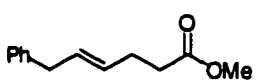


(eq. 1.1)

Table 1.12. Asymmetric Epoxidation of Representative *trans*-Disubstituted Olefins by Ketone **1-28**

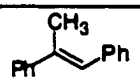
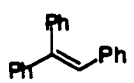
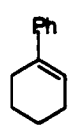
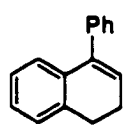
Entry	Substrate	T (°C)	Yield (%)	ee(%)	Configuration
1		20	85	98	(+)-(*R*,*R*)
2		-10	94	95	(+)-(*R*,*R*)
		-10 (**ent 1-28**)	94	95	(-)-(*S*,*S*)
3		0	87	94	(+)-(*R*,*R*)
4		0	55	94	(+)-(*R*,*R*)
5		0	49	96	(+)-(2*S*,3*R*)

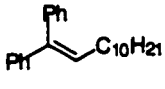
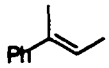
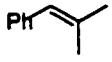
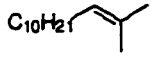
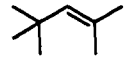
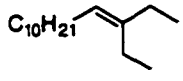
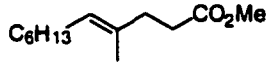
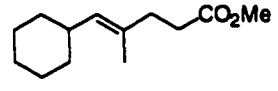
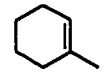
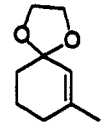
[28] Adam, W.; Fell, R.T.; Saha-Moller, C.R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 397.
[29] Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.
[30] Zhu, Y.; Manske, K.J.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4080.
[31] Feng, X.; Shu. L.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11002.
[32] Warren, J.D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675.

6		-10	91	93	(+)-(*R*,*R*)
7		-10	78	96	(-)-(*R*,*R*)
8		-10	83	94	(+)-(*R*,*R*)
9		-10	85	93	(+)-(*R*,*R*)
10		-10	89	95	(+)-(*R*,*R*)
11		-10	92	92	(+)-(*R*,*R*)
12		0	68	92	(+)-(*R*,*R*)

For details see ref. 21.

Table 1.13. Asymmetric Epoxidation of Representative Trisubstituted Olefins by Ketone **1-28**

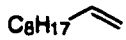
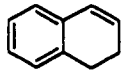
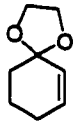
Entry	Substrate	T (°C)	Yield (%)	ee(%)	Configuration
1		0	89	95	(+)-(*R*,*R*)
2		0	54	97	(-)-(*R*)
3		-10	94	98	(-)-(*R*,*R*)
4		-10	98	95	(-)-(1*S*,2*R*)

5		0	92	97	(+)-(*R*)
6		-10	89	97	(*R*,*R*)
7		-10	93	76	(+)-(*R*)
8		-10	97	86	(+)-(*R*)
9		-10	>99 (conv.)	91	(-)-(*R*)
10		-10	94	88	(+)-(*R*)
11		-10	91	83	(+)-(*R*,*R*)
12		-10	89	94	(+)-(*R*,*R*)
13		-10	77	81	(-)-(1*S*,2*R*)
14		-10 (**ent 1-28**)	41	97	(-)-(*R*,*R*)

For details see ref. 21.

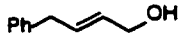
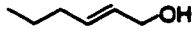
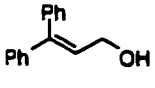
Table 1.14. Asymmetric Epoxidation of *cis*-Disubstituted & Terminal Olefins by Ketone **1-28**

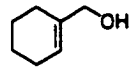
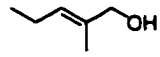
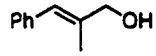
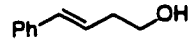
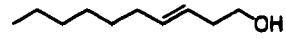
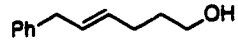
Entry	Substrate	T (°C)	Yield (%)	ee(%)	Configuration
1		-10	90	24	(+)-(*R*)

2		-10	80	27	(+)-(*R*)
3		-10	92	35	
4		-10	81	28	(-)-(*S*)
5		-10	85	32	(-)-(1*S*,2*R*)
6		-10	43	61	(+)-(*R*,*R*)

For details see ref. 21.

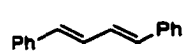
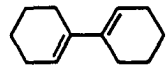
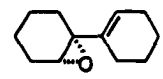
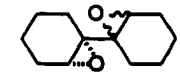
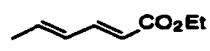
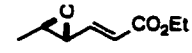
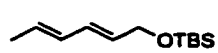
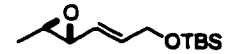
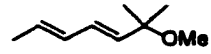
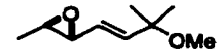
Table 15. Asymmetric Epoxidation of Representative Hydroxyalkenes Catalyzed by Ketone **1-28**

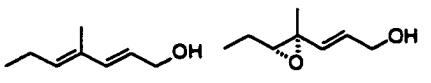
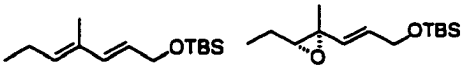
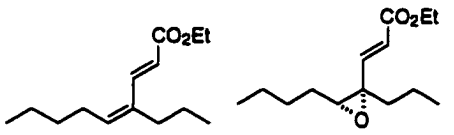
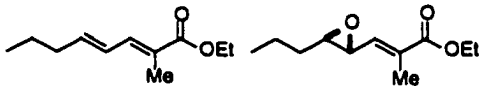
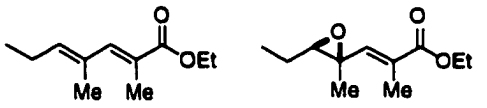
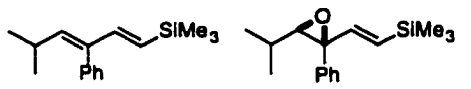
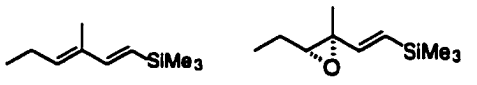
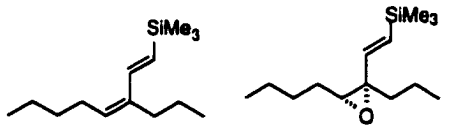
Entry	Substrate	T (°C)	Yield (%)	ee(%)	Configuration
1		-10	85	94	(+)-(*R*,*R*)
2		-10	45	91	(+)-(*R*,*R*)
3		-10	68	91	(+)-(*R*,*R*)
4		0	87	94	(+)-(*R*,*R*)

5		-15	93	94	(+)-(*R*,*R*)
6		-15	85	92	(+)-(*R*,*R*)
7		-15	75	74	(+)-(*R*,*R*)
8		-10	82	90	(+)-(*R*,*R*)
9		0	90	91	(+)-(*R*,*R*)
10		-15	83	91	(+)-(*R*,*R*)
11		0	87	91	(+)-(*R*,*R*)

For details see ref. 24

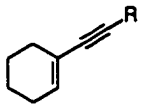
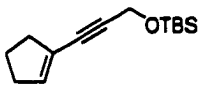
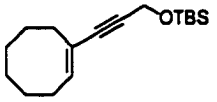
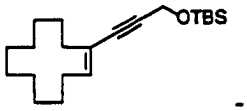
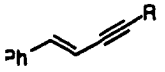
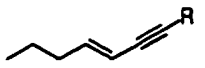
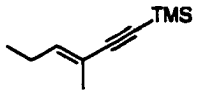
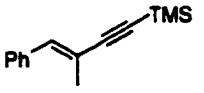
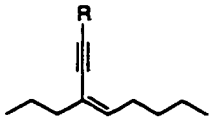
Table 1.16. Asymmetric Epoxidation of Representative Dienes by Ketone **1-28**

Entry	Dienes	Epoxides		Ratio	Yield (%)	ee (%)
1				22:1	77	97
2				12:1	54	95
3				7:1	41	96
4				4.6:1	68	96
5					65	89

6				68	90
7				81	96
8				68	95
9				82	95
10				61	94
11				89	94
12			14:1	77	94
13				81	95
14				60	92
15				79	95

For details see ref. 25

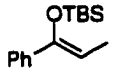
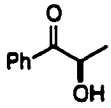
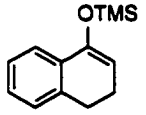
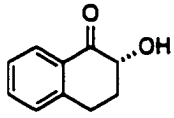
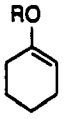
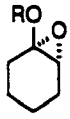
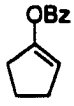
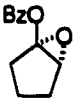
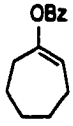
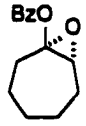
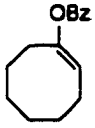
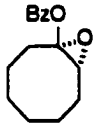
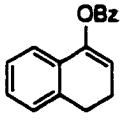
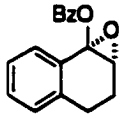
Table 1.17. Asymmetric Epoxidation of Representative Enynes by Ketone **1-28**

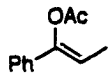
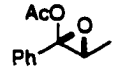
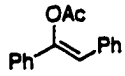
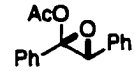
Entry	Substrate	T (°C)	Yield (%)	ee (%)	Configuration
					
1	R = H	-10	78	93	(*R*,*R*)
3	R = CH_3	-10	88	90	(*R*,*R*)
4	R = TMS	-10	86	93	(*R*,*R*)
5	R = CO_2Et	0	71	93	(*R*,*R*)
6		-10	97	77	(*R*,*R*)
7		-10	98	96	(*R*,*R*)
8		-10	99	86	(*R*,*R*)
					
9[b]	R = TMS	0	59	96	(*R*,*R*)
10[b]	R = TBS	0	60	96	(*R*,*R*)
11[b]	R = Me	0	35	94	(*R*,*R*)
					
12	R = TMS	-10	71	89	(*R*,*R*)
13	R = TBS	-10	69	89	(*R*,*R*)
14	R = CH_2OMe	-10	35	89	(*R*,*R*)
15		-10	84	95	(*R*,*R*)
16		0	64	94	(*R*,*R*)
					

17	R = H	-10	60	93	(*R*,*R*)
18	R = TMS	-10	83	97	(*R*,*R*)
19	R = TBS	-10	93	97	(*R*,*R*)

For details see refs. 26 & 27

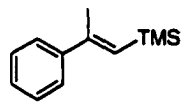
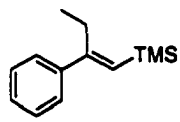
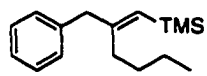
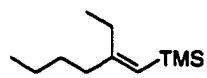
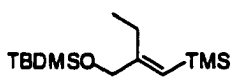
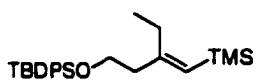
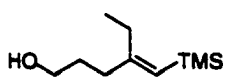
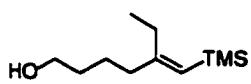
Table 1.18. Asymmetric Epoxidation of Enol Silyl Ethers and Esters by Ketone **1-28**

Entry	Substrate	Product	Yield (%)	ee (%)
1			80	90
2			70	83
				
3	R = Ac		59	74
4	R = Bz		82	93
5			79	80
6			87	91
7			82	95
8			92	88

9			66	91
10			46	91

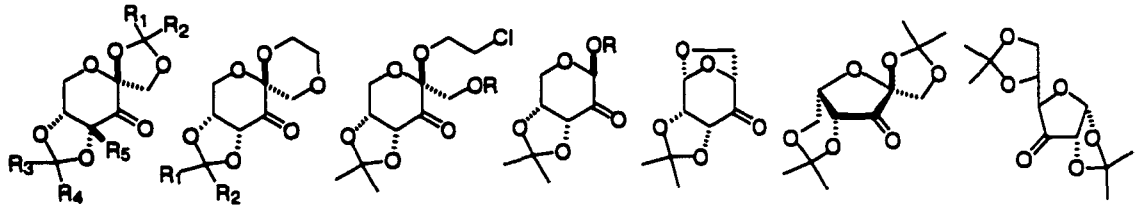
For details see ref. 29.

Table 1.19. Asymmetric Epoxidation of Representative 2,2-Disubstituted Vinylsilanes by Ketone **1-28**

Entry	Substrate	Yield (%)	ee (%)	Configuration.
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		71	93	(*R*,*R*)
8		75	91	(*R*,*R*)

For details see ref. 32

To further probe the structural requirements for the chiral ketone catalysts, a number of related ketones were prepared from carbohydrates (Scheme 1.4).[33] As shown in Table 1.20, the catalytic properties of these ketones were highly dependent on the precise nature of the ketone structure. It was found that the rigid 5-membered ring spiro ketal of **1-28** was structurally superior to the 6-membered cyclic ketal of **1-34** and the acyclic groups of **1-35** and **1-36** for both reactivity and enantioselectivity of the epoxidation. Studies with ketone **1-28** and **1-28a - 1-28m** showed that the epoxidation was also largely affected by the size of the groups attached to the ketals (R_1, R_2, and R_3, R_4). Generally speaking, the smaller R_1 and R_2, the higher the reactivity and selectivity. The size of R_3 and R_4 also affects the yield and ee of the epoxidation. Among all these ketones, **1-28** is the most generally effective catalyst considering the yield, enantiomeric excess of the formed epoxides, and ease of preparation; although slightly higher ee's are obtained with ketones **1-28b**, **1-28e**, **1-28g**, **1-28l**, **1-28m** in certain cases (Table 1.20, Entries 3, 6, 8, 13, and 14).



1-28a-n **1-34** **1-35** **1-36** **1-37** **1-38** **1-39**

	R_1, R_2	R_3, R_4	R_5		R_1, R_2
1-28	Me, Me	Me, Me	H	**1-34a**	Me, Me
1-28a	Et, Et	Et, Et	H	**1-34b**	Et, Et
1-28b	-$(CH_2)_4$-	-$(CH_2)_4$-	H	**1-34c**	Pr, Pr
1-28c	-$(CH_2)_5$-	-$(CH_2)_5$-	H	**1-34d**	Bn, Bn
1-28d	-$(CH_2)_6$-	-$(CH_2)_6$-	H	**1-34e**	Ph, Ph
1-28e	Me, Me	Et, Et	H	**1-34f**	-$(CH_2)_4$-
1-28f	Me, Me	Bn, Bn H		**1-34g**	-$(CH_2)_5$-

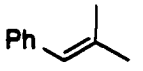
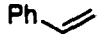
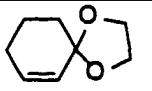
[33] Tu, Y.; Wang, Z-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475.

1-28g	Me, Me	$-(CH_2)_4-$	H		
1-28h	Me, Me	$-(CH_2)_5-$	H	**1-35a**	R = TBS
1-28i	Me, Me	Et, H	H	**1-35b**	R = H
1-28j	Me,Me	iPr, H	H	**1-35c**	R = Ac
1-28k	Et, Et	Me, Me	H		
1-28l	$-(CH_2)_4-$	Me, Me	H	**1-36a**	R = Me
1-28m	$-(CH_2)_5-$	Me, Me	H	**1-36b**	R = $(CH_2)_2Cl$
1-28n	Me, Me	Me, Me	F		

Scheme 1.4

Ketones **1-38** and **1-39** with 5-membered rings were found to be less effective catalysts (Table 1.20, Entries 29 and 30), owing to their facile Baeyer-Villiger oxidative decomposition caused by the ring strain associated with the 5-membered ring.

Table 1.20. Epoxidation of Olefins Catalyzed by Ketones **1-28**, **1-28a** - **1-28n**, and **1-34** - **1-39** at 0 °C

Entry	Ketone (eq.)	 conv.(ee) (%)	 conv.(ee) (%)	 conv.(ee) (%)	 conv.(ee) (%)	 conv.(ee) (%)
1	**1-28** (0.3)	75 (97)	93 (92)	100 (72)	100 (15)	53 (51)
2	**1-28a** (0.3)	16 (96)	32 (86)	40 (57)	26 (12)	17 (47)
3	**1-28b** (0.3)	57 (99)	89 (94)	100 (68)	100 (30)	73 (47)
4	**1-28c** (0.3)	41 (98)	51 (87)	80 (58)	59 (14)	43 (44)
5	**1-28d** (0.3)	30 (98)	37 (91)	37 (66)	43 (17)	6 (51)
6	**1-28e** (0.3)	38 (94)	91 (93)	98 (57)	92 (16)	19 (43)
7	**1-28f** (0.3)	7 (93)	18 (66)	15 (29)	6 (3)(*S*)	0
8	**1-28g** (0.3)	52 (98)	95 (93)	100 (69)	100 (18)	56 (48)
9	**1-28h** (0.3)	59 (92)	100 (89)	100 (63)	77 (17)	46 (46)
10	**1-28i** (0.3)	38 (96)	79 (91)	100 (65)	79 (10)	55 (42)

11	**1-28j** (0.3)	39 (95)	64 (89)	83 (61)	60 (7)	55 (53)
12	**1-28k** (0.3)	36 (98)	81 (90)	77 (71)	77 (12)	24 (55)
13	**1-28l** (0.3)	66 (98)	100 (93)	100 (72)	92 (27)	57 (49)
14	**1-28m** (0.3)	59 (98)	100 (91)	100 (72)	93 (16)	50 (52)
15	**1-28n** (0.3)	3 (11)	11 (5)	23 (12)	8 (32)	23 (12)
16	**1-34a** (0.3)	34 (90)	44 (61)	65 (84)	38 (38)	30 (60)
17	**1-34b** (0.3)	25 (85)	33 (61)	63 (76)	42 (42)	24 (49)
18	**1-34c** (0.3)	--	28 (82)	43 (73)	29 (43)	13 (46)
19	**1-34d** (0.3)	10 (82)	19 (56)	17 (29)	6 (21)	8 (39)
20	**1-34e** (0.3)	10 (67)	26 (48)	36 (21)	30 (20)	8 (4)
21	**1-34f** (0.3)	34 (91)	36 (61)	81 (76)	39 (37)	29 (57)
22	**1-34g** (0.3)	35 (78)	52 (52)	80 (74)	42 (36)	31 (52)
23	**1-35a** (0.3)	0	10 (40)	8 (17)	0	--
24	**1-35b** (0.3)	2 (nd)	8 (65)	6 (68)	0	--
25	**1-35c** (0.3)	6 (96)	5 (66)	11 (67)	5 (23)	8 (44)
26	**1-36a** (0.3)	10 (88)	15 (59)	17 (30)	14 (27)	13 (42)
27	**1-36b** (0.3)	10 (90)	16 (67)	18 (29)	15 (29)	9 (41)
28	**1-37** (0.3)	27 (74)	5 (41)	5 (35)	40 (10)	0
29	**1-38** (1.0-1.5)	14 (75)	41 (62)	57 (20)(*S*)	41 (15)	46 (71)
30	**1-39** (1.0)	--	4 (23)(*S*)	--	--	--

For details see ref. 33. All epoxides have (*R*) configurations unless otherwise noted.

1.E.1. Transition State Analysis

Understanding the reaction mode of the dioxirane-mediated epoxidation is important for predicting the stereochemical outcome of the reaction and for designing an effective

ketone catalyst. The two extreme transition state geometries for the epoxidation of olefins with dioxiranes are spiro and planar (Figure 1.12).[34,35,36,1c,1d,17,21,8,9,37,38] Baumstark and coworkers observed that *cis*-hexenes were 7-9 fold more reactive than the corresponding *trans*-hexenes for epoxidation using dimethyldioxirane.[34] After analyzing steric effects in both transition states, they found that a spiro transition state is consistent with this observation (Figure 1.13).[34,35] Computational studies also show the optimized transition state for oxygen atom transfer from dimethyldioxirane to ethylene is the spiro transition state.[36,37,38]

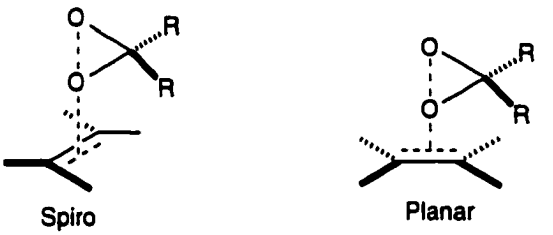


Figure 1.12. The spiro and planar transition states for the dioxirane epoxidation of olefins

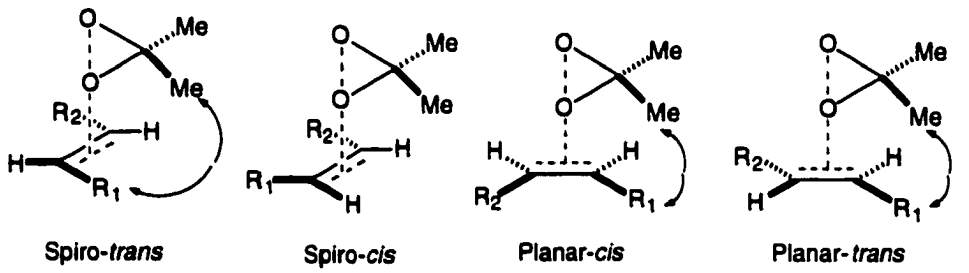


Figure 1.13. The spiro and planar transition states for the epoxidation of *trans* and *cis*-olefins with dimethyldioxirane

[34] Baumstark, A.L.; McCloskey, C.J. *Tetrahedron Lett.* **1987**, *28*, 3311.
[35] Baumstark, A.L.; Vasquez, P.C. *J. Org. Chem.* **1988**, *53*, 3437.
[36] Bach, R.D.; Andres, J.L.; Owensby, A.L.; Schlegel, H.B.; McDouall, J.J.W. *J. Am. Chem. Soc.* **1992**, *114*, 7207.
[37] Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* **1997**, *119*, 10147.
[38] Jenson, C.; Liu, J.; Houk, K.N.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1997**, *119*, 12982.

Analyzing the stereochemistry of epoxides produced by chiral dioxiranes provides the opportunity for further exploration of the transition state. A few possible transition states for the epoxidation between the olefin and the dioxirane of ketone **1-28** are shown in Scheme 1.5.[17,21] Steric repulsion disfavors transition states **B-G** (For *trans* disubstituted olefins where R_2 = H, **B** is similar to **A**, and **G** is similar to **H**). Spiro **A** and Planar **H** are the two sterically favored transition states, giving the opposite stereochemistry for the epoxide product. Analysis of product configuration reveals the mode of epoxidation. Nearly every example of *trans*-disubstituted and trisubstitued olefins studied with this catalyst is consistent with the spiro transition state.[17,20,21,24-28,30]

The favoring of a spiro transition state over a planar one could be due to the stabilizing interaction of an oxygen lone pair with the π^* orbital of the alkene in the spiro transition state (stereoelectronic origin). Such stabilizing orbital interaction can not be achieved geometrically in the planar transition state.[36,37] Analyzing transition states spiro **A** and planar **H** indicates that the energy difference should also be subject to the steric effect of substituents on the olefin. Higher ee can be obtained by decreasing the size of R_1 (favoring spiro **A**) and increasing the size of R_3 (disfavoring planar **H**). The results presented in Figures 1.14 and 1.15 show that this is indeed the case, particularly for trisubstituted olefins[39] (for *trans*-disubstituted olefins where R_2 = H, transition state **B** is also feasible, which provides an additional option to minimize the steric interaction). Overall, these studies strongly suggest that the epoxidation proceeds through spiro **A** and the main competing mode is planar **H**. The extent of involvement of the planar transition state is dependent on the substituents on the olefins.[21,40,41] In their studies, Yang and

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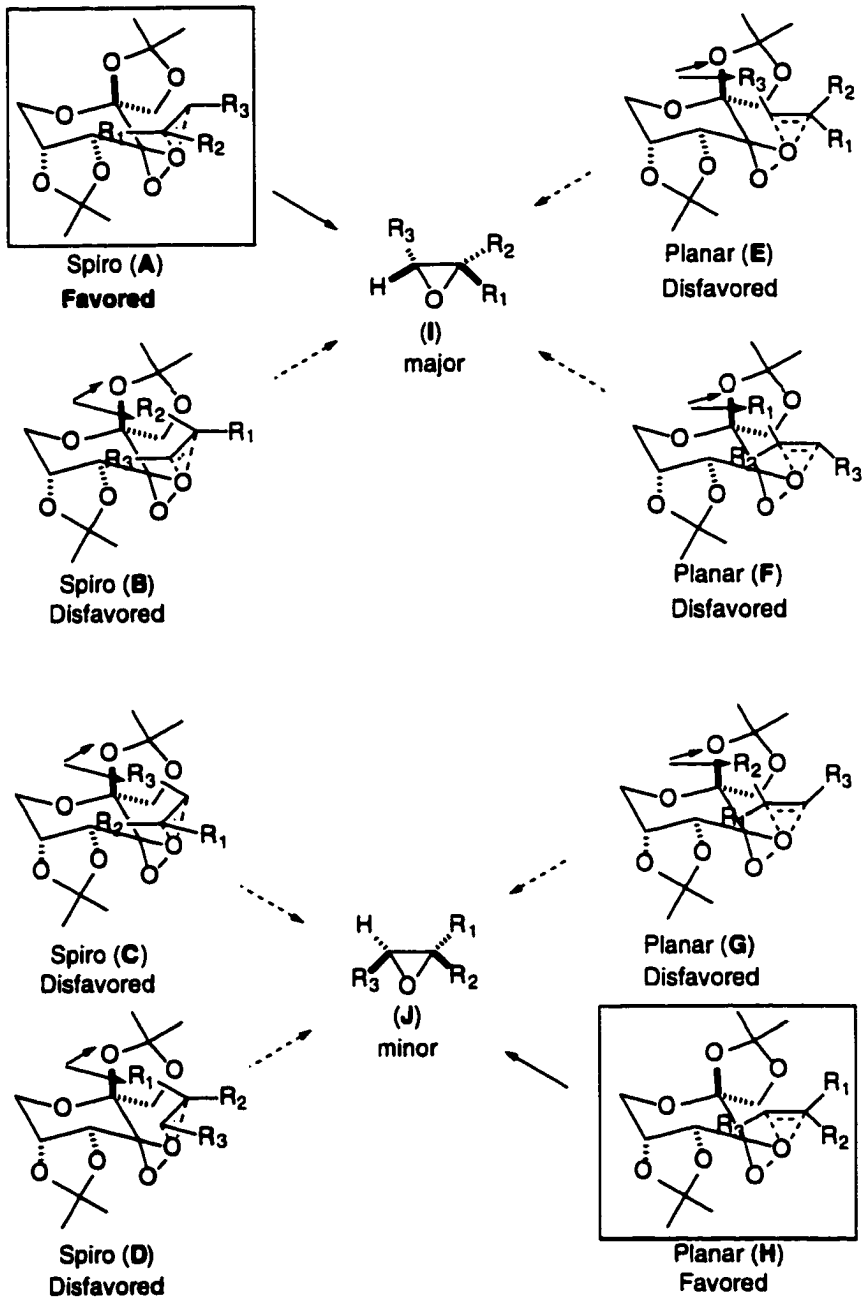
[39] The phenyl group acts as a smaller group than the methyl, probably due to its planar nature.

[40] Based on the above analysis, it is conceivable that planar transition state **H** could become the major reaction mode if a large R_1 group is chosen to strongly discourage spiro **A** and a small R_3 group is chosen to strongly encourage planar **H**. One such an example has been observed. The epoxidation of (Z)-3,3-dimethyl-1-phenyl-2-trimethylsiloxy-1-butene with **1-28** led to the formation of (S)-3,3-dimethyl-1-hydroxy-1-phenyl-2-butanone in 43% ee (see ref. 29). The *S* configuration of the product suggested that a planar transition state is favored.



Scheme 1.5

coworkers also showed that a spiro transition state is preferred for the epoxidation catalyzed by ketone **1-9**.[8,9]

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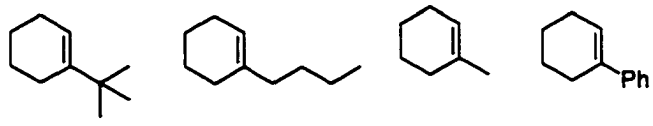
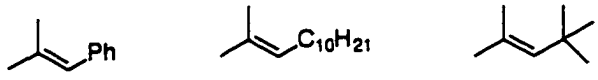
[41] The absolute configuration of 1-*t*-butylcyclohexene oxide presented in Figure 1-6 has not been determined. The possibility of the planar transition state being favored in this case cannot be ruled out at this time.



26% ee 79% ee 81% ee 98% ee

Figure 1.14. The effect of the size of R_1 on enantioselectivities (the smaller R_1, the higher the ee)



76.4% ee 86.5% ee 91% ee

Figure 1.15. The effect of the size of R_3 on enantioselectivities (the larger R_3 , the higher the ee)

This information regarding transition state for the ketone catalyzed epoxidation is extremely valuable for predicting the stereochemistry of the reaction product and for designing new ketone catalysts. The understanding of these transition states also led us to envision that kinetic resolution of certain types of racemic olefins using chiral dioxiranes could be possible.[42] Transition states **A** and **B** in Figure 1.16 represents the spiro transition states for the epoxidation of each enantiomer of a racemic 1,6-disubstituted cyclohexene using ketone **1-28** as catalyst. Transition state **B** is expected to be disfavored compared to transition state **A** due to the steric interaction between R_2 and one of the dioxirane oxygens. Consequently one enantiomer would be epoxidized faster than the other. Analysis of the spiro transition states for 1,3-disubstituted cyclohexenes shows a similar situation (Figure 1.17), with transition state **D** being disfavored. The results in Table 1.21 show that a kinetic resolution of 1,3 and 1,6-disubstituted cyclohexenes via chiral dioxirane are indeed feasible. High resolution efficiency has been obtained for a number of trisubstituted cyclic olefin substrates, which provides a valuable way to prepare certain chiral intermediates.

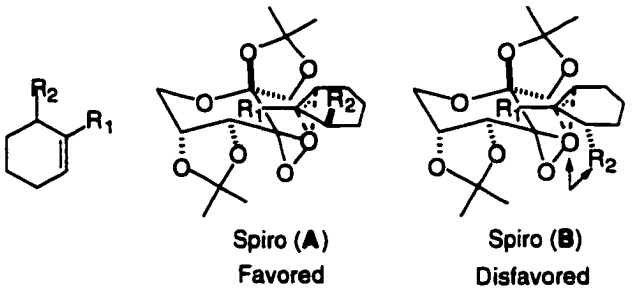


Figure 1.16 Spiro transition states for 1,6-disubsitituted cyclohexenes

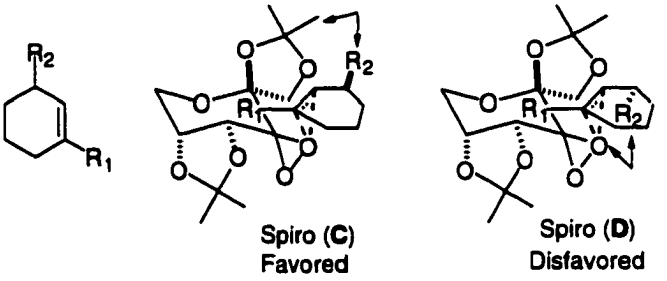
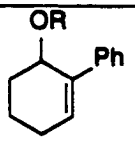
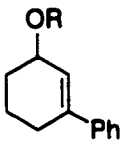
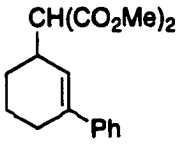
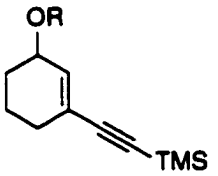
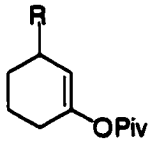


Figure 1.17 Spiro transition states for 1,3-disubsitituted cyclohexenes

Table 1.21. Kinetic Resolution of Representative Olefins by Ketone **1-28** Catalyzed Asymmetric Epoxidation

Entry	Substrate	Temp (°C)	Conv. (%)	Recovered S.M ee (%)	Epoxide ee (%)	Epoxide (trans/cis)	k_{rel} (k_f/k_s)
							
1	R = TMS	-10	49	96 (*S*)	95	>20	>100
2	R = Me	-10	65	99 (*S*)	85	6	15
3	R = COMe	0	54	96 (*S*)	88	12	43
4	R = COOEt	-10	51	94 (*S*)	97	>20	79

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

							
5	R = TBS	-10	70	99 (*R*)	81	4	15
6	R = Me	-10	61	95 (*R*)	nd	6	14
7		0	72	81 (*R*)	nd	1.7	4
							
8	R = TBS	-10	49	75 (*R*)	nd	13	18
9	R = TBS	20	66	96 (*R*)	nd	8	11
							
10	R = OTMS	-10	61	91 (*R*)	76	4	11
11	R = ^{i}Pr	-10	59	93 (*R*)	85	8	15
12	R = ^{t}Bu	-10	54	99 (*R*)	84	>20	60

For details see ref. 42.

1.F. CARBOCYCLIC ANALOGUES

Ketone **1-28** uses a fused ring and a quaternary carbon α to the carbonyl group to place the stereogenic centers close to the reacting center and to minimize potential epimerization of chiral elements (Figure 1.18). A ketone containing two fused rings at each

side of the carbonyl group would also be very interesting (Scheme 1.6). A member of this class of ketones, pseudo C_2 symmetric ketone **1-40**, was prepared from quinic acid (Figure 1.18).[43,44]

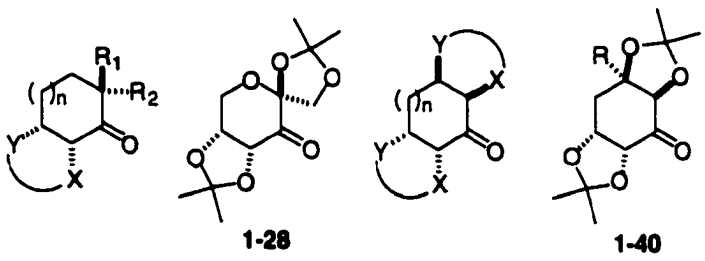
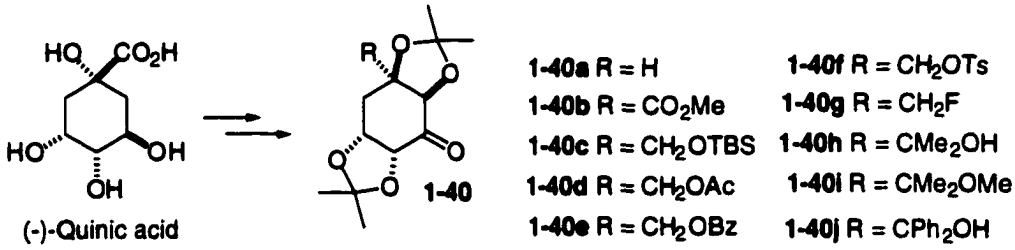


Figure 1.18 A new type of carbohydrate-based ketone



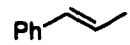
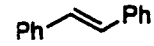
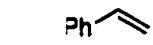
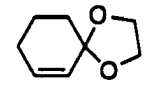
Scheme 1.6

Tables 1.22 and 1.23 summarize the selected epoxidation examples with ketone **1-40**. A few noticeable features are worth mentioning: (1) These ketones are very active catalysts, and low catalyst loadings (5-10 mol%) are required to achieve good conversion; (2) Certain electron deficient olefins can be epoxidized (Table 1.23, Entries 5-8), indicating that the formed dioxirane is very electrophilic. The high enantioselectivity obtained with enones (Table 1.23, Entries 6-8) suggests that the catalyst can effectively compete with the ketone present in the substrate and the epoxide product; (3) The enantiomeric excess for the epoxidation of the *cis*- and terminal olefins is encouragingly high, showing promise for the asymmetric epoxidation of these olefins; (4) The reactivity, selectivity, and Baeyer-Villiger

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

oxidative decomposition of the ketone catalyst can be greatly affected by the ketone conformations imposed by the substituents on the ring. It is interesting to note that C_2 symmetric ketone **1-40a**, which has no additional substituent at the β-position is one of the least effective ketones. All these observations provide intriguing insight into designing new ketone catalysts.

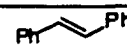
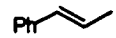
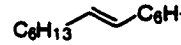
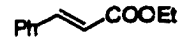
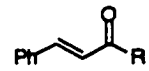
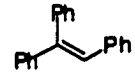
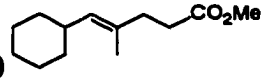
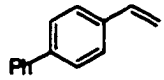
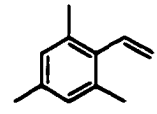
Table 1.22. Asymmetric Epoxidation of Four Representative Olefins by Ketone **1-40** (5-10 mol%)

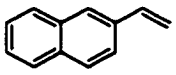
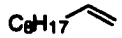
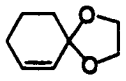
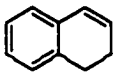
Ketone								
	Conv. (%)	ee (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)
1-40a R = H	29	73	11	93	13	67	9	66
1-40b R = CO_2Me	61	75	66	95	90	67	56	66
1-40c R = CH_2OTBS	77	73	77	90	100	66	70	73
1-40d R = CH_2OAc	95	75	95	90	96	65	82	68
1-40e R = CH_2OBz	76	72	91	90	99	65	67	71
1-40f R = CH_2OTs	60	72	74	90	70	67	62	71
1-40g R = CH_2F	78	73	71	89	76	67	66	71
1-40h R = CMe_2OH	97	80	91	96	79	69	55	45
1-40i R = CMe_2OMe	95	80	94	96	100	70	47	40
1-40j R = CPh_2OH	7	50	--	--	7	59	7	88

For details see refs. 43 and 44.

[44] Wang, Z-X.; Miller, S.M.; Anderson, O.P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.

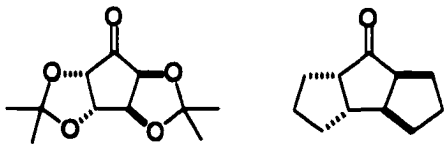
Table 1.23. Asymmetric Epoxidation of Representative Olefins by Ketone **1-40d** and **1-40h**

Entry	Substrate	Cat (mol%)	T (°C)	t (h)	Yield (%)	ee (%)	Configuration
1		**1-40h** (10)	-10	6	91	96	(+)-(*R*,*R*)
2		**1-40h** (5)	-15	4	94	80	(+)-(*R*,*R*)
3		**1-40h** (10)	0	6	95	82	(+)-(2*S*,3*R*)
		1-40h (10)	-10	6	95	84	(+)-(2*S*,3*R*)
4		**1-40d** (10)	-10	4	51	42	(+)-(*R*,*R*)
5		**1-40h** (10)	0	8	35	89	(+)-(2*S*,3*R*)
							
6	R = Ph	**1-40h** (10)	0	6	85	96	(+)-(2*S*,3*R*)
7	R = Me	**1-40h** (10)	0	8	75	82	(+)-(2*S*,3*R*)
8	R = ^{i}Pr	**1-40h** (10)	0	8	70	89	(+)-(2*S*,3*R*)
9		**1-40h** (10)	0	6	95	92	(+)-(*R*,*R*)
10		**1-40d** (5)	-10	4	96	43	(+)-(*R*,*R*)
							
11	R = Ph	**1-40h** (5)	-10	4	94	85	(+)-(*R*,*R*)
12	R = Me	**1-40h** (5)	-15	4	100	12	(-)-(1*R*,2*S*)
13	R = Bu	**1-40h** (5)	-15	4	96	13	(-)-(1*R*,2*S*)
14		**1-40h** (5)	-15	4	79	69	(-)-(*R*)
15		**1-40d** (5)	-10	4	54	65	
16		**1-40d** (5)	-10	4	83	66	

17		**1-40d** (5)	-10	4	89	54	(-)-(*R*)
18		**1-40d** (5)	-10	4	85	15	(+)-(*R*)
19		**1-40d** (5)	-10	3	92	52	(+)-(*R*)
20		**1-40d** (10)	-10	6	78	68	(+)-(*R*,*R*)
21		**1-40d** (5)	-10	4	93	21	(+)-(1*R*,2*S*)

For details see refs. 43 and 44.

Armstrong and coworkers recently reported two C_2-symmetric cyclopentanones **1-41** and **1-42** (Figure 1.19). Ketone **1-41** underwent the Baeyer-Villiger oxidative decomposition rapidly and showed little activity for epoxidation.[45,16,46] Unactivated C_2-symmetric carbocycle ketone **1-42** proved to be completely unreactive in the epoxidation of *trans*-stilbene, and was recovered from the reaction mixture.[45] The steric hindrance around the carbonyl might also be an an important contributing factor for its inactivity.



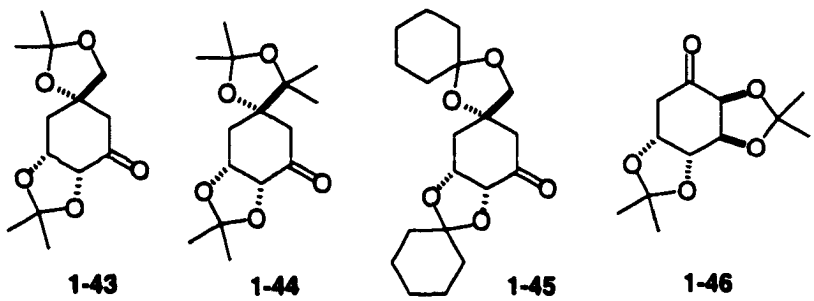
1-41 **1-42**

Figure 1.19 C_2 Symmetric cyclopentanones

Ketones **1-28** and **1-40** have ketals at both α positions. These ketals act both as activating groups and chiral control elements. To further explore the structural requirements for ketone catalysts, ketones **1-43**, **1-44**, **1-45**, and **1-46** having a ketal at the β-

[45] Armstrong, A.; Hayter, B.R. *Tetrahedron: Asymmetry* **1997**, *8*, 1677.

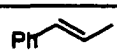
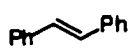
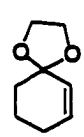
position have been studied (Figure 1.20) (Table 1.24).[47] Recently, Adam and coworkers also reported their studies on ketones **1-43** and **1-45** (Figure 1.20, Table 1.25).[48] As can be seen, moving the ketal from the α to β positions generally lowered the catalyst reactivity and selectivity, decreasing both the conversion and ee of the epoxidation reaction.



1-43 **1-44** **1-45** **1-46**

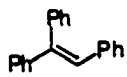
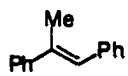
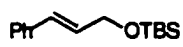
Figure 1.20 Ketones with the ketal at the β-position

Table 1.24. Asymmetric Epoxidation of Olefins with Ketones **1-43**, **1-44**, and **1-46**[47]

Entry	Substrate	Ketone (eq.)	Conv. (%)	ee (%)	Configuration
1		**1-43** (0.5)	58	46	(*R,R*)
2		**1-44** (0.5)	56	38	(*R,R*)
3		**1-46** (0.3)	60	35	(*S,S*)
4		**1-43** (0.5)	33 (yield)	66	(*R,R*)
5		**1-44** (0.5)	16 (yield)	72	(*R,R*)
6		**1-46** (0.3)	30 (yield)	50	(*R,R*)
7		**1-43** (0.5)	36	26	(*R*)
8		**1-46** (0.3)	40	24	(*S*)
9		**1-43** (0.5)	28	36	(*R,R*)
10		**1-44** (0.5)	16	12	(*R,R*)

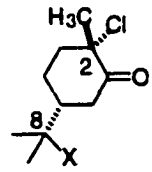
[46] We also observed that ketone **1-41** had a extremely low reactivity. Zhou, X.; Tu, Y.; Shi, Y. Unpublished results.
[47] Wang, Z-X.; Shi, Y. Unpublished results.

Table 1.25. Asymmetric Epoxidation of Olefins with Ketones **1-43** and **1-45**[48]

Entry	Substrate	Ketone (eq.)	Conv. (%)	ee (%)	Configuration
1		**1-43** (1.0)	20	78	(*R*,*R*)
2		**1-43** (3.0)	35	85	(*R*,*R*)
3		**1-45** (1.0)	12	32	(*R*,*R*)
4		**1-43** (3.0)	36	85	(*R*)
5		**1-45** (1.0)	32	25	(*R*)
6		**1-43** (3.0)	47	70	(*R*,*R*)
7		**1-43** (1.0)	26	18	(*R*,*R*)
8		**1-43** (1.0)	23	57	(*R*,*R*)
9		**1-43** (3.0)	29	87	(*R*,*R*)

In 1998, Yang and coworkers reported a ketone which contains a quaternary carbon at the α-position of one side, and a subsitituent at the β-position of the other side of the carbonyl group (**1-47**) (Figure 1.21).[49] Epoxidations of a series of *meta*- and *para*-substituted *trans*-stilbenes with **1-47** were studied (Table 1.26). Interestingly, it was found that the epoxide ee was dependent on the substituent on the phenyl group of the olefin (Table 1.26, Entries 1-13). This observed ee difference was postulated to be due to the n-π electronic repulsion effect between the Cl atom of **1-47b** and the phenyl group, rather than the steric interaction. As shown in entries 14-18, the substituent at C_8 could also significantly influence the ee through electrostatic interaction between of the polar C-X bond and the phenyl group of the stilbene.

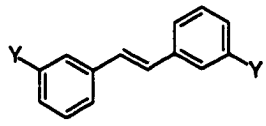
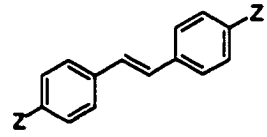
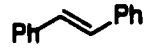
[48] Adam, W.; Saha-Moller, C.R.; Zhao, C-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749.
[49] Yang, D.; Yip, Y-C.; Chen, J.; Cheung, K-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.



1-47a X = F
1-47b X = Cl
1-47c X = OH
1-47d X = OEt
1-47e X = H

Figure 1.21 Yang's cyclohexanone-based ketone

Table 1.26. Asymmetric Epoxidation of *trans*-Stilbenes with Ketones **1-47** (pH 7-7.5)

Entry	Substrate	Ketone (eq.)	ee (%)	Configuration
				
1	Y = Me	**1-47b** (3.0)	88.9	(*S,S*)
2	Y = H	**1-47b** (3.0)	85.9	(*S,S*)
3	Y = OMe	**1-47b** (3.0)	84.6	(*S,S*)
4	Y = F	**1-47b** (3.0)	77.7	(*S,S*)
5	Y = Cl	**1-47b** (3.0)	74.3	(*S,S*)
6	Y = OAc	**1-47b** (3.0)	73.8	(*S,S*)
				
7	Z = *t*-Bu	**1-47b** (3.0)	87.3	
8	Z = Me	**1-47b** (3.0)	87.2	(*S,S*)
9	Z = H	**1-47b** (3.0)	85.9	(*S,S*)
10	Z = F	**1-47b** (3.0)	78.5	(*S,S*)
11	Z = Br	**1-47b** (3.0)	74.8	(*S,S*)
12	Z = OAc	**1-47b** (3.0)	71.5	(*S,S*)
				
13		**1-47a** (1.0)	87.4	(*S,S*)
14		**1-47b** (1.0)	85.4	(*S,S*)
15		**1-47c** (1.0)	80.9	(*S,S*)
16		**1-47d** (1.0)	73.8	(*S,S*)
17		**1-47e** (1.0)	42.0	(*S,S*)

1.G. Exploring Other Oxidants

In almost every case of dioxirane generation potassium peroxomonosulfate ($KHSO_5$) is used as oxidant.[50] Its effectiveness in the formation of dioxiranes is probably due to the fact that the sulfate moiety is a good leaving group, which facilitates the ring closure of intermediate **1-50** to form dioxirane **1-51** (Scheme 1.7). As close analogues of potassium peroxomonosulfate, arenesulfonic peracids generated from (arenesulfonyl)imidazole / H_2O_2 / NaOH also produce dioxiranes from acetone and trifluoroacetone as illustrated by ^{18}O-labeling experiments.[51] It is of particular interest to know whether oxidants with poorer leaving groups than sulfate are capable of generating dioxiranes. Among many oxidants, hydrogen peroxide (H_2O_2) is highly desirable since it has a high active oxygen content and its reduction product is water.[52] A recent study with the fructose-derived ketone **1-28** showed that indeed H_2O_2 could be used as primary oxidant in combination with a nitrile (eq. **1.2**).[53] Peroxyimidic acid **1-52** is likely to be the active oxidant (eq. **1.3**). High yields and ee's were obtained for a number of olefins (Table 1.27).[53] Epoxidation using hydrogen peroxide as the primary oxidant proceeds under mild conditions and requires less solvent and salts to be used in the reaction.

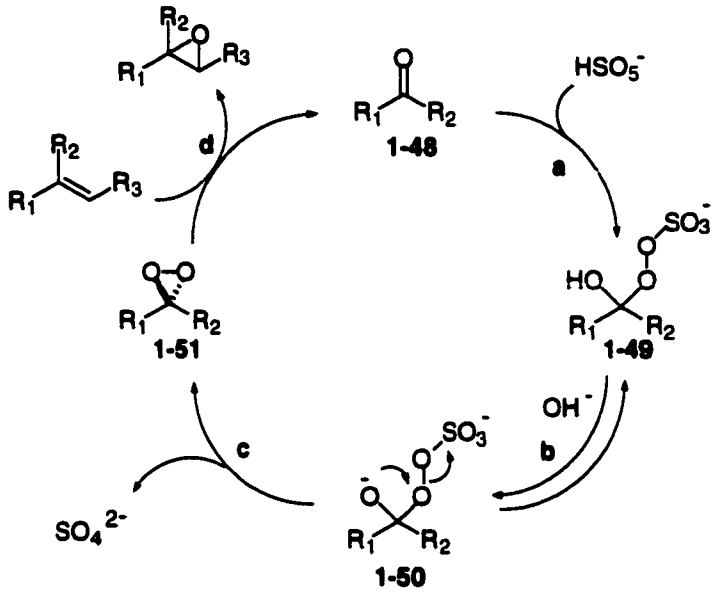
---

[50] Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is currently the common source of potassium peroxomonosulfate ($KHSO_5$).

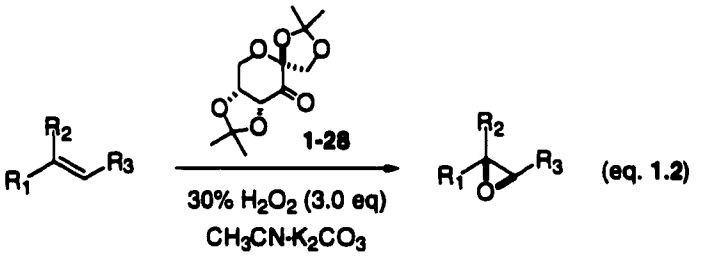
[51] Schulz, M.; Liebsch, S.; Kluge, R.; Adam, W. *J. Org. Chem.* **1997**, *62*, 188.

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

[53] Shu, L.; Shi. Y. *Tetrahedron Lett.* **1999**, *40*, 8721.



Scheme 1.7



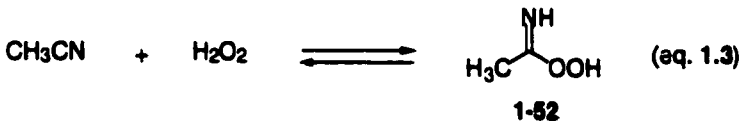
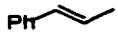
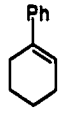
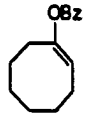


Table 1.27. Asymmetric Epoxidation of Olefins Catalyzed by Ketone **1-28** (0.3 eq) Using H_2O_2

Entry	Substrate	t (h)	Yield (%)	ee (%)	Configuration
1		7	84	92	(*R,R*)
2		15	74	93	(*R,R*)
3		18	55	89	(*R,R*)
4		7	90	95	(*R,R*)
5		7	75	93	(*R,R*)

For details see ref. 53.

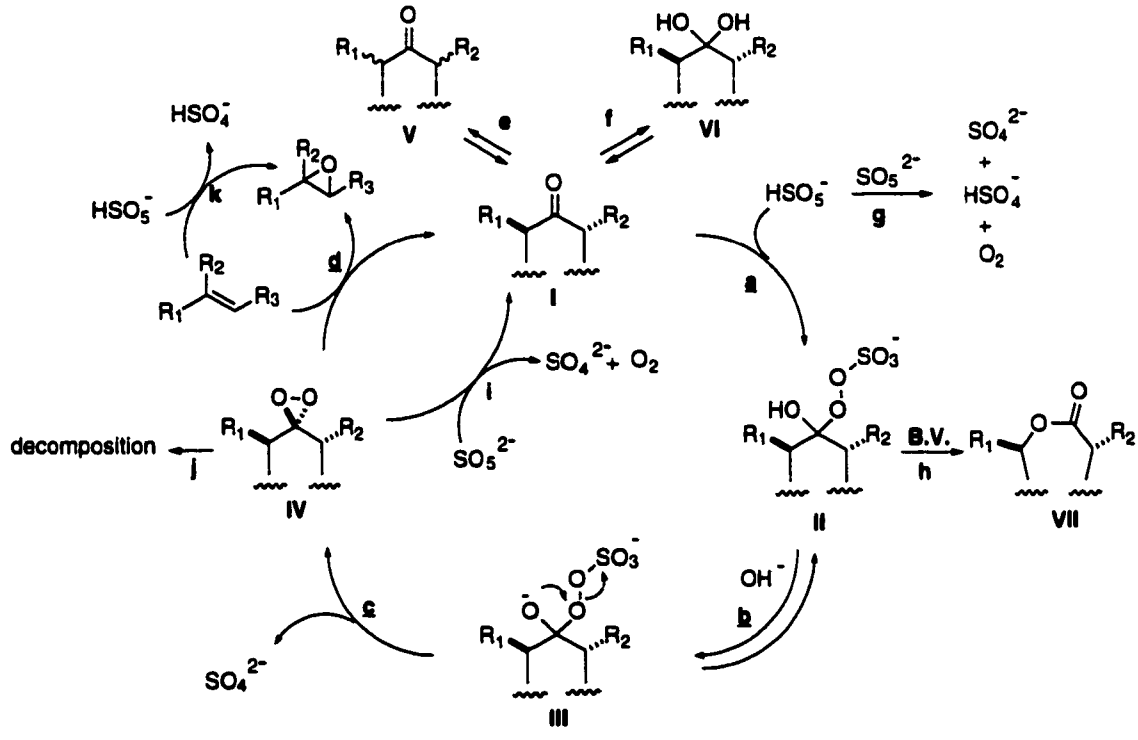
1.H. Conclusions

Chiral ketone-catalyzed asymmetric epoxidation has received intensive interest since the first chiral ketone mediated epoxidation reported by Curci in 1984.[4] However, discovering efficient chiral ketone catalysts has proven to be a challenging process. Balancing the effects of sterics and electronics on the catalyst is not at all trivial.

Scheme 1.22 lists a number of possible pathways involved in the catalytic cycle of the ketone mediated epoxidation. Achieving the desired outcome from this deceivingly simple-looking reaction requires a delicate balance among all the possible pathways (**a-j**).[54,33] Generally speaking, when the stereogenic centers are closer to the reacting center (carbonyl group), efficient stereochemical communication between substrate and catalyst

[54] For leading references on the discussion of these pathways see: refs. 1, 2a-c, & 2h.

could be more readily achieved, leading to higher enantioselectivity of the epoxidation.[55] However, the potential racemization of the chiral centers associated with this type of ketone due to the acidity of the protons at the α positions (path **e** in Scheme 25) puts restrictions on the choice of these groups.



Pathways **a-j**: (**a**) Nucleophilic attack of the ketone by Oxone; (**b**) Deprotonation of the peroxy intermediate; (**c**) Formation of the dioxirane; (**d**) Epoxidation of an olefin by the dioxirane; (**e**) Epimerization of chiral centers of the ketone; (**f**) Hydration of the ketone; (**g**) Oxone self-decomposition; (**h**) Baeyer-Villiger reaction of the peroxy intermediate; (**i**) Consumption of the dioxirane by Oxone; (**j**) Self-decomposition of the dioxirane. (**k**) Epoxidation of the olefin by Oxone itself.

Scheme 1.8

[55] High enantioselectivity has been obtained for the epoxidation of 4,4'-substituted stilbenes using ketones in which the chiral element is actually away from the carbonyl group (see: refs 7-9). In these cases, the substituted phenyl groups can reach the distant chiral control units causing efficient sterochemical interaction.

Aside from the epimerization problem, the epoxidation reaction is also greatly affected by the steric and electronic properties of the substituents. If R_1 and R_2 are too small, the stereochemical communication between the olefin and the chiral elements of the dioxirane may not be efficient enough to give high enantioselectivity. On the other hand, the large R_1 and R_2 groups could retard the formation of tetrahedral intermediate **II** and/or dioxirane **IV**. Consequently, Oxone would decompose nonproductively via pathway **g**. The steric hindrance of R_1 and R_2 could also slow down the reaction between dioxirane **IV** and the olefin, which would result in undesired consumption of the dioxirane via pathway **i** and/or **j** (many dioxiranes are short-lived).

Electronically, R_1 and R_2 are also important. If R_1 and R_2 are electron-donating or weakly electron-withdrawing, tetrahedral intermediate **II** will not be efficiently formed due to the poor electrophilicity of the carbonyl group. At the same time, these groups will favor the detrimental Baeyer-Villiger reaction (pathway **h**). However, if R_1 and R_2 are too electron deficient, ketone **I** will be too electrophilic and will largely exist in a hydrate form **VI**, which could potentially shut down the whole catalytic cycle. The electron deficiency of these groups will also enhance the acidity of the protons at the α position thus facilitating the racemization. If ketone **I** is cyclic, the ring strain will also affect the reaction efficiency. These and the aforementioned factors put high structural stringency on chiral ketone catalysts in order for them to be effective in terms of both reactivity and selectivity.

During the past few years, a variety of chiral ketones have been investigated in a number of laboratories, and significant progress has been made in the field. Chiral dioxiranes have shown to be very effective oxidants for the asymmetric epoxidation of olefins, particularly for unfunctionalized *trans*- and trisubstituted olefins. Further studies of ketone structure and catalytic properties will certainly facilitate the development of more efficient ketone catalysts.

CHAPTER TWO

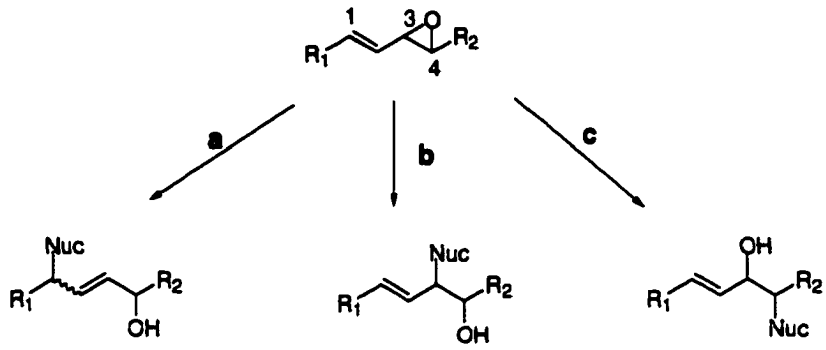
ASYMMETRIC SYNTHESIS OF VINYL EPOXIDES AND BISEPOXIDES FROM CONJUGATED POLYENES

2.A. INTRODUCTION AND BACKGROUND

2.A.1. Reactivity of Vinyl Epoxides

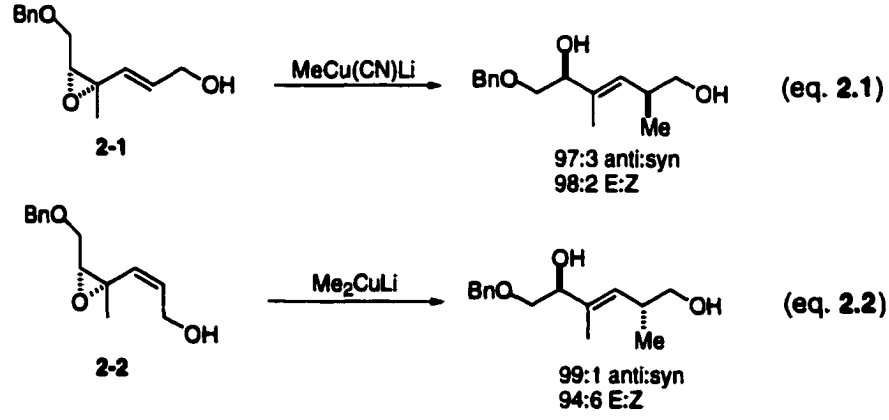
Vinyl epoxides are versatile synthetic intermediates. Of the four carbons that comprise the fragment, nucleophilic attack at three of them can be envisioned (Scheme 2.1). Reaction with soft nucleophiles in an S_N2' fashion (1,4-addition) at C(1) to form allylic alcohols is possible, and has been extensively developed (pathway **a**).[1] Alternatively, regioselective S_N2 displacement at C(3) to form homoallylic alcohols is also possible (pathway **b**). This pathway is usually favored over reaction at C(4) due to activation by the olefin. Methods that achieve high selectivity for attack at this site typically take advantage of its inherent acidity to further activate this center. Ring-opening at C(4) is also possible (pathway **c**), however selective reactions at this site are rarely observed.

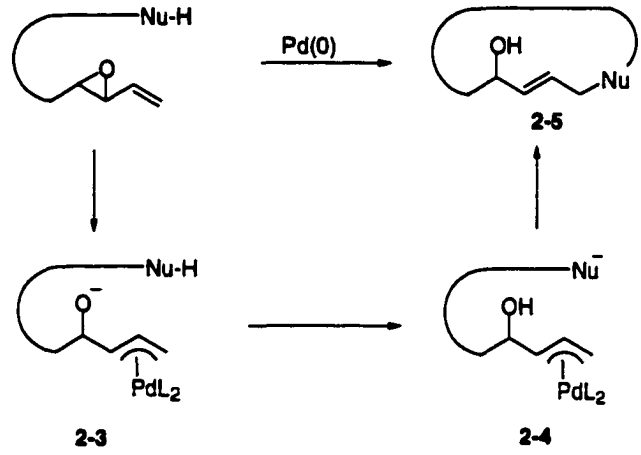
[1] For a review, see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.



Scheme 2.1

1,4-addition of organocuprates to vinyl epoxides has been studied extensively.[1] The reactions proceed with a wide variety of unfunctionalized organocuprates with high selectivity for attack *anti* to the epoxide. For example, both (*E*)-vinyl epoxide **2-1** (eq. **2.1**) and (*Z*)-vinyl epoxide **2-2** (eq. **2.2**) can be converted to their corresponding allylic alcohol with complete selectivity for 1,4-addition. Thus, this strategy can provide access to both *syn* and *anti* alkylation products, depending on the stereochemistry of the olefin.





Scheme 2.2

Alternatively, vinyl epoxides are activated toward nucleophilic attack by low-valent transition metals, particularly Pd(0) (Scheme 2.2).[2] The electrophilic palladium π-allyl complex **2-3** is formed upon attack of the palladium species on the vinyl epoxide. This intermediate can be trapped by a variety of soft nucleophiles, either inter- or intramolecularly, to form allylic alcohol products. Addition typically occurs with overall 1,4-regiochemistry, particularly when the olefin is terminal. Nucleophilic partners include activated methylenes, heteroatoms such as carboxylic acids and amines (primary or secondary), and aryl or allyl stannanes.[3] If a pronucleophile is located elsewhere in the molecule, an especially mild cyclization results since the liberated alkoxide in **2-3** activates it towards attack (**2-3** to **2-4**). This strategy has been successfully applied to form macrocycles of various size in high yield. A particularly elegant example has been demonstrated by Furstner and coworkers in their synthesis of Roseophilin (Scheme 2.3).[4]

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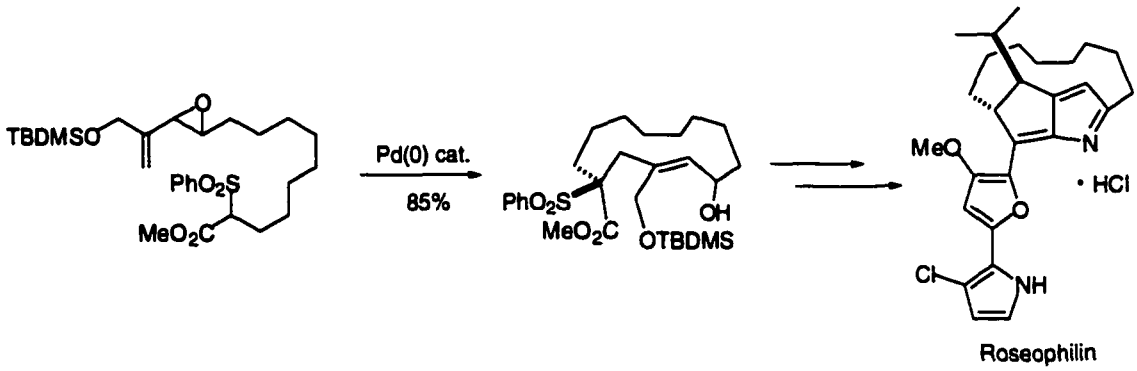
[2] For a review, see : Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173.

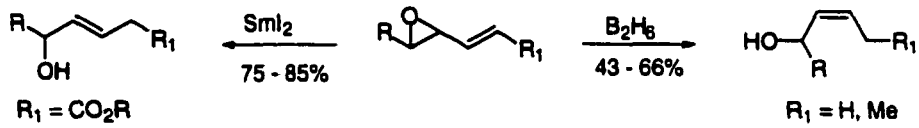
[3] Eschavarren, A.M.; Tueting, D.R.; Stille, J.K. *J. Am. Chem. Soc.* **1988**, *110*, 4039.

[4] Furstner, A.; Weintritt, H. *J. Am. Chem. Soc* **1998**, *120*, 2817.



Scheme 2.3

1,4-Reduction protocols have also been developed, and both versions are stereoselective with respect to the olefin produced (Scheme 2.4). When the vinyl epoxide is conjugated to an ester, single-electron reduction with samarium (II) iodide is facile, and gives the (*E*) olefin predominantly.[5] Alternatively, reduction with diborane gives the (*Z*) olefin, presumably through a closed transition state involving a boron-oxygen chelate.[6]

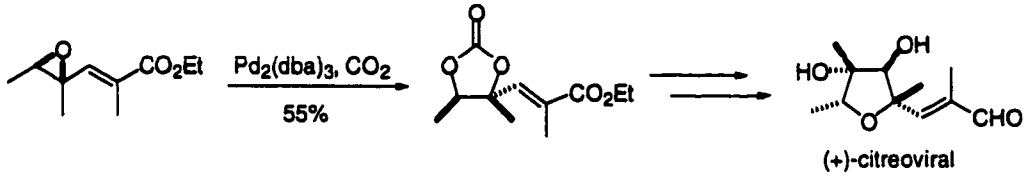


Scheme 2.4

The chemistry discussed thus far results in overall 1,4-addition to the vinyl epoxide (pathway **a**, Scheme 2.1). However, methods that produce overall reaction at C(3) (pathway **b**, Scheme 2.1) have also been developed. For example, the aforementioned π-allylpalladium intermediates can be shuttled through entirely different reaction manifolds when an electrophile is present to react with the alkoxide

[5] Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.
[6] Zaidlewicz, M.; Uzarewicz, A.; Sarnowski, R. *Synthesis*, **1979**, 62.

intermediate. Trapping of the alkoxide with carbon dioxide followed by cyclization provides a stereospecific route towards *syn* carbonates, which can be considered as *syn* diol equivalents since removal of the carbonate is rather simple.[7] This strategy has been used in the syntheses of (+)-citreoviral[8] (Scheme 2.5) and (-)-exo-brevicomin.[9]



Scheme 2.5

Analogous reaction with aryl isocyanates results in 1,2-aminoalcohol equivalents, and has been used in a route towards (-)-N-acetyl-O-methylacosamine.[10] A particularly nice variant of this strategy includes electrophilic trapping with carbodiimides in the presence of chiral phosphine ligands, which leads to optically-active amino alcohol products directly from the racemic vinyl oxirane (eq. **2.3**). Addition of the palladium species and trapping of the intermediate alkoxide with the carbodiimide produces a pendent nitrogen nucleophile, which selectively traps one of the two equilibrating π-allylpalladium species, providing up to 98% yield and 94% ee.[11]

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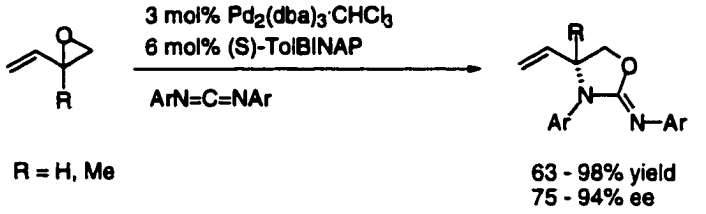
[7] (a) Trost, B.M., Angle, S.R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. (b) Fujinami, T.; Suzuki, T.; Kamiya, M.; Fukuzawa, S.; Sakai, S. *Chem. Lett.* **1985**, 199.

[8] Trost, B.M.; Lynch, S.R. *Tetrahedron Lett.* **1987**, *28*, 375.

[9] Wershofen, S.; Scharf, H.-D. *Synthesis*, **1988**, 854.

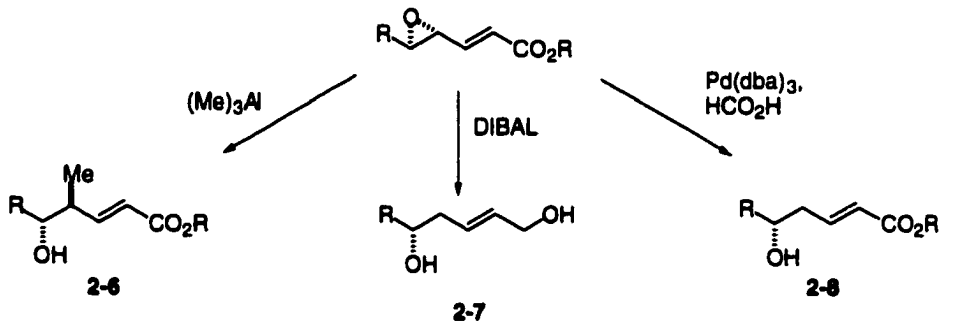
[10] Trost, B.M.; Sudhakar, A.R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

[11] Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709.



(eq. **2.3**)

Nucleophilic systems that include Lewis or mild protic acids typically react at C(3) due to activation by the olefin, with organoaluminum compounds enjoying the most success in this area. For example, trimethylaluminum ring-opens the epoxide at C(3) in an *anti* fashion, which provides direct access to the *anti* aldol product **2-6** (Scheme 2.6) from the vinyl epoxide.[12] Reduction with diisobutylaluminum hydride (DIBAL) selectively opens the epoxide at C(3) with concominant reduction of the ester to give diol **2-7**.[13]



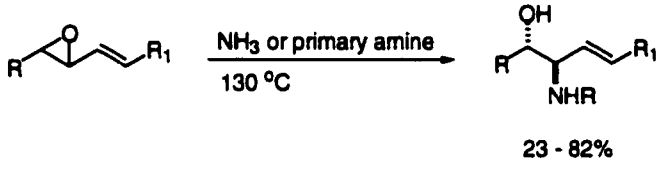
Scheme 2.6

[12] Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1998**, 109.

[13] (a) Nicolaou, K.C.; Uenishi, J. *J. Chem Soc. Chem. Comm.* **1982**, 1292. (b) Nicolaou, K.C.; Daines, R.A.; Uenishi, J.; Li, W.S.; Papahatjis, D.P.; Chakraborty, T.K. *J. Am. Chem. Soc.* **1987**, *109*, 2205. (c) Nicolaou, K.C.; Daines, R.A.; Uenishi, J.; Li, W.S.; Papahatjis, D.P.; Chakraborty, T.K. *J. Am. Chem. Soc.* **1988**, *110*, 4672.

A less invasive reduction using palladium(0) proceeds chemoselectively at the epoxide, leaving the ester intact to give **2-8**.[14] In addition to these, a variety of allyl stannanes also react exclusively at C(3) under Lewis acid catalysis.[15]

A notable exception to these acidic reagents is the direct aminolysis with ammonia or a primary amine to give S_N2 displacement at C(3).[16] The reaction requires elevated temperatures, but usually produces the amino alcohol in good yield (eq. **2.4**).



(eq. **2.4**)

As can be seen, vinyl epoxides are versatile synthetic intermediates that undergo selective reaction with a variety of nucleophiles to give allylic or homoallylic alcohols in good to high yield. These alcoholic products are themselves versatile building blocks, and the combination has been shown to be a valuable strategy for the synthesis of a variety of naturally occurring compounds. Therefore investigation into their synthesis in optically active form is of interest.

2.A.2. Synthesis of Vinyl Epoxides

The importance of vinyl epoxides has drawn attention from researchers for some time, and methods for their asymmetric synthesis have already been developed. Traditionally, they have been prepared in a stepwise fashion utilizing the Sharpless

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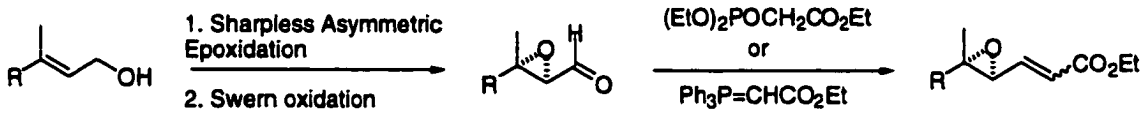
[14] Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.
[15] Naruta, Y.; Maruyama, K. *Chem. Lett.* **1987**, 963.
[16] Lindstrom, U.M.; Franckowiak, R.; Pinault, N.; Somfai, P. *Tetrahedron Lett.* **1997**, *38*, 2027.

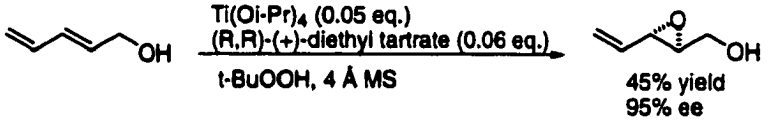
Asymmetric Epoxidation of allylic alcohols to install the requisite stereochemistry (Scheme 2.7).[17] Subsequent olefination completes the synthesis of the fragment.



Scheme 2.7

Advantages include the reliability of the epoxidation step and the ability to construct either stereoisomer of the olefin.

The direct regio-and stereoselective epoxidation of dienyl alcohols via Sharpless Asymmetric Epoxidation provides a direct route to hydroxy-substituted vinyl epoxides (eq. **2.5**).[18] Since the reaction proceeds through chelation of the alcohol to the titanium center, it is completely regioselective for the olefin proximal to the alcohol. The asymmetric induction is excellent; however, the Lewis acidity of the metal causes partial decomposition of formed epoxide, thus limiting its use on preparative scale.

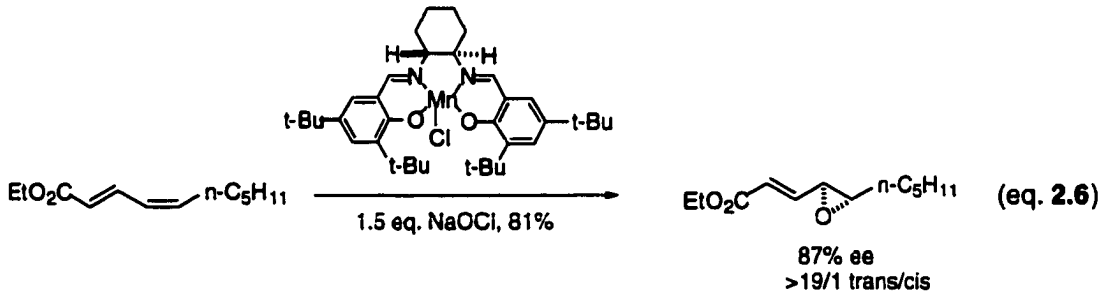


(eq. **2.5**)

The Mn(III)(salen)-catalyzed regio- and stereoselective epoxidation of *cis,trans* conjugated dienes provides an alternative direct approach (eq. **2.6**).[19] Through a combination of favorable steric and electronic properties, high regioselectivity for the olefin distal to the ester can be obtained when it is *cis*. Presumably, the reaction proceeds

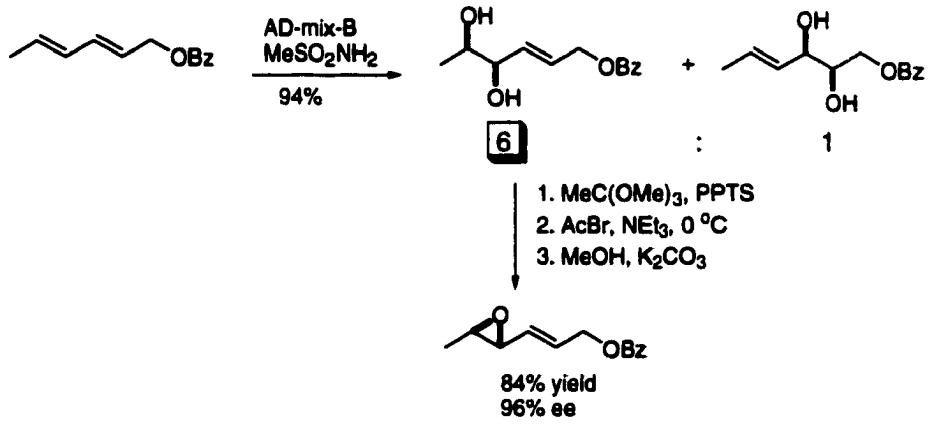
[17] For an example, see: Marshall, J.A.; Trometer, J.D. *Tetrahedron Lett.* **1987**, *28*, 4985.
[18] Katsuki, T.; Martin, V.S. *Org. Rxn.* **1996**, *48*. 1.
[19] Chang, S.; Lee, N.H.; Jacobsen, E.N. *J. Org. Chem.* **1993**, *58*, 6939.

by a stepwise process that involves radicals, and so the more stable *trans* epoxide is observed as the major product.



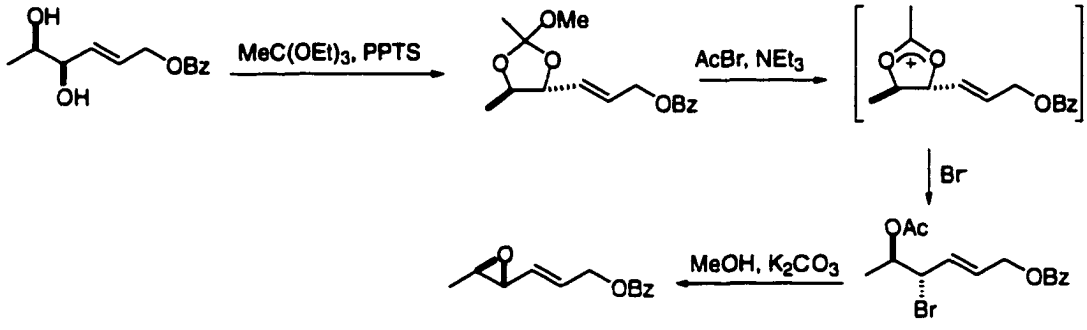
(eq. **2.6**)

A final alternative is a one pot, two step process involving a Sharpless Asymmetric Dihydroxylation of a conjugated diene with subsequent conversion to the epoxide (Schemes 2.8, 2.9).[20] The rationale for the transformation is provided in Scheme 2.8. The ortho ester is formed with triethyl orthoactetate using catalytic amounts of pyridinium-p-toluenesulfonate (PPTS). Addition of acetyl bromide and a proton scavenger forms the vicinal acetoxy bromide, which ring-closes to the epoxide after saponification of the acetoxy group. Although the method looks complex, a couple of examples have been disclosed with very good results.[20a]



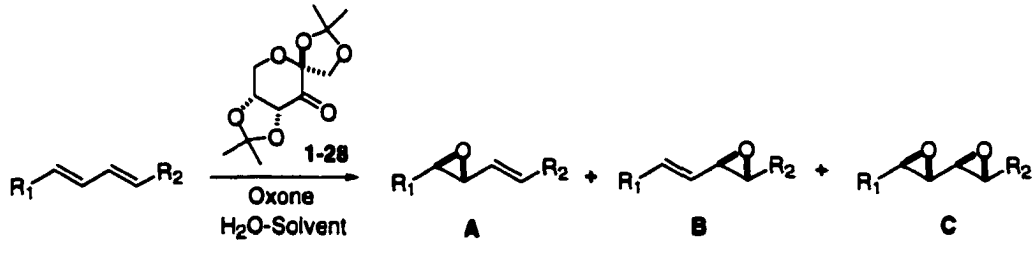
Scheme 2.8

[20] (a) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483. (b) Becker, H.; Soler, M.A.; Sharpless, K.B. *Tetrahedron*, **1995**, *51*, 1345.



Scheme 2.9

With this background in mind we decided to test our epoxidation method for the formation of these useful synthetic intermediates using ketone **1-28** as catalyst, Oxone as oxidant, and conjugated *trans,trans* dienes as substrates (eq. **2.7**). The major issues which needed to be addressed for the diene epoxidation included regioselectivity (**A** *vs* **B**), selectivity between monoepoxidation and bisepoxidation (**A** & **B** *vs* **C**), and enantioselectivity.



(eq. **2.7**)

2.B. RESULTS AND DISCUSSION

Scheme 2.10 shows the synthesis of one symmetrical and various bis-disubstituted dienes from readily available starting materials. Symmetrical diene **2-9** was

prepared by pinacol coupling of cyclohexanone[21] followed by acid-catalyzed dehydration.[22] Protection of *trans, trans*-2,4-hexadien-1-ol as the *tert*-butyldimethylsilyl (TBS) ether [23] and the acetate (OAc) gave **2-11** and **2-12**, respectively. These substrates were prepared hoping they would direct the epoxidation to the distal olefin through a combination of steric interactions and inductive effects. Further deactivation through steric effects was tested using the 3° methyl ether in **2-14**, which was prepared from ethyl sorbate by addition of 2.5 equivalents of MeLi followed by protection as the methyl ether. The directing effect of a conjugated ester was examined with ethyl sorbate (**2-13**) as well as substrates **2-15** - **2-17**, which were prepared by Wittig reaction of *trans*-2-hexenal, *trans*-cinnamaldehyde, and 2-methoxy-*trans*-cinnamaldehyde, respectively.

More highly-substituted unsymmetrical dienes were also prepared (Scheme 2.11) to test the effect of higher olefin substitution on the reaction. Wittig reaction of *trans*-2-pentenal with (Carbethoxymethylene)triphenylphosphorane gave **2-18**. Reduction of the ester with diisobutylamluminum hydride (DIBAL) gave alcohol **2-19**, which was protected as the TBS ether **2-20**. All three of these were utilized in the epoxidation study. Horner- Emmons olefination of (*Z*)-2-propyl-2-nonenal gave **2-21** in good yield; and Wittig reaction of (*E*)-5-methyl-2-phenyl-2-hexenal, (*E*)-4-methyl-2-phenyl-2-pentenal, α-methyl-*trans*-cinnamaldehyde, *trans*-2-hexenal, and (*E*)-2-methyl-2-pentenal all proceeded in good yield and high stereoselectivity to give **2-22** – **2-26**. All of these dienes could be isolated in at least 15/1 *E/Z* selectivity for the newly-formed olefin by column chromatography on silica gel. Diene **2-26** was also reduced (DIBAL) and protected as both the TBS (**2-28**) and the *tert*-butyldiphenylsilyl (TBDPS) (**2-29**) ethers.

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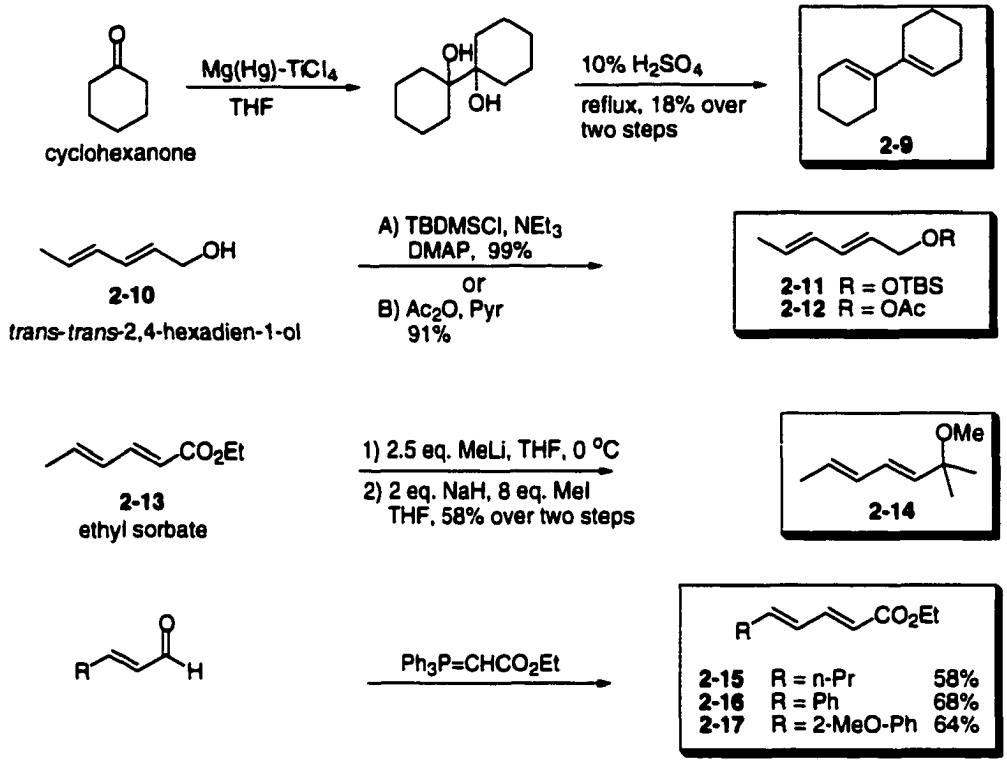
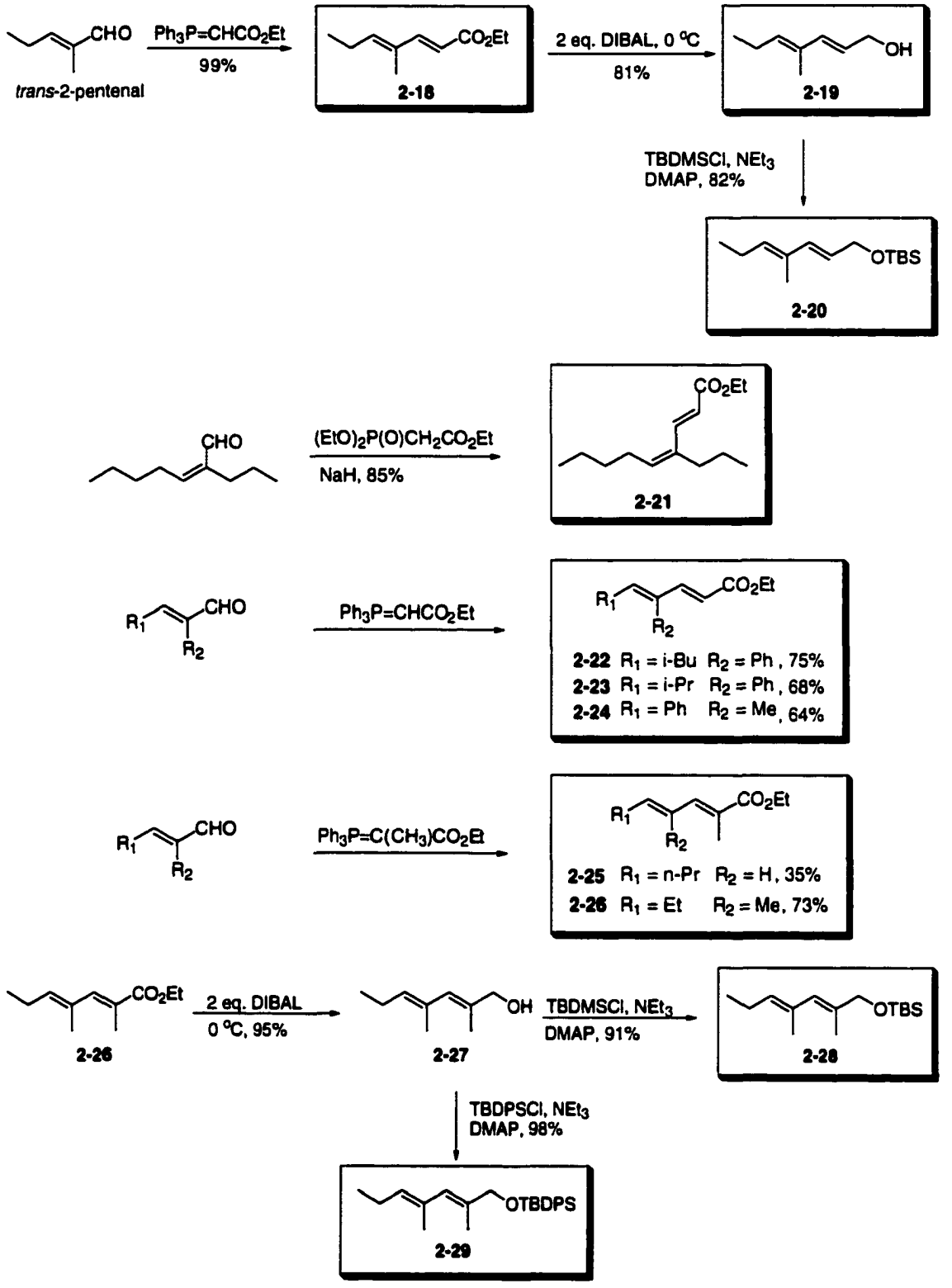
[21] Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S.J. *J. Org. Chem.* **1976**, *41*, 260.
[22] Saltiel, J.; Marchand, G.R.; *J. Am. Chem. Soc.* **1991**, *113*, 2702.
[23] Corey, E.J.; Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.



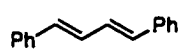
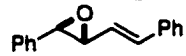
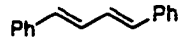
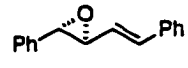
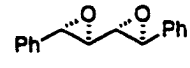
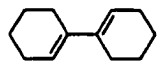
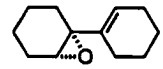
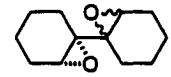
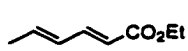
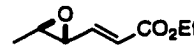
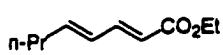
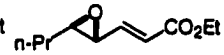
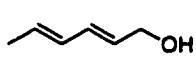
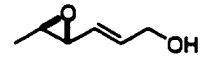
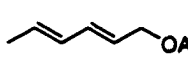
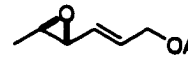
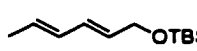
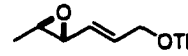
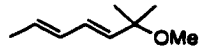
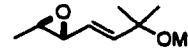
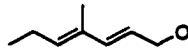
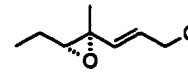
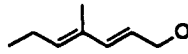
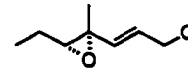
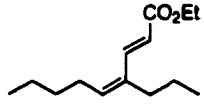
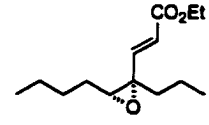
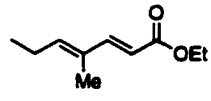
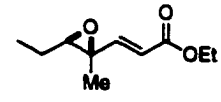
Scheme **2.10**

Tabulated results for the asymmetric monoepoxidation of conjugated dienes with ketone **1-28** and its enantiomeric **ent 1-28** are presented in Table 2.1. The investigation started with a symmetric conjugated diene, *trans,trans*-1,4-diphenyl-1,3-butadiene as the test substrate (Table 2.1, Entry 1). Subjecting this diene to the epoxidation conditions gave the monoepoxide along with the bisepoxide. The formation of the bisepoxide could be minimized by controlling the amount of catalyst to reduce the further epoxidation of the formed monoepoxide. When 25% mole of catalyst **1-28** was used, 94% conversion of the substrate could be achieved at 0 °C with 1.5 h reaction time. The selectivity of monoepoxidation over bisepoxidation remained high (22/1). The high selectivity could be due to inductive deactivation of the remaining olefin by the epoxide.



Scheme 2.11

Table 2.1. Asymmetric Monoepoxidation of Representative Dienes by Ketone **1-28** & **ent-1-28**[a]

Entry	Dienes	Epoxides		Conv[b] (%)	Ratio[c]	Yield[d] (%)	ee[p] (%)
1				94[f]	22:1	77	97[k]
2				87[e]	26:1	65	97[k]
			(ent-1-28)				
3				100[e]	12:1	54	95[k]
4				69[g,h]	7:1	41	96[k]
5				52[g]	3:1	43[j]	96(67)[k]
6				100[f]	1.5:1		87(81)[k]
7				100[f]	4:1	62(16)	93(87)[l]
8				100[f]	4.6:1	68(13)	96(91)[m]
9				100[e]		65	89[k]
10				100[f]		68[i]	90[n]
11				100[f]		81[i]	96[o]
12				76[g]		68	95[k]
13				88[g]		82	95[k]

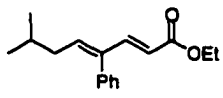
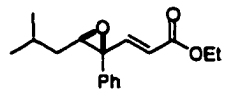
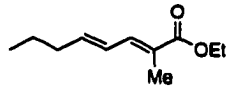
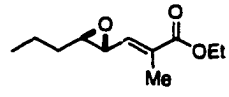
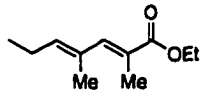
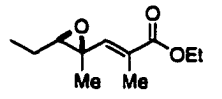
14			66[j]	32	92[k]
15			72[g]	61	94[k]
16			100[f]	89[i]	94[n]

Table 2.1 legend

[a] All reactions were carried out at 0 °C with diene (1 eq.), ketone (0.2-0.3 eq.), Oxone (1.12-1.38 eq.), and K_2CO_3 (5.0-6.2 eq.) in CH_3CN - DMM - 0.05 M $Na_2B_4O_7 \cdot 10\ H_2O$ of aqueous EDTA (4 x 10^{-4} M) solution (1 : 2 : 2, V/V/V). Oxone was added over 1.5 h unless otherwise stated and the reactions were stopped immediately. [b] The conversions were determined by the ^1H NMR of the crude reaction mixtures. [c] The ratios were determined by the ^1H NMR of the crude reaction mixtures. For symmetric dienes the ratio refers to the monoepoxide/bisepoxide ratio (the precise stereochemistry of the bisepoxides has not been determined). For unsymmetrical dienes it refers to the ratio of the two monoepoxides. For entries 9-16, the other monoepoxide regioisomers were barely detectable by ^1H NMR if there was any. [d] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. The number in parentheses refers to the yield of the minor epoxide. It should be noted that the vinyl epoxides are not very stable and portions are lost during the column isolation. [e] 0.20 eq. catalyst used. [f] 0.25 eq. catalyst used. [g] 0.30 eq. catalyst used. [h] Oxone was added over 4 h and the reaction was stopped immediately. [i] Trace amounts of bisepoxide were detected in the crude reaction mixtures by ^1H NMR. [j] The epoxide products could not be completely separated from one another, therefore the yield represents the total isolated yield. [k] Enantioselectivities were determined by chiral HPLC (Chiralcel OD). [l] The acetate was converted to the alcohol with KCN/MeOH and the enantioslectivities were determined by chiral HPLC (Chiralcel OD). [m] The TBS ether was converted to the corresponding alcohol with TBAF and enantioselectivities were determined by chiral GC (Chiraldex γ-TA column). The number in parentheses refers to the ee of the minor epoxide. [n] Enantioselectivities were determined by chiral HPLC (Chiralcel OB). [o] The

TBS ether was converted to the corresponding alcohol with TBAF and enantioselectivities were determined by chiral HPLC (Chiralcel OB). [p] The absolute configurations of the epoxides for entries 1 & 13 were determined by comparing to the authentic samples prepared by different routes The configurations for the remaining epoxides were tentatively assumed by analogy based on the spiro reaction mode.

Not only was the selective monoepoxidation feasible, the enantiomeric excess for the monoepoxide was high (97%). High conversion and selectivity were also obtained for the symmetric cyclic trisubstituted diene (Table 2.1, Entry 3). It is worth noting that the epoxidations of dienes under the current reaction conditions were generally clean as judged by the ^{1}H NMR spectra of the crude reaction mixtures. The somewhat low isolated yields compared to the substrate conversions in most cases were due to the high sensitivity of these vinyl epoxides towards flash column isolation using silica gel.

The good selectivities obtained with the symmetric dienes encouraged the further exploration of unsymmetrical dienes. As shown in Table 2.1, the results were very encouraging. In many cases, monoepoxides were predominately obtained if the amount of catalyst was properly controlled. The enantiomeric excesses for the formed monoepoxides were also high. Some of the reaction features are highlighted as the following. If both olefins were disubstituted, regioselectivity (**A** *vs* **B**) could be regulated by using steric and electronic control. Introducing an electron-withdrawing group deactivated the proximal olefin, resulting in the formation of the distal epoxide as the major product. For example, a 7/1 ratio was obtained for the epoxidation of ethyl sorbate (Table 1, Entry 4). The allylic electron-withdrawing groups such as TBS ether which eliminates conjugation to the olefin could also substantially deactivate the proximal olefin by both inductive and steric effects (Table 1, Entry 8). The regioselectivity could be further enhanced by introducing further steric hindrance next to

one olefin. Such an example is illustrated in entry 9, in which only one monoepoxide was detected.

Introducing an additional alkyl group on one of the olefins further regulated the regioselectivity. For example, entries 12 and 13 show that the epoxidation was highly selective for the trisubstituted olefin distal to the hydroxyl and the TBS groups. The regioselectivity shown in entries 6 and 10 is complementary to the Sharpless asymmetric epoxidation, which selectively epoxidizes the olefin proximal to the hydroxyl group. In the case of the more substituted diene esters (Table 2.1, Entries 12-16), it is rather interesting to note that the epoxidation regioselectively occurred on the distal olefin regardless of whether the alkyl group was introduced to the distal or to the proximal olefins or both. A possible reason for the observed selectivity could be that the introduced alkyl group(s) prevented full conjugation of the diene due to the $A_{1,3}$ strain, thereby reducing its conjugation to the carbonyl.

The epoxidation of isolated *trans*-disubstituted and trisubstituted olefins with catalyst **1-28** proceeds mainly via spiro transition state **A** (Figure 2.1).[24] The main competing transition state is believed to be planar transition state **B** (Figure 2.1).[24h] The nature of the substituents on the olefins has noticeable effects on the competition between the two transition states, consequently affecting the enantioselectivities of the epoxidation.[24h] It is believed that the spiro transition state is generally favored due to the

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[24] For leading references on the transition states of the dioxirane-mediated epoxidation see: (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. (c) Bach, R.D.; Andres, J.L.; Owensby, A.L.; Schlegel, H.B.; McDouall, J.J.W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (d) Yang, D.; Wang, X-C.; Wong, M-K.; Yip, Y-C.; Tang, M-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (e) Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (f) Jenson, C.; Liu, J.; Houk, K.N.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1997**, *119*, 12982. (g) Tu, Y.; Wang, Z-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (h) Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *118*, 11224.

stabilizing interaction of an oxygen lone pair of the dioxirane with the π* orbital of the alkene.[24c] Transition states **C** & **D** are anticipated as the two main competing transition states for the epoxidation of the dienes. As shown in Table 2.1, the enantioselectivities of the epoxidation of the dienes are high for both disubstituted and trisubstituted olefins. This observation shows that the spiro transition state is further favored when a conjugated diene is used as substrate. The increased favorability of the spiro transition state is presumably due to the fact that a conjugated diene has a lower LUMO than an isolated olefin leading to a greater stabilizing interaction between an oxygen lone pair of the dioxirane with the LUMO of the alkene.

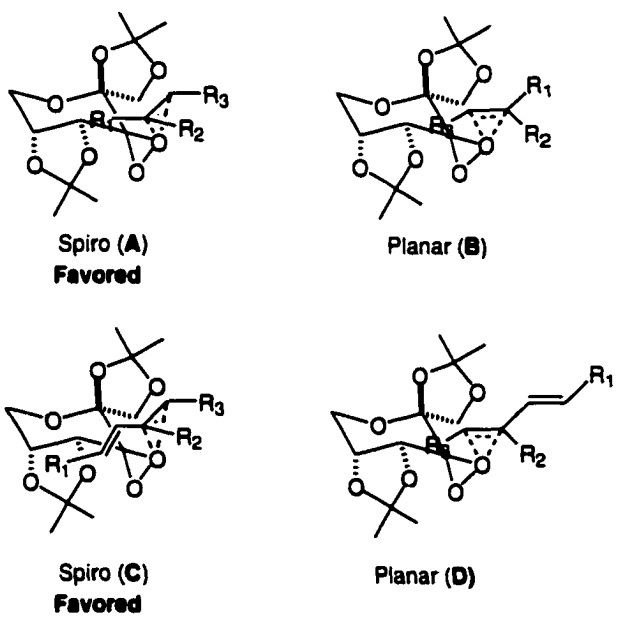
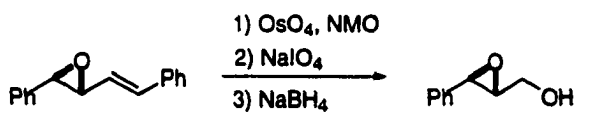


Figure 2.1 Spiro and planar transition states for the monoepoxidation.

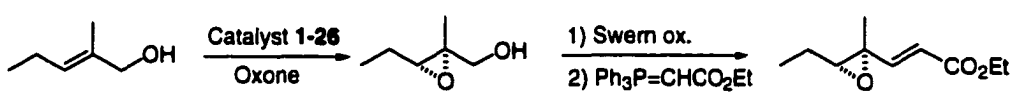
As discussed above, the spiro transition state is expected for the epoxidation of dienes. The stereochemistry of the epoxides in Table 2.1 is assigned based on this model. To further validate the assignment, the absolute configurations of two representative examples (Entries 1 & 13) were further defined either by converting the vinyl epoxide to

an epoxide with known configuration (eq. **2.8**)[25] or by preparing an authentic sample from an epoxy alcohol with known configuration following a reported sequence for the exact compound (eq. **2.9**).[26,27] In our case, the route presented in eq. **2.8** was not a very efficient sequence, particularly for the $NaBH_4$ reduction. As a result, the overall yield for the transformation was extremely low. Nevertheless, a small amount of the hydroxy epoxide was obtained, which was sufficient for comparison with an authentic sample by chiral HPLC. The results in both cases support the initial assignment based on the spiro mode of reaction.



2-30
Configuration known

(eq. **2.8**)



2-31 **2-32**
Configuration known

(eq. **2.9**)

This epoxidation procedure was not universal, and some problems were encountered with certain substrates (Figure 2.2). Sluggish reactivity was the major challenge encountered with some substrates, since the reactivity of the diene was severely compromised when it was conjugated to an aryl group. In addition to being less nucleophilic, these substructures were only sparingly soluble in the standard reaction medium. In some cases

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[25] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

[26] Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

[27] (a) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280. (b) Shimizu, I.; Hayashi, K.; Ide, N.; Oshima, M. *Tetrahedron* **1991**, *47*, 2991.

this could be overcome by increasing the amount of organic solvent in the reaction mixture, as in Table 2.1, Entry 1, which gave a better yield with 25 mL organic solvent for every mmol substrate. However, the low solubility for this type of substrate was a problem that was difficult to overcome using the present system. On a positive note, these factors had little effect on the enantioselectivity, since the major epoxide of **2-16** was obtained in 98% ee. Diene **2-23** shows the effect of changing the appending alkyl group from isobutyl (**2-22**, Table 2.1, Entry 14) to an isopropyl group. For reasons as yet undetermined, the isopropyl derivative was much less reactive.

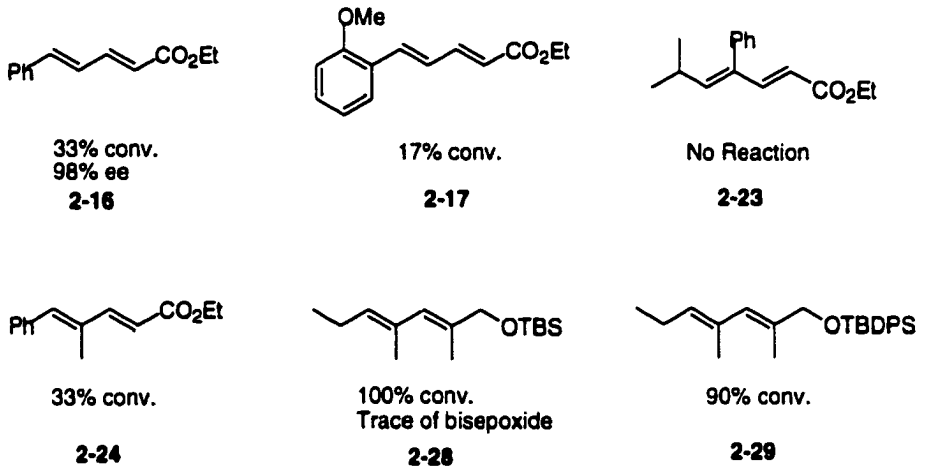

Figure 2.2 Additional examples.

In summary, this work shows a highly effective and mild epoxidation of conjugated dienes using the fructose-derived chiral ketone **1-28** as catalyst and Oxone as oxidant. The regioselectivities and enantioslectivities are very high in most cases. As a result, a variety of synthetically useful vinyl epoxides can be readily produced in optically enriched form. The current method is complementary to the selective epoxidation of conjugated dienes catalyzed by chiral (salen)Mn complexes, in which the

cis-olefins are preferentially epoxidized.[28] It is also complementary to the Sharpless asymmetric epoxidation of dienyl alcohols, which gives complete regioselective epoxidation at the epoxide proximal to the alcohol.[18]

2.C. BISEPOXIDATION OF CONJUGATED POLYENES

If the above reaction conditions was properly controlled, the monoepoxide was observed as the sole product. However, in some cases a small amount of the bisepoxide was observed (typically less than 5%). This indicates the possibility of pushing the epoxidation to give the bisepoxide as the main product. If the enantioselectivity were high in the second epoxidation, then a stereodefined synthesis of *cis* bisepoxides would result. The major issues that needed to be addressed were the ease of reaction and diastereoselectivity of the second epoxidation.

Trans,trans-1,4-diphenyl-1,3-butadiene was used as test substrate since it provided the highest facial bias of all the dienes tested in the monoepoxidation (97% ee). Table 2.2 highlights some of the challenges with this strategy. Initial experiments were run with 60 mol% catalyst, twice as much as the typical epoxidation procedure. However, this proved to be unsatisfactory since only 15% of the bisepoxide formed (Entry 1). A reduction in the amount of the organic solvent increased the amount of the bisepoxide, but only to 45% (Entry 2). Increasing the amount of catalyst did not help at all (Entries 3,4); however, screening of solvents showed that 100% CH_3CN (Entry 5)

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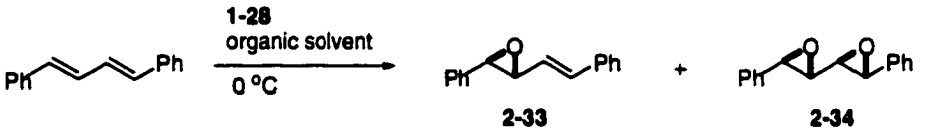
[28] For leading references on enantioselective epoxidations of *cis*-olefins of conjugated dienes using chiral (salen)Mn catalysts see: (a) Lee, N.H.; Jacobsen, E.N. *Tetrahedron Lett.* **1991**, *32*, 6533. (b) Chang, S.; Lee, N.H.; Jacobsen, E.N. *J. Org. Chem.* **1993**, *58*, 6939. (c) Chang, S.; Heid, R.M.; Jacobsen, E.N. *Tetrahedron Lett.* **1994**, *35*, 669. (d) Zhang, W.; Lee, N.H.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1994**, *116*, 425. (e) Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479. (f) Mikame, D.; Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 827. (g) Hentemann, M.F.; Fuchs, P.L. *Tetrahedron Lett.* **1997**, *38*, 5615.

produced a more active system, as about 80% of the product formed was bisepoxide. In addition, the ^{1}H NMR spectrum of the bisepoxide (acetone-d_6) showed an 18/1 diastereomeric ratio, which was close to the expected outcome of about 19/1 (two epoxidations of 97% ee should give about 96% *cis* bisepoxide). Unfortunately, further efforts to increase the conversion failed; however, in the best case scenario about 90% of the olefins present in the reaction mixture underwent oxidation with high diastereoselectivity.



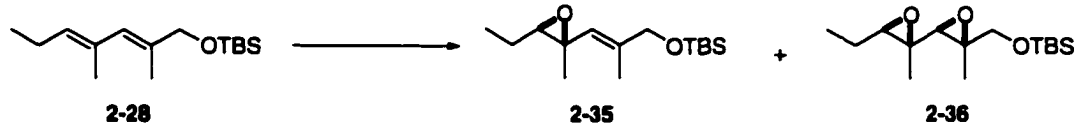
2-33 2-34

Table 2.2. Bisepoxidation of *trans,trans*-1,4-diphenyl-1,3-butadiene with **1-28**

Entry	**1-26**(mol%)	Oxone (eq.)	Solvent (mL)	Time (h)	**2-33/2-34**[a]
1	60	4.15	DMM/CH_3CN (25)	1.5	5.7/1
2	60	4.15	DMM/CH_3CN (15)	1.5	1.2/1
3	75	4.15	DMM/CH_3CN (15)	1.5	1.2/1
4	85	4.15	DMM/CH_3CN (15)	1.5	1.2/1
5	**60**	**2.76**	**CH_3CN (15)**	**4**	**1/4**
6	55	2.76	CH_3CN (15)	4	1/1.9

[a] The ratio of mono- to bisepoxide was determined by integration of the crude ^{1}H NMR spectrum.

These results showed promise for a general bisepoxidation procedure, so attention was turned to diene **2-28**, primarily because a small amount of the bisepoxide **2-36** was isolable during the monoepoxidation experiments (eq **2.10**).

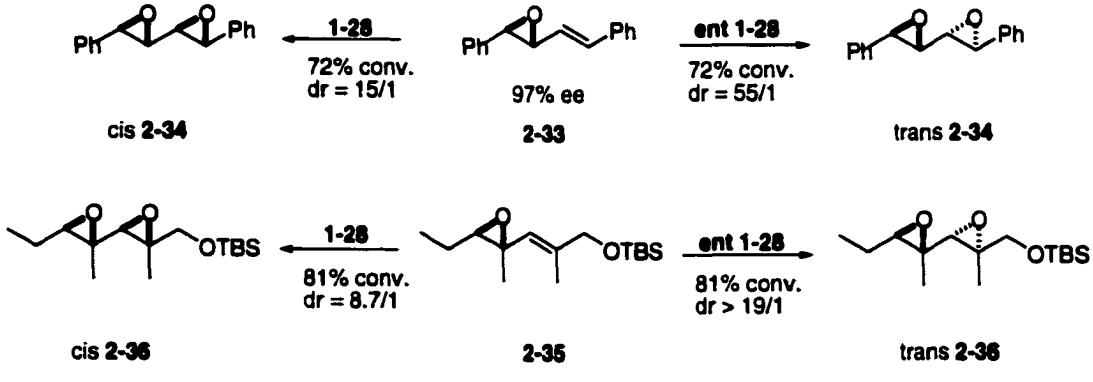


2-28 **2-35** **2-36**

(eq. **2.10**)

However, after screening various reaction conditions it was found that bisepoxide **2-36** could only be formed in about a 1/1 ratio along with **2-35**. Furthermore, the observed dastereoselectivity of 7/1 was disappointing. Thus, it appears that the diastereoselective bisepoxidation of conjugated dienes is not general.

These experiments indicate that the oxygen of the intermediate monoepoxide reduces the reactivity of the remaining olefin, possibly by directing it through the typically disfavored planar transition state. To further probe the factors involved in the low diastereoselectivity, a stepwise bisepoxidation study was undertaken with monoepoxides **2-33** and **2-35** (Scheme 2.12).



Scheme 2.12

When **2-33** was subjected to epoxidation with ketone **1-28**, a 15/1 ratio of diastereomers was produced, which is similar to the direct bisepoxidation in Table 2.2. On the other hand, if the **ent 1-28** was used, a 55/1 diastereomeric ratio in favor of the opposite diastereomer was measured by ^{1}H NMR. These results show that the facial bias of the second epoxidation was definitely influenced by the epoxide of the substrate.

To further verify the results, monoepoxide **2-35** was subjected to the same analysis (Scheme 2.13), and the results paralleled those of Scheme 2.12. These results suggest that the diastereoslective synthesis of *cis* bisepoxides is not a general process using the fructose-derived ketone, and that high diastereoselectivity can only be obtained with select substrates.

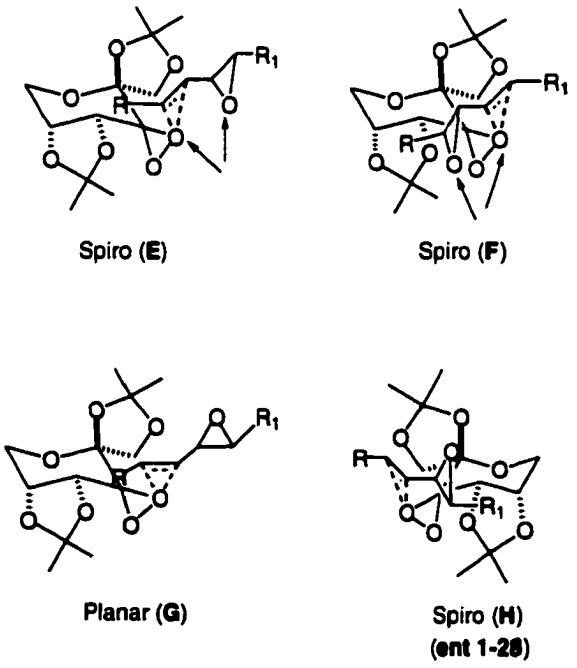


Figure 2.3 Spiro and planar transition states for the second epoxidation.

Examination of the possible transition states is helpful in determining the factors involved in these reactions (Figure 2.3). Spiro (E) and Spiro (F) both show distinct steric

interactions when the epoxide is present. On the other hand, Planar (**G**) accommodates the olefin nicely since the epoxide is directed away from the catalyst. Therefore, the spiro transition states are disfavored relative to the planar in this case. On the other hand, when **ent 1-28** is used as catalyst the epoxide is directed away from the catalyst in Spiro (**H**), and the spiro mode is again highly favored over the planar. The result is a highly diastereoselective epoxidation when **ent 1-28** is employed as catalyst.

A particularly interesting point is that the conversions of **2-33** and **2-35** are essentially the same with either antipode of the catalyst. Although the diastereoselectivity of the reaction is effected by the steric interactions in the transition state, these interactions do not seem to control the extent of reaction to any particular degree. Therefore, it is reasonable to speculate that the lower reactivity of the vinyl epoxide with respect to its parent diene is primarily due to the inductive effect of the epoxide oxygen. These results show that a direct bisepoxidation to produce *cis* bisepoxides in high diastereoselectivity is not a general phenomenon. However, they also imply that a stepwise bisepoxidation sequence can be utilized to form *trans* bisepoxides with high levels of selectivity (see below).

Vicinal bisepoxides are somewhat rare in nature,[29] but they have been postulated as biogenic precursors to natural products. An interesting example is citreoviral, which is a neurotoxic mycotoxin that inhibits mitochondrial ATPase and oxidative phosphorylase.[30] The proposed biogenic cyclization is shown in Scheme 2.13.

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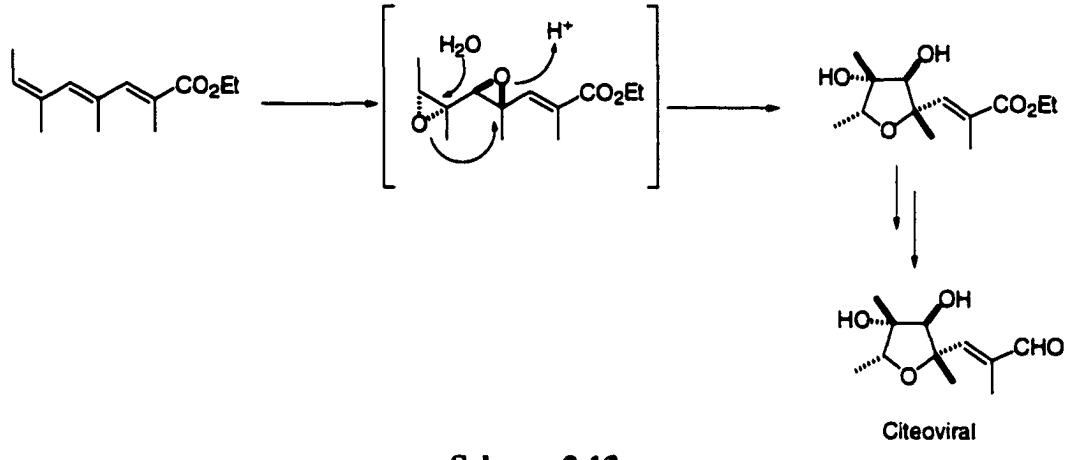
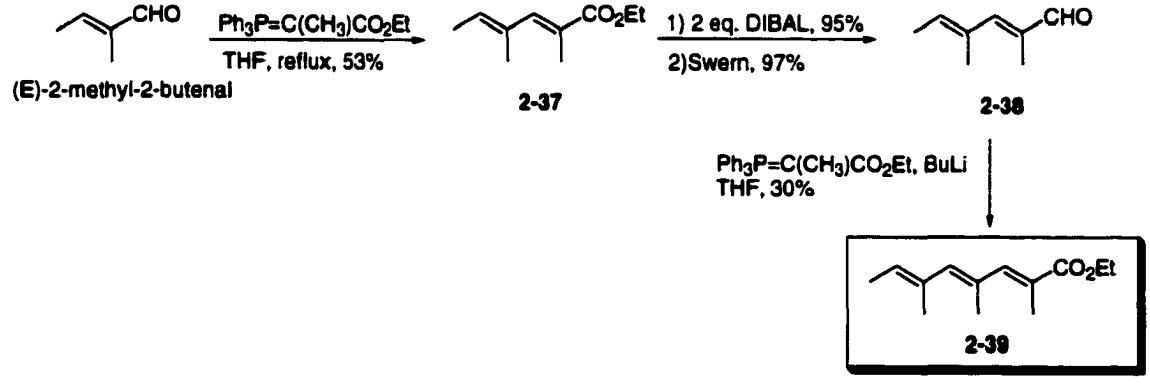
[29] An interesting example is (+)-Spatol, a marine algal metabolite that inhibits T242 Melanoma and 224C Astrocytoma neoplastic cell lines. (a) Solomon, R.G.; Basu, B.; Roy, S.; Sharma, R.B. *Tetrahedron Lett.* **1989**, *30*, 4621. (b) For isolation and structure determination, see: Gerwick, W.H.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 3325. Crotepoxide is another example: (c) Kupchan, S.M.; Hemmingway, R.J.; Coggon, P.; McPhail, A.T.; Sim, G.A. *J. Am. Chem. Soc.* **1968**, *90*, 2982. and (d) Kupchan, S.M.; Hemmingway, R.J.; Smith, R.M. *J. Org. Chem.* **1969**, *34*, 3898. For the interesting vicinal triepoxides in triptolide and tripdiolide, see: Beker, A.A.; Janusz, J.M.; Bruice, T.C. *J. Am. Chem. Soc.* **1979**, *101*, 5679.

[30] For a leading reference, see: Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053.

Since these vicinal bisepoxides are important biomimetic precursors, it seemed that our epoxidation strategy would constitute a valuable approach towards these types of molecules. We tested our hypothesis on triene **2-39** since this could lead to a close structural analogue of citreoviral upon cyclization. The synthesis of the triene precursor is shown in Scheme 2.14. Wittig olefination of (*E*)-2-methyl-butenal under refluxing conditions gave diene **2-37** smoothly. After DIBAL reduction to the alcohol, the diastereomers proved to be present in a 20/1 ratio by integration of the ^{1}H NMR spectrum. Swern oxidation provided aldehyde **2-38** in high yield; and a second Wittig olefination gave the desired triene **2-39**, albeit in low yield due to difficult separation of olefin isomers by column chromatography.

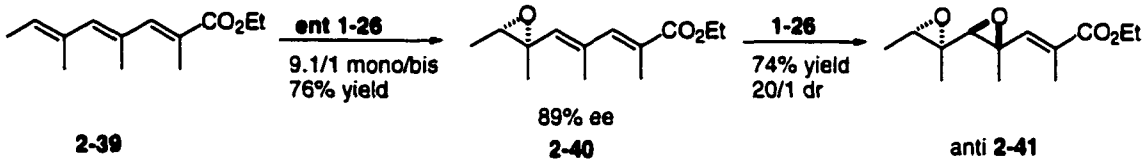


Scheme 2.13



Scheme 2.14

To achieve the correct stereochemistry in the cyclization product, it was required to use **ent 1-28** in the first epoxidation step, and the monoepoxide was formed as a 9.1/1 ratio of mono- to bisepoxide using 30 mol% catalyst. Furthermore, ^{1}H NMR analysis of the epoxide using Eu(hfc)$_3$ as the chiral shift reagent showed the monoepoxide had been formed in 89% ee (Scheme 2.15).[31] Importantly, this shows that the ester is also an effective directing group in the triene system, providing the opportunity to obtain the monoepoxide in synthetically useful yields.



Scheme 2.15

Further reaction of the monoepoxide with **1-28** (this time using 60 mol% ketone to override the deactivation of the epoxide oxygen) provided the bisepoxide in a 74% yield and 20/1 diastereoselectivity. These results show that the stepwise epoxidation of trienes to give vicinal bisepoxides in a stereodefined manner is feasible.

Another interesting observation is the fact that the *trans* bisepoxide is also formed in high diastereoselectivity in the racemic series when 1,3-dichloroacetone is used as the dioxirane precursor.[32] This implies that the epoxide of **2-40** can be used as a directing group with dichloroacetone as dioxirane precursor to give anti **2-41** in high diastereoselectivity as well as **1-28**.

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[31] It was later found that the ee of the monoepoxide could be determined by chiral HPLC, and epoxidation with **1-28** gave a 94% ee.

2.D. CONCLUSIONS

The monoepoxidation of conjugated dienes proceeds with good to high regioselectivity and high enantioselectivity. Synthetically useful yields of a wide variety of the product vinyl epoxides are available in optically active form directly from their diene precursors using this strategy. Since this class of epoxides is synthetically useful, the reaction has the potential to be of much use in the future. However, the direct bisepoxidation of conjugated dienes to give high diastereoselectivity for *cis* bisepoxides with control of absolute configuration is tenuous due to significant substrate control of the second epoxidation. The stepwise bisepoxidation to form *trans* vicinal bisepoxides is feasible, providing products with high diastereoselectivity and control of the absolute stereochemistry. This stepwise strategy also has the potential to be applied to higher homologues of polyepoxides provided the proper electronic controlling group is located at one terminus of the polyolefin.

2.E. EXPERIMENTAL

General Methods: Oxone was purchased from Aldrich (it has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches). All glassware used for the epoxidation was carefully washed to be free of any trace metals which catalyze the decomposition of Oxone. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Bruker ACE-300 spectrometer in $CDCl_3$. Proton chemical shifts (δ) are given relative to internal TMS (0.00 ppm), and Carbon

[32] The use of dimethyldioxirane provides a relatively low diastereoselectivity of 9/4 for this substrate.

chemical shifts are given relative to $CDCl_3$ (77.00 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrometer. High-resolution mass spectra were performed by the mass spectrometry facility of Colorado State University. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Optical rotations were measured on an Autopol III automatic polarimeter in a 10 cm cell. Silica gel 60 of E-Merck Co. was employed for all flash chromatography.

General epoxidation procedure: To a 150 mL 3-necked flask were added buffer (0.05 M $Na_2B_2O_4$ 10 H_2O in 4 X 10^{-4} M EDTA, 10 mL) , dimethoxymethane/acetonitrile (2/1, 15 mL), *trans*, *trans*-1,4-diphenyl-1,3-butadiene (0.206 g, 1 mmol), tetrabutylammonium hydrogen sulfate (0.015g, 0.04 mmol), and ketone (0.065g, 0.25 mmol). The reaction mixture was cooled to 0 °C with an ice bath. A solution of Oxone (0.69 g, 1.13 mmol) in aqueous EDTA (4 X 10^{-4} M, 6.0 mL) and a solution of K_2CO_3 (0.69 g, 4.99 mmol) in water (6.0 mL) were added separately via syringe pump over 1.5 h. The reaction was immediately quenched by the addition of hexanes (15 mL). The aqueous layer was extracted with hexanes (3 X 25 mL), washed with brine (50 mL), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (the silica gel was buffered with 1 % Et_3N in hexane; 1 % Et_3N in 3:1 CH_2Cl_2/hexane was used as the eluent) to afford (*R*,*R*)-2-phenyl-3-(*trans*-2-phenylvinyl)oxirane as a white solid (0.171 g, 77 % yield, 97% ee) (Table 1, Entry 1)

(Table 2.1, Entry 1)

(*R*,*R*)-2-Phenyl-3-(*trans*-2-phenylvinyl)oxirane (MF336). White solid; $[\alpha]^{20}_D$ = +252.2° (*c* 0.24, $CHCl_3$); IR (NaCl): 3027, 1953, 1755, 1598, 1489, 1448, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10H), 6.81 (d, J = 15.9 Hz, 1H), 6.09 (dd, J =

15.9, 7.5 Hz, 1H), 3.89 (d, J = 2.1 Hz, 1H), 3.53 (dd, J = 7.5, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 136.0, 134.4, 128.7, 128.5, 128.2, 128.1, 126.5, 126.2, 125.5, 63.12, 60.70; Anal calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.34. Found: C, 86.43; H, 6.55.

(Table 2.1, Entry 2)

(*S,S*)-2-Phenyl-3-(*trans*-2-phenylvinyl)oxirane (MF1012). White solid; $[\alpha]^{20}_D$ = -251.9° (*c* 0.45, $CHCl_3$).

(Table 2.1, Entry 3)

1-Cyclohexenylcyclohexene (2-9)(MF441, MF442). A 3-necked roundbottom flask equipped with a solid addition funnel was charged with $HgCl_2$ (0.22 g, 0.8 mmol) and then placed under a N_2 atmosphere. Distilled THF (15 mL) was added, and then Mg (50 mesh, 0.73 g, 30 mmol) via the solid addition funnel. The resulting mixture was stirred at room temperature for 15 m, the liquid was withdrawn via syringe, and the gray solid was washed with THF (3 X 10 mL). The amalgam was then taken up in THF (25 mL), cooled to –10 °C, and $TiCl_4$ (2.85 g, 15 mmol) was added dropwise via syringe. To the resulting yellow/green suspension was added cyclohexanone (0.98 g, 10 mmol) as a solution in THF (25 mL). The mixture was then stirred at 0 °C for 1.25 h, during which time it turned into a deep purple color. The reaction was then quenched with saturated K_2CO_3 (2.5 mL) and stirred for an additional 15 m at 0 °C. The suspension was diluted with Et_2O (50 mL), filtered through celite, washed with brine (1 X 75 mL), dried (Na_2SO_4), and concentrated to give an off white solid, which was recrystallized with Et_2O/ petroleum ether to give the diol as a white solid (598 mg, 60.4%). This diol was taken on without characterization.

To the diol (598 mg, 3.02 mmol) was added 10% H_2SO_4 (25 mL) and the solution was heated to reflux for 4 h, then extracted with hexanes (2 X 25 mL). The combined organics were washed with H_2O (1 x 20 mL), brine (1 X 25 mL), dried (Na_2SO_4), and run through a plug of silica gel (hexanes) to give the diene 93% pure by GC. This diene was then recrystallized with boiling MeOH followed by cooling to –30 °C and filtering at that temperature. This gave the diene >99% pure as a white solid (140 mg, 28.5%, 17.5% over two steps). IR (NaCl): 3037, 2924, 2855, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (br s, 2H), 2.20-2.05 (m, 8H), 1.70-1.50 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 121.4, 25.85, 25.50, 23.13, 22.51.

(*R,R*)-1-Cyclohexenylcyclohexene oxide (MF445). Colorless oil; $[\alpha]^{20}_D$ = +6.7° (*c* 0.29, $CHCl_3$); IR (NaCl): 2932, 2857, 1439, 1344, 1220, 1136, 980, 920, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 3.04 (dd, J = 3.6, 1.5 Hz, 1H), 2.1-1.1 (m, 16H); ^{13}C NMR (75MHz, $CDCl_3$) δ 138.3, 122.6, 61.81, 58.81, 27.39, 24.93, 24.80, 24.55, 22.62, 22.33, 20.09, 19.91; HRMS calcd for $C_{12}H_{19}O$ (M^++1): 179.1437. Found: 179.1437.

(Table 2.1, Entry 4)

(*R,R*)-2-[*Trans*-2-(ethoxycarbonyl)vinyl]-3-methyloxirane (MF842).

Colorless oil; $[\alpha]^{20}_D$ = +12.6° (*c* 0.48, $CHCl_3$); IR (NaCl): 2984, 2933, 1721, 1655, 1446, 1370, 1340, 1188, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (dd, J = 15.6, 7.2 Hz, 1H), 6.13 (d, J = 15.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.18 (dd, J = 7.2, 1.8 Hz, 1H), 2.98 (qd, J = 5.1, 1.8 Hz, 1H), 1.39 (d, J = 5.1 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 144.6, 123.7, 60.50, 57.37, 57.21, 17.50, 14.19; HRMS calcd for $C_8H_{13}O_3$ (M^++1): 157.0864. Found: 157.0865.

(Table 2.1, Entry 5)

(*E,E*)-2,4-octadienoic acid ethyl ester (2-15)(MF542). To a solution of *trans*-2-hexenal (687 mg, 7.00 mmol) in CH_2Cl_2 (10 mL) was added (carbethoxymethylene)triphenylphosphorane (4.86 g, 14.00 mmol) and the yellow solution was stirred under nitrogen at room temperature for 2 d. The solvent was removed under reduced pressure, the resulting solid was taken up in hexanes (25 mL) and the solution was decanted. This was then repeated 5 times. The combined organics were concentrated under reduced pressure and purified by flash column chromatography (100/1 hexanes/Et_2O) to give the diene as a colorless oil (685 mg, 58.2%) IR (NaCl): 1711, 1646, 1254, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 15.6, 9.9 Hz, 1H), 6.15 (m, 2H), 4.78 (d, J = 15.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.14 (q, J = 5.0 Hz, 2H), 1.46 (sextet, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 145.0, 144.3, 128.5, 119.2, 60.08, 34.96, 21.50, 14.26, 13.58.

***(R,R)*-2-[*Trans*-2-(ethoxycarbonyl)vinyl]-3-propyloxirane (MF626, MF646).** Colorless oil; $[\alpha]^{20}_D$ = +13.8° (*c* 0.22, $CHCl_3$); IR (NaCl): 1719, 1663, 1482, 1342 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (ddd, J = 16.2, 6.9, 1.5 Hz, 1H), 6.12 (d, J = 16.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.20 (d, J = 6.9 Hz, 1H), 2.89 – 2.87 (m, 1H), 1.45 – 1.65 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 144.8, 123.5, 61.25, 60.55, 56.28, 33.88, 19.12, 14.19, 13.81.

***(R,R)*-2-Ethoxycarbonyl-*3*-(*trans*-2-propylvinyl)oxirane (MF626, MF646).** Colorless oil; $[\alpha]^{20}_D$ = +25.5° (*c* 0.17, $CHCl_3$); IR (NaCl): 1719, 1654, 1297 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (dt, J = 15.6, 6.9 Hz, 1H), 5.16 (ddt, J = 15.6, 8.1, 1.5, 1H), 4.23 – 4.20 (dq, J = 7.2, 4.5 Hz, 1H), 4.24 (dq, J = 7.2, 4.5 Hz, 1H); 3.54 (dd, J = 8.4, 2.1 Hz, 1H), 3.38 (d, J = 2.1 Hz, 1H), 2.12 – 2.02 (qd, J = 7.8, 1.5 Hz, 1H), 1.50 – 1.35 (m, 2H),

1.31 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 139.3, 125.1, 61.60, 60.56, 58.24, 34.36, 29.70, 21.88, 14.13.

(Table 2.1, Entry 6)

(*R,R*)-2-[*Trans*-2-(hydroxymethyl)vinyl]-3-methyloxirane (MF432). Colorless oil; IR (NaCl): 3387, 1650, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (ddt, J = 15.6, 5.4, 0.9 Hz, 1H), 5.47 (ddt, J = 15.6, 7.8, 1.5 Hz, 1H), 4.18 (dd, J = 5.4, 1.5 Hz, 2H), 3.10 (dd, J = 7.8, 2.4 Hz, 1H), 2.93 (dq, J = 2.4, 5.4 Hz, 1H), 1.61 (s, 1H), 1.35 (d, J = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 128.8, 62.70, 58.83, 56.47, 17.49.

(*R,R*)-2-Hydroxymethyl-3-(*trans*-2-methylvinyl)oxirane (MF432). Colorless oil; IR (NaCl): 3409, 1652, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dq, J = 15.6, 6.9 Hz, 1H), 5.23 (ddt, J = 15.6, 8.1, 1.8 Hz, 1H), 3.95 (ddd, J = 12.6, 5.4, 2.4 Hz, 1H), 3.67 (ddd, J = 11.7, 7.5, 4.2 Hz, 1H), 3.38 (dd, J = 8.1, 2.4 Hz, 1H), 3.10 – 3.04 (m, 1H), 2.01 (s, 1H), 1.75 (dd, J = 6.6, 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 127.7, 61.30, 59.87, 55.82, 17.83.

(Table 2.1, Entry 7)

(E,E)-2,4-Hexadien-1-ol acetate (2-12)(MF343). To a solution of *trans,trans*-2,4 hexadien-1-ol (0.93 g, 10.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added acetic anhydride (2.08 g, 20.0 mmol) and pyridine (1.58 g, 20.0 mmol) and the solution was stirred overnight with gradual warming to room temperature. The reaction was quenched with H_2O (10 ml) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 20 mL), the combined organics were washed with brine (1 X 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (10/1 hexanes/Et_2O) to give the acetate as a colorless oil (1.28 g, 91.4%). IR (NaCl): 3021.1651, 1373 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 6.27 (dd, J = 15.0, 10.2 Hz, 1H), 6.05 (ddd, J = 15.0, 10.2, 1.5 Hz, 1H), 5.76 (dq, J = 15.0, 7.2 Hz, 1H), 5.63 (dt, J = 15.0, 7.2 Hz, 1H), 4.57 (d, J = 7.2 Hz, 2H), 2.13 (s, 3H), 1.77 (J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.0, 131.3, 130.4, 123.6, 65.00, 21.02, 18.16.

(*R,R*)-2-[*Trans*-2-(acetoxy)vinyl]-3-methyloxirane (MF346). Colorless oil; IR (NaCl): 1739, 1443, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (ddt, J = 15.6, 6.0, 0.6 Hz, 1H), 5.51 (dqt, J = 15.6, 7.8, 0.6 Hz, 1H), 4.57 (dd, J = 6.0, 1.5 Hz, 2H), 3.08 (dd, J = 7.8, 2.1 Hz, 1H), 2.92 (dq, J = 5.1, 2.1, 0.6 Hz, 1H), 2.08 (s, 3H), 1.35 (d, J = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 131.8, 128.6, 63.78, 58.44, 56.44, 20.83, 17.43.

(*R,R*)-2-[(Acetoxy)methyl]-3-(*trans*-2-methylvinyl)oxirane (MF346). Colorless oil; IR (NaCl): 1744, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (dq, J = 15.3, 6.6 Hz, 1H), 5.20 (qq, J = 15.3, 8.1, 1.5 Hz, 1H), 4.39 (dd, J = 12.6, 3.6 Hz, 1H), 3.96 (dd, J = 12.6, 6.0 Hz, 1H), 3.26 (dd, J = 8.4, 2.1 Hz, 1H), 3.12 (m, 1H), 2.10 (s, 3H), 1.75 (dd, J = 7.2, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 132.8, 127.3, 64.38, 56.83, 56.47, 20.75, 17.87.

(Table 2.1, Entry 8)

(*E,E*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-hexadiene (2-11)(MF420). The a solution of (*E,E*)-2,4-hexadien-1-ol (1.17 g, 11.9 mmol) and *tert*-butyldimethylsilyl chloride (1.98 g, 13.1 mmol) in CH_2Cl_2 (40 mL) was added NEt_3 (1.45g, 20 mmol) and N,N,-dimethylamino pyridine (25 mg). The reaction was stirred overnight, quenched with H_2O (25 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 X 20 mL). The combined organics were washed with brine (1 X 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (10/1 hexanesEt_2O) to give the silyl ether as a colorless oil (2.50 g, 99.1%). IR (NaCl): 3020, 2954, 2931, 2856, 1467,

1379, 1255, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, J = 14.7, 10.2 Hz, 1H), 6.04 (ddd, J = 14.7, 10.2, 1.5 Hz, 1H), 5.65 (dq, J = 14.7, 6.9 Hz, 1H), 5.59 (dt, J = 14.7, 5.4 Hz, 1H), 4.19 (d, J = 4.5 Hz, 2H), 1.75 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0, 130.3, 129.9, 129.0, 63.70, 26.00, 18.46, 18.11, -5.13.

(*R,R*)-2-{*Trans*-2-[(*tert*-butyldimethylsilyloxy)methyl]vinyl}-3-methyloxirane (MF420). Colorless oil; $[\alpha]^{20}_D$ = +28.6° (*c* 0.71, EtOH); IR (NaCl): 2956, 2931, 2857, 1620, 1468, 1381, 1255, 1125 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (dt, J = 15.3, 4.5 Hz, 1H), 5.45 (ddtd, J = 15.3, 8.1, 1.8, 0.9 Hz, 1H), 4.19 (dd, J = 4.5, 1.8 Hz, 2H), 3.09 (dd, J = 8.1, 2.1 Hz,1H), 2.91 (qdd, J = 5.1, 2.1, 0.9 Hz,1H), 1.34 (d, J = 5.1 Hz, 3H), 0.91,(s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 127.2, 62.87, 59.08. 56.40, 25.89, 18.36, 17.54, -5.41; Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 62.96; H, 10.30.

(*R,R*)-2-[(*t*-Butyldimethylsilyloxy)methyl]-3-(*trans*-2-methylvinyl)oxirane (MF420). Colorless oil; $[\alpha]^{20}_D$ = +17.7° (c 0.45, EtOH); IR (NaCl): 3051, 2955, 2928, 2857, 1464, 1382, 1260, 1109 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (dq, J = 15.3, 6.6 Hz, 1H), 5.22 (ddq, J = 15.3, 8.1, 1.81 Hz, 1H), 3.84 (dd, J = 12.3, 3.6 Hz, 1H), 3.70 (dd, J = 12.3, 4.5 Hz, 1H), 3.24 (dd, J = 8.1, 2.4 Hz, 1H), 3.02-2.97 (m, 1H), 1.74 (dd, J = 6.6, 1.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.072 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 128.2, 63.23, 60.17, 56.16, 25.88, 18.30, 17.86, -5.31. Anal Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.02; H, 10.46.

(Table 2.1, Entry 9)

(*E,E*)-2-methyl-2-methoxy-3,5-heptadiene (2-14)(MF440, 743). To a solution of ethyl sorbate (0.5 g, 3.57 mmol) in THF (25 ml) at 0 °C was added under a nitrogen

atmosphere was added MeLi (6.4 mL, 8.95 mmol) dropwise via syringe. The solution was stirred at 0 °C for 4 h, quenched by the dropwise addition of H_2O (25 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 X 20 mL). The combined organics were washed with brine (1 X 30 mL), dried (Na_2SO_4), filtered, and the concentrated under reduced pressure. The light yellow oil was filtered through a plug of silica gel (1/1 hexanes/Et_2O) to give the alcohol, which was carefully concentrated under reduced pressure and taken directly to the next step.

A flame-dried 125 mL roundbottom flask was charged with NaH (893 mg, 15.0 mmol as a 60% suspension in mineral oil), and the gray solid was washed with pentane (3 X 5 mL). The NaH was taken up in THF (22 mL) and the alcohol (938 mg, 7.4 mmol) was added dropwise as a solution in THF (22 mL). The orange suspension was stirred for 30 m and MeI (8.44 g, 59.4 mmol) was added. The resulting solution was heated to reflux for 8 h, cooled, quenched with H_2O (20 mL), and extracted with hexanes (3 X 30 mL). The combined organics were washed with brine (1 X 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was filtered through a plug of silica gel to give the methyl ether as a colorless oil (594 mg, 57.6% over two steps). IR (NaCl): 3017, 2922, 2856, 1454, 1373, 1241, 1161, 1073, 992 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 - 6.00 (m, 2H), 5.76 - 5.64 (m, 1H), 5.57 - 5.45 (m, 1H), 3.14 (s, 3H), 1.76 (d, J = 6.6, 0.6 Hz, 3H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 131.1, 129.7, 129.2, 74.80, 50.27, 25.82, 18.00.

(*R,R*)-2-[*trans*-2-(1-Methoxy-1-methylethyl)vinyl]-3-methyloxirane (MF519). Colorless oil; $[\alpha]^{20}_D$ = +22.0° (*c* 0.20, $CHCl_3$); IR (NaCl) δ 2977, 2934, 2825, 1455, 1378, 1246, 1169, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (d, J = 15.9 Hz, 1H), 5.30 (dd, J = 15.9, 8.1 Hz, 1H), 3.16 (s, 3H), 3.08 (dd, J = 8.1, 1.8 Hz, 1H), 2.93 (dq, J = 5.1, 1.8 1 Hz, 1H), 1.35 (d, J = 5.1 Hz, 3H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

140.7, 127.4, 74.51, 59.24, 56.39, 50.43, 25.61, 17.51; HRMS calcd for $C_9H_{17}O_2$ (M^++1): 157.1228. Found: 157.1225.

(Table 2.1, Entry 10)

***(E,E)*-4-Methyl-2,4-heptadien-1-ol (2-19)(MF641).** To a solution of **2-18** (475 mg, 2.83 mmol) in distilled THF (3 mL) at –20 °C was added DIBAL (6.2 mL, 6.2 mmol, 1.0 M in hexanes) and the solution was stirred for 10 m. The mixture was taken to 0 °C and stirred for 2 h. The reaction was quenched with saturate NH_4Cl (5 mL) and the aluminum salts were filtered through a sintered glass funnel. The filtrate was then extracted with Et_2O (3 X 5 mL). The combined organics were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was purified by flash chromatogrphy (1/1 hexanes/Et_2O) to give the alcohol as a light yellow oil (325 mg, 81.1%). IR (NaCl): 3332, 3027, 2961, 2925, 2867, 1646, 1450, 1392, 1305, 1087, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (d, J = 15.6 Hz, 1H), 5.71 (dt, J = 15.6, 6.3 Hz, 1H), 5.49 (t, J = 7.4 Hz, 1H), 4.18 (d, J = 6.3 Hz, 2H), 2.14 (septet, J = 7.4 Hz, 2H), 1.78 (br s, 1H), 1.75 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 135.1, 132.3, 125.1, 63.87, 21.45, 13.90, 12.17.

***(R,R)*-3-Ethyl-2-[*trans*-2-(hydroxymethyl)vinyl]-2-methyloxirane (MF720).** Colorless oil; $[\alpha]^{20}_D$ = -8.14° (*c* 0.52, $CHCl_3$); IR (NaCl): 3416, 2970, 2934, 2875, 1670, 1460, 1385, 1276, 1222, 1096, 1071, 1013, 971, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (dt, J = 15.9, 5.1 Hz, 1H), 5.53 (d, J = 15.9 Hz, 1H), 4.12 (t, J = 5.1 Hz, 2H), 2.76 (t, J = 6.3 Hz, 1H), 2.29 (br s, 1H), 1.65-1.5 (m, 2H), 1.37 (s, 3H), 1.01 (t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 130.7, 66.61, 62.65, 59.07, 21.89, 15.24, 10.32; HRMS calcd for $C_8H_{15}O_2$ (M^++1): 143.1073. Found 143.1073.

(Table 2.1, Entry 11)

(*E,E*)-4-Methyl-1-(*tert*-butyldimethylsilyloxy)-2,4-heptadiene (2-20)(MF723). The TBS ether was prepared according to the procedure provided for **2-11** to give product as a colorless oil (1.00 g, 82% yield). IR (NaCl): 3034, 2954, 2925, 2852, 1646, 1465, 1377, 1297, 1254, 1123, 1072, 963, 840, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, J = 15.6 Hz, 1H), 5.63 (dt, J = 15.6, 5.7 Hz, 1H), 5.46 (t, J = 6.9 Hz, 1H), 4.25 (d, J = 5.7 Hz, 2H), 2.14 (septet, J = 7.5 Hz, 2H), 1.75 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 134.2, 132.5, 125.7, 64.17, 25.98, 21.45, 18.42, 14.01, 12.24, -5.13.

(*R,R*)-3-Ethyl-2-{*trans*-2-[(*tert*-butyldimethylsilyloxy)methyl]vinyl}-2-methyl oxirane (MF732). Colorless oil; $[\alpha]^{20}_D$ = -9.2° (*c* 1.57, $CHCl_3$); IR (NaCl): 2959, 2935, 2857, 1456, 1386, 1252, 1118, 1071, 961, 835, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dt, J = 15.6, 4.5 Hz, 1H), 5.54 (dt, J = 15.6, 1.8 Hz, 1H), 4.19 (dd, J = 4.5, 1.8 Hz, 2H), 2.77 (t, J = 6.0 Hz, 1H), 1.61 (m, 2H), 1.39 (s, 3H), 1.04 (t, J = 8.4 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7, 130.8, 66.64, 63.21, 59.10, 25.97, 22.06, 18.43, 15.48, 10.45, -5.21. Anal calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.01. Found: C, 65.70; H, 10.84.

(Table 2.1, Entry 12)

(*E,Z*)-3-propyl-2,4-nonadienoic acid ethyl (2-21)(MF549). To a 100 mL flame-dried roundbottom flask was added NaH (185 mg, 7.7 mmol, 60% dispersion in mineral oil) and the gray solid was washed with pentane (3 X 5 mL). The solid was then taken up in THF (20 mL) and triethyl phosphonoacetate (1.72 g, 7.7 mmol) was added. The mixture was stirred for 30 m and the (*Z*)-2-propyl-2-heptenal (1.08 g, 7.00 mmol) was added dropwise. The mixture was stirred overnight at room temperature under nitrogen

atmosphere, quenched with H_2O (20 mL), the layers separated, and the aqueous layer was extracted with Et_2O (2 X 25 mL). The combined organics were washed with brine (1 X 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The oil was purified by flash column chromatography (100/1 hexanes/Et_2O) to give the diene as a colorless oil (1.33 g, 84.8%). IR (NaCl): 2959, 2931, 2871, 1714, 1624, 1463, 1367, 1301, 1258, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 15.9 Hz, 1H), 5.88 (t, J = 7.5 Hz, 1H), 5.79 (d, J = 15.9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.25 - 2.15 (m, 4H), 1.48 - 1.27 (m, 9H), 0.96 - 0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 149.0, 142.6, 137.2, 115.1, 60.08, 31.37, 28.60, 28.46, 22.42, 21.92, 14.31,14.16, 13.88.

(*2S,3R*)-3-Butyl-2-[*trans*-2-(ethoxycarbonyl)vinyl]-2-propyloxirane (MF628, 647). Colorless oil; $[\alpha]^{20}_D$ = -58.8° (*c* 0.39, $CHCl_3$); IR (NaCl): 2961, 2932, 2872, 1722, 1655, 1464, 1367, 1305, 1265, 1165, 1041, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 15.6 Hz, 1H), 6.00 (d, J = 15.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.74 (t, J = 6.3 Hz, 1H), 1.8-1.32 (m, 13H), 1.0-0.9 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 148.5, 120.9, 67.11, 61.90, 60.44, 32.02, 28.55, 28.17, 22.50, 18.75, 14.28, 14.21, 13.93; Anal calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.17; H, 9.97.

(Table 2.1, Entry 13)

(*E,E*)-4-Methyl-2,4-heptadienoic acid ethyl ester (2-18)(MF513). The diene was prepared according to the procedure provided for **2-15** to give product as a colorless oil (866 mg, 99.0%). IR (NaCl): 3066, 2971, 2935, 2874, 1713, 1625, 1294, 1263, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 15.6 Hz, 1H), 5.89 (t, J = 7.2 Hz, 1H), 5.79 (d, J = 15.6 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.21 (septet, J = 7.2 Hz, 2H), 1.77 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 149.6, 143.6, 132.2, 115.5, 60.08, 22.05, 14.31, 13.45, 11.93.

(*R,R*)-2-[*trans*-2-(ethoxycarbonyl)vinyl]-3-ethyl-2-methyloxirane (MF525).[28a] Colorless oil; $[\alpha]^{20}_D = -36.8^o$ (*c* 0.65, $CHCl_3$).

(Table 2.1, Entry 14)

(*E,E*)-7-Methyl-4-phenyl-2,4-octadienoic acid ethyl (2-22)(MF 544). The TBS ether was prepared according to the procedure provided for **2-11** to give product as a colorless oil (1.34 g, 75.0%). ^{1}H NMR showed >19/1 selectivity for the E olefin. IR (NaCl): 1712, 1622, 1301 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 15.6 Hz, 1H), 7.40 – 7.25 (m, 3H), 7.09 – 7.05 (m, 2H), 6.15 (t, J = 7.2 Hz, 1H), 5.36 (d, J = 15.6 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.91 (dd, J = 7.2 Hz, 2H), 1.68 (septet, J = 7.2 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.84 (d, J = 7.2 Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 148.8, 141.9, 140.7, 136.8, 129.4, 128.4, 127.3, 118.7, 60.18, 38.63, 28.67, 22.41, 14.31.

(*R,R*)-2-Phenyl-2-[*trans*-2-(ethoxycarbonyl)vinyl]-3-isobutyloxirane (MF648). Colorless oil; IR (NaCl): 1720, 1651, 1303 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 7.06 (d, J = 15.6 Hz, 1H), 5.93 (d, J = 15.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.21 (dd, J = 6.9, 4.8 Hz, 1H), 1.76 (septet, J = 6.9 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.21 (ddd, J = 6.9, 4.8 Hz, 1H), 1.00 (dt, J = 7.2, 6.9 Hz, 1H), 0.89 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 148.3, 135.1, 128.3, 127.9, 122.9, 67.15, 63.30, 60.53, 37.62, 26.43, 22.65, 22.54, 14.21.

(Table 2.1, Entry 15).

(*E,E*)-2,-Methyl-octadienoic acid ethyl (2-25)(MF1112). To a solution of 2-(carbethoxyethyl)triphenylphosphonium bromide (10.84 g, 24.5 mmol) in THF (15 mL) at 0 °C was added n-BuLi (20.4 mmol, 51 mmol, 2.5 M in hexanes) and the resulting slurry was stirred for 1 h at 0 °C. *Trans*-2-hexenal (2.0 g, 20.4 mmol) was then added

dropwise and the solution was stirred at room temperature for 3 h. The reaction was quenched with H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 X 20 mL). The combined organics were washed with brine (1 X 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude product in a 18/1 ratio of *E/Z* olefin. The oil was purified by flash column chromatography (200/1 hexanes/Et_2O) to give the pure *E,E*-diene as a colorless oil (1.29 g, 34.7 % yield). IR (NaCl): 2960, 2931, 2872, 1705, 1641, 1610, 1464, 1389, 1367, 1291, 1238, 1167, 1103, 1038, 971, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 11.1 Hz, 1H), 6.34 (dd, J = 15.0, 11.1 Hz, 1H), 6.06 (dt, J = 15.0, 7.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.18 (dt, J = 7.2, 6.6 Hz, 2H), 1.93 (s, 3H), 1.55-1.40 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 142.7, 138.4, 126.0, 124.9, 60.35, 35.30, 22.17, 14.33, 13.67, 12.53.

(*R,R*)-2-[(*E*)-2-(Ethoxycarbonyl)-2-methylvinyl]-3-propyloxirane (MF1303). Colorless oil; $[\alpha]^{20}_D$ = + 40.6° (*c* 1.61, $CHCl_3$); IR (NaCl): 2962, 2934, 2874, 1714, 1654, 1465, 1368, 1311, 1253, 1236, 1160, 1103, 1033, 976, 914, 858, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J = 8.4 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.38 (dd, J = 8.4, 1.8 Hz, 1H), 2.96 (td, J = 5.7, 1.8 Hz, 1H), 2.00 (s, 3H), 1.65 - 1.40 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 137.9, 132.0, 60.72, 59.99, 54.43, 33.91, 19.19, 14.17, 13.84, 12.75. Anal calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.77; H, 8.96.

(Table 2.1, Entry 16)

(*E,E*)-2,4-Dimethylheptadienoic acid ethyl ester (2-26)(MF1044). The diene was prepared according to the procedure provided for **2-25** to give the olefin as a 19/1 ratio of *E/Z* olefins as a colorless oil (1.52 g, 91.1% yield). IR (NaCl): 2966, 2933, 2872, 1703,

1626, 1456, 1364, 1246, 1108, 1031, 1010, 923, 872, 749, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.62 (t, J = 7.2 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 2.15 (septet, J = 6.9 Hz, 2H), 2.01 (s, 3H), 1.84 (s, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 142.8, 138.2, 131.4, 124.9, 60.40, 21.63, 16.03, 14.26, 13.89, 13.66.

(*R,R*)-2-[(E)-2-(Ethoxycarbonyl)-2-methylvinyl]-3-ethyl-2-methyloxirane (MF1246). $[\alpha]^{20}_D$ = -90.7° (*c* 1.63, $CHCl_3$) [lit.[28b] $[\alpha]^{23}_D$ = +78.3° (*c* 1.15, $CHCl_3$) for (*S,S*)]

Absolute Configuration Study

(*R,R*)-*Trans*-3-phenyloxiranemethanol (2-30)(MF813).[33] To a solution of (*R,R*)-2-phenyl-3-(*trans*-2-phenylvinyl)oxirane (30.6 mg, .13 mmol) in a solution of t-BuOH/THF/H_2O (0.8 mL, 10/3/1, v/v/v) was added OsO_4 (3 mg, 0.01 mmol) and 4-methylmorpholine-N-oxide (32.4 mg, 0.28 mmol), and the flask was placed under nitrogen atmosphere. The resulting off-yellow solution was stirred for 0.75 h, at which time $NaHCO_3$ (57.5 mg, 0.69 mmol) and $NaIO_4$ (87.9 mg, 0.41 mmol) were added and the suspension was stirred for an additional 1.5 h. H_2O (1 mL) and CH_2Cl_2 (1 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 3 mL) and the combined organics were washed with brine (1 X 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude product. The oil was purified by flash column chromatography (CH_2Cl_2) to give the alcohol (3.2 mg, 7.8%). ^1H NMR (300 MHz, $CDCl_3$)[34] δ 7.45 – 7.20 (m, 5H), 4.18 (dd, J = 13.0, 3.0 Hz, 1H), 3.95 (d, J = 3 Hz, 1H), 3.81 (d, J = 13.0 Hz, 1H), 3.30 – 3.25 (m, 1H), 1.75 (br s, 1H). The sample was compared to an authentic sample prepared via the Sharpless asymmetric epoxidation by

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chiral HPLC (Chiralcel OD, 8/2 Hexanes/IPA, 0.8 mL/min) and proved to be the (2*S*, 3*R*) enantiomer, thus confirming the spiro transition state.

***Trans*-2-methyl-2-penten-1-ol** (2–31)**(MF814)**. To a solution of the *trans*-2-methyl-2-pentenal (2.0 g, 20.4 mmol) in MeOH (100 mL) at 0 °C was added $NaBH_4$ (1.16 g, 30.6 mmol) portionwise over 1 h. The suspension was warmed to room temperature and stirred for an additional 1 hour. The reaction was then quenched with H_2O (2 mL) and the MeOH was removed under reduced pressure. The white suspension was then taken up in H_2O (20 mL) and CH_2Cl_2 (20 mL) and the layers were separated. The combined organics were washed with brine (1 X 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude product. The oil was purified by flash column chromatography (1/1 hexanes/Et_2O) to give the alcohol as a colorless oil (1.59 g, 78.1%). IR (NaCl): 3329, 1671, 1304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[34] δ 5.40 (dt, J = 6.9, 1.5 Hz, 1H), 3.99 (d, J = 6.0, Hz, 2H), 2.05 (septet, J = 7.2 Hz, 2H), 1.73 – 2.64 (m, 4H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 128.1, 68.91, 20.83, 13.96, 13.43.

(*R*,*R*)-*Trans*-3-ethyl-2-methyloxiranemethanol (2–32)**(MF819).** The epoxide was prepared using the general epoxidation procedure with 30 mol% ketone. The absolute configuration of the epoxide was confirmed by comparing the optical rotation to the known rotation for the (2*S*, 3*S*) epoxy alcohol. $[\alpha]^{20}_D$ = +14.9° (c 1.49). lit[35] $[\alpha]^{22}_D$ = + 14.2° (c 1.02, $CHCl_3$). IR (NaCl): 3418, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[34]

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δ 3.67 (dd, J = 12.0, 4.2 Hz, 1H), 3.55 (dd, J = 12.0, 7.8 Hz, 1H), 2.99 (t, J = 6.9 Hz, 1H), 2.65 – 2.50 (m, 1H), 1.70 – 1.50 (m, 2H), 1.29 (s, 3H), 1.04 (t, J = 7.8 Hz, 3H). The epoxy alcohol was converted to (*R,R)*-2-[*trans*-2-(ethoxycarbonyl)vinyl]-3-ethyl-2-methyloxirane, which proved to be enriched with the same enantiomer as the sample from the direct monoepoxidation of **2-18** by chiral HPLC (Chiralcel OD, 95/5 Hexane/IPA, 1.0 mL/min).

Additional Examples

(*E,E*)-4-Phenyl-2,4-butadienoic acid ethyl ester (2-16)(MF542). The diene was prepared by Wittig reaction of *trans*-cinnamaldehyde according to the procedure provided for **2-15** to give product as a yellow oil (956 mg, 67.6%). IR (NaCl): 1960, 1886, 1704, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 6H), 6.88 (m, 2H), 5.99 (d, J = 15.3 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 144.4, 140.3, 136.0, 129.0, 128.7, 127.1, 60.26, 14.28.

***(R,R)*-2-[*trans*-2-(ethoxycarbonyl)vinyl]-3-phenyloxirane (MF625)**. Colorless oil; (98% ee, chiral HPLC, Chiralcel OD column, 95/5 Hexane/IPA, 1.0 mL/min elution). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 5H), 6.81 (dd, J = 15.6, 6.9 Hz, 1H), 6.19 (d, J = 15.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.83 (d, J = 1.8 Hz, 1H), 3.48 (ddd, J = 6.9, 1.8, 0.9 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H).

(*E,E*)-4-(2-methoxyphenyl)-2,4-butadienoic acid ethyl ester (2-17)(MF630). The diene was prepared by Wittig reaction with 2-methoxy-*trans*-cinnamaldehyde according to the procedure provided for **2-15** to give product as a white solid (642 mg, 39.5%). IR (NaCl): 1708, 1621, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 2H), 7.30 – 7.23 (m, 1H), 7.25 (d, J = 15.6 Hz, 1H), 6.95 – 6.85 (m, 3H), 5.96 (d, J = 15.6 Hz, 1H),

4.22 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 157.4, 145.5, 135.5, 130.1, 127.3, 126.8, 125.0, 120.7, 120.6, 111.0, 60.17, 55.45, 14.31.

(*E*,*E*)-5-Methyl-3-phenyl-2,4-heptadienoic acid ethyl ester (2-23)(MF543). The diene was prepared by Wittig reaction with (*E*)-4-methyl-2-phenyl-2-pentenal according to the procedure provided for **2-15** to give product as a yellow oil (6.10 g, 67.7%). IR (NaCl): 1712, 1623, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 15.3 Hz, 1H), 7.40 – 7.25 (m, 4H), 7.12 – 7.06 (m, 1H), 5.92 (d, J = 9.9 Hz, 1H), 5.36 (d, J = 15.3 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 2.29 (d of septets, J = 9.9, 6.9 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 149.5, 148.9, 137.8, 136.8, 129.1, 128.4, 127.3, 119.0, 60.13, 28.71, 22.51, 14.27.

(*E*,*E*)-3-Methyl-4-phenyl-2-4-pentadienoic acid ethyl (2-24)(MF737). The diene was prepared by Wittig reaction with α-methyl-*trans*-cinnamaldehyde according to the procedure provided for **2-15** to give product as a yellow oil (4.72 g, 64.2%). IR (NaCl): 1711, 1620, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 15.6, 1H), 7.41 – 7.25 (m, 5H), 6.85 (s, 1H), 6.00 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.05 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 149.7, 138.8, 136.7, 134.1, 129.4, 128.3, 127.7, 117.6, 60.27, 14.31, 13.67.

(*E*,*E*)-4-Methyl-2,4-heptadien-1-ol (2-27)(MF1333). The alcohol was prepared by DIBAL reduction of ester **2-26** according to the procedure provided for **2-19** to give product as a light yellow oil (374 mg, 95.4%).

(*E,E*)-1-(*tert*-Butyldimethylsilyloxy)-4-methyl-2,4-heptadiene (2-28)(MF1335). The TBS ether was prepared from **2-27** according to the procedure provided for **2-11** to give product as a colorless oil (612 g, 90.9% yield). IR (NaCl): 1630, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.32 (t, J = 7.2 Hz, 1H), 4.06 (s, 2H), 2.11 (quintet, J = 7.2 Hz, 2H), 1.76 (s, 6H), 1.01 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8, 131.9, 131.7, 128.1, 69.14, 26.08, 25.97, 21.55, 18.55, 16.84, 15.16, 14.32, -5.10.

Epoxide (2-35)(MF1337). Colorless oil; IR (NaCl): 1630, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (d, J = 0.6 Hz, 1H), 3.98 (s, 2H), 2.82 (t, J = 6.3 Hz, 1H), 1.67 (d, J = 0.6 Hz, 3H), 1.62 (m, 2H), 1.34 (s, 3H), 1.08 (t, J = 7.5 Hz, 3H), 0.91 (s, 9H), 0.59 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 124.6, 67.38, 62.59, 60.92, 34.70, 25.93, 22.22, 18.41, 14.40, 13.69, -5.25.

(*E,E*)-1-(*tert*-Butyldiphenylsilyloxy)-4-methyl-2,4-heptadiene (2-29)(MF1405) The TBDPS ether was prepared from **2-27** according to the procedure provided for **2-11** with TBDPSCl to give product as a colorless oil (2.96 g, 97.9% yield). IR (NaCl): 1957, 1888, 1822, 1653, 1589, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 4H), 7.45 – 7.35 (m, 6H), 5.95 (s, 1H), 5.31 (t, J = 7.2 Hz, 1H), 4.08 (s, 2H), 2.10 (quintet, J = 7.2 Hz, 2H), 1.74 (s, 6H), 1.07 (s, 9H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.8, 133.3, 131.8, 131.7, 129.5, 128.0, 127.5, 69.40, 26.92, 21.52, 19.40, 16.85, 15.19, 14.29.

Epoxide (MF1410). Colorless oil; IR (NaCl): 1960, 1890, 1824, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 4H); 7.46 – 7.30 (m, 6H), 5.75 (s, 1H), 4.01 (s, 2H), 2.81 (t, J = 6.6 Hz, 1H), 1.65 (s, 3H), 1.67 – 1.55 (m, 2H), 1.34 (s, 3H), 1.08 (t, J = 7.2

Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 135.5, 133.6, 129.6, 127.6, 125.0, 67.89, 65.60, 59.37, 26.88, 22.20, 19.32, 18.03, 14.39, 10.60.

Bisepoxidation

***Trans*-2'-(*trans*-3-phenyloxirane)-3'-phenyloxirane (*Cis* 2-34) (MF1641).** ^1H NMR (300 MHz, aceone-d_6); Colorless oil; δ 7.41 (m, 10H), 3.26 (dd, J = 1.2, 0.6 Hz, 2H), 4.06 (s, 2H).

***Trans*-2'-(*trans*-3-phenyloxirane)-3'-phenyloxirane (*Trans* 2-34) (MF1642).** white solid; ^1H NMR (300 MHz, aceone-d_6) δ 7.41 (m, 10H), 4.05 (s, 2H), 3.32 (t, J = 0.6 Hz, 2H).

Trans-(3'-Ethyl-3,2'-dimethyl-[2,2']dioxiranyl-3-yl-methoxy)-*tert*-butyldimethylsilane (*Cis*-2-36) (MF1535). Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (d, J = 14.7 Hz, 1H), 3.56 (d, J = 14.7 Hz, 1H), 3.07 (s, 1H), 1.68 – 1.54 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.64 (s, 3H), 0.53 (s, 3H).

***Trans*-(3'-Ethyl-3,2'-dimethyl-[2,2']dioxiranyl-3-yl-methoxy)-*tert*-butyldimethylsilane (*Trans*-2-36) (MF1534).** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.61 (d, J = 13.5 Hz, 1H), 3.58 (d, J = 13.5 Hz, 1H), 3.19 (s, 1H), 3.10 (t, J = 6.3 Hz, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.66 – 1.48 (m, 2H), 1.38 (t, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.67 (s, 3H), 0.06 (s, 3H).

(*E*,*E*)-2,4-Dimethyl-2,4-hexadienoic acid ethyl ester(2-37)(MF1428). The diene was prepared by Wittig reaction of (*E*)-2-methyl-2-butenal according to the procedure provided for **2-15** to give product as a colorless oil (4.24 g, 53.0%). IR (NaCl): 1706, 1626, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.71 (q, J = 7.2 Hz, 1H), 4.21 (qd, J = 6.9 Hz, 2H), 2.00 (s, 3H), 1.84 (s, 3H), 1.74 (d, J = 7.2 Hz, 3H), 1.30 (t, J =

6.9 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 142.7, 132.9, 130.6, 124.7, 60.38, 15.88, 14.25, 13.91.

(*E,E*)-2,4-(Dimethyl)hexadienal (2-38)(MF2432, 1439). The alcohol was prepared by DIBAL reduction of ester **2-37** according to the procedure provided for **2-19** to give product as a light yellow oil (2.95 g, 94.7%) as a 15/1 *E/Z* mixture. IR (NaCl): 3323, 1652, 1009 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.41 (q, J = 6.9 Hz, 1H), 4.02 (d, J = 5.7 Hz, 2H), 2.00 (s, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8, 132.9, 129.4, 124.5, 69.42, 16.47, 15.31, 13.66.
To a solution of distilled oxalyl chloride (4.30 g, 33.9 mmol) in CH_2Cl_2 (300 mL) at –78 °C was added distilled dimethylsulfoxide (DMSO) (3.53 g, 45.2 mmol) dropwise over 5 m. The solution was stirred at –78 °C for 15 m and the alcohol (2.85 g, 22.6 mmol) was added as a solution in CH_2Cl_2 (60 mL). The solution was stirred at –78 °C for 1 h, at which time NEt_3 (11.4 g, 113 mmol) was added via syringe. After 1 h at –78 °C the product was partitioned between H_2O (200 mL) and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 200 mL), the combined organics were washed with brine (1 X 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was filtered through a plug of silica gel (1/1 hexanes/ Et_2O) to give the aldehyde as a light yellow oil (2.71 g, 96.6%). IR (NaCl): 1685, 1623 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.73 (s, 1H), 5.99 (q, J = 6.9 Hz, 1H), 1.98 (s, 3H), 1.96 (s, 3H), 1.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 154.9, 135.5, 134.9, 134.0, 15.61, 14.40, 10.63.

(*E,E,E*)-2,4,6-Trimethyl-2,4,6-octatrienoic acid ethyl ester (2-39)(MF1442). The diene was prepared by Wittig reaction of aldehyde **2-38** according to the procedure

provided for **2-15** to give product as a colorless oil (1.38 g, 30.0%). IR (NaCl): 1705, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.03 (s, 1H), 5.54 (q, J = 6.9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.99 (s, 3H), 1.79 (s, 3H), 1.73 (d, J = 6.9 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 144.0, 139.1, 133.1, 130.9, 126.9, 125.4, 60.55, 18.32, 16.57, 14.40, 14.17, 13.92.

(2*R*,3*R*)-5-(2,3-Dimethyloxiranyl)-2,4-(dimethyl)pentadienoic acid ethyl ester (2-40)(MF1514). The epoxide was prepared using the standard epoxidation conditions described above with 30 mol% **ent 1-26**. IR (NaCl): 1708, 1627, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.78 (s, 1H), 4.20 (q, J = 6.9 Hz, 2H), 3.02 (q, J = 5.7 Hz, 1H), 1.99 (s, 3H), 1.89 (s, 1H), 1.39(d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.36 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 141.1, 134.9, 134.0, 127.3, 60.71, 60.09, 59.07, 17.70, 17.57, 14.32, 14.11, 14.00.

2-Methyl-3-[3,2',3'-trimethyl-(2,2')dioxiranyl-3-yl]-acrylic acid ethyl ester (2-41)(MF1526). (*Trans* bisepoxide) colorless oil; IR (NaCl): 1714, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.21 (q, J = 5.7 Hz, 1H), 3.16 (s, 1H), 1.91 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.27 (d, J = 5.7 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 134.5, 125.6, 59.29, 59.22, 56.37, 54.97, 54.87, 51.43, 12.89, 10.50, 9.67, 8.79.

CHAPTER THREE

KINETIC RESOLUTION OF RACEMIC OLEFINS VIA CHIRAL DIOXIRANES

3.A. INTRODUCTION

Kinetic resolution is a powerful method for obtaining chiral, nonracemic compounds in high optical purity. This process involves a reaction in which one enantiomer of a racemic mixture is transformed into product while the other enantiomer is left unreacted. Chiral reagents or a chiral catalyst may be used, although most successful approaches use the latter. This constitutes a unique approach when compared to traditional resolutions, in which both enantiomers are typically transformed into a pair of diastereomers and then are separated by crystallization or chromatography.

The effectiveness of a kinetic resolution is maximized when the starting material is readily available since, at best, 50% yield of a single enantiomer can be obtained. This fact sometimes can limit its potential applications. However, the process involves differential reaction rates due to inherent energy differences of diastereomeric transition states. This force is inherent regardless of the extent of reaction, and can be relied on to prepare compounds of very high optical purity, even when differences in rates of reaction

are small (provided that a diminished yield is acceptable). Therefore, kinetic resolution can many times be the only way to prepare compounds in *optically pure* form (>99% ee).

3.A.1. Kinetic Theory

Kinetic resolutions are critically dependent on the relative rates of reaction of the two starting enantiomers. Therefore, kinetic theory can be used to derive equations that relate the ee of recovered starting material, conversion, and the relative rates of reaction of each eantiomer (k_{rel}).[1] A kinetic resolution that uses a chiral catalyst can be represented by equations **3.1** and **3.2**, where *R* represents the (*R*) enantiomer and *S* represents the (*S*) enantiomer.

$$R \xrightarrow{k_R} P \qquad \text{(eq. 3.1)}$$

$$S \xrightarrow{k_S} Q \qquad \text{(eq. 3.2)}$$

If *C* is the conversion ($0 < C < 1$), then the amount of recovered starting material at any time during the reaction is $[R] + [S] = 1\text{-}C$. The definition of enantiomeric excess is as follows: $ee = ([S]-[R])/([S]+[R])$ ($ee > 0$ if $k_R > k_S$, which would leave (*S*) as the unreacted starting material). If equations **3.1** and **3.2** are combined with the definition of ee, the resulting equations **3.3** and **3.4** may be used to calculate the amount of (*R*) and (*S*) from the measured conversion and ee of the starting material.

$$[S] = \frac{(1-C)(1+ee)}{2} \qquad \text{(eq. 3.3)}$$

$$[R] = \frac{(1-C)(1-ee)}{2} \qquad \text{(eq. 3.4)}$$

[1] This kinetic treatment was taken from: Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* **1988**, *18*, 249.

When **3.1** and **3.2** are pseudo first order in (*R*) and (*S*) and the chiral source is a catalyst, then the simple relations **3.5** and **3.6** are also true.

$$\frac{d[R]}{dt} = -k_R[R] \qquad \text{(eq. 3.5)}$$

$$\frac{d[S]}{dt} = -k_S[S] \qquad \text{(eq. 3.6)}$$

Integrating equations **3.5** and **3.6** followed by combination of the two gives equation **3.7**, which defines k_{rel}.

$$k_{rel} = \frac{k_R}{k_S} = \frac{\ln([R]/[R_0])}{\ln([S]/[S_0])} \qquad \text{(eq. 3.7)}$$

By substituting for [R] and [S] with eq.'s **3.3** and **3.4**, and by assuming that R_0 and S_0 are equal to 0.5 (we begin the reaction with a racemic mixture), **3.7** can be expressed as **3.8**.

$$k_{rel} = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} \qquad \text{(eq. 3.8)}$$

Equation **3.8** becomes the fundamental equation for any kinetic resolution study since the k_{rel} can be calculated from the measurable quantities of conversion and enantiomeric excess (*ee*) of the recovered starting material. Equation **3.8** also shows that k_{rel} is independent of the conversion.

In addition, if the products of the kinetic resolution are themselves chiral, then an analogous equation can be derived to calculate k_{rel} from the ee of the product (*ee'*) and the conversion (equation **3.9**). Importantly, the reaction must be completely or highly diastereoselective for this equation to hold.

$$k_{rel} = \frac{\ln[1 - C(1 + ee')]}{\ln[1 - C(1 - ee')]} \qquad \text{(eq. 3.9)}$$

Combination of eq.'s **3.8** and **3.9** and further manipulation results in eq. **3.10**, which expresses the conversion as a function of ee and ee'.

$$\frac{ee}{ee'} = \frac{C}{1 - C} \qquad \text{(eq. 3.10)}$$

Equations **3.8 – 3.10** are the three main equations used in kinetic resolution studies since k_{rel} can be calculated using either the ee of starting material (eq **3.8**) or product (eq **3.9**), and the experimentally determined conversion can be cross-checked by measuring the ee of both the starting material and the product (eq. **3.10**).

The consequences of these equations can be more easily seen by graphical representation. Figure 3.1 shows the dependence of starting material and product ee on the extent of reaction for k_{rel} 7.[1] As expected, the ee of the starting material is low at low conversion, increases dramatically at moderate conversions, and then levels off. The opposite behavior for the ee of the product(s) is observed. Figure 3.2[2] shows plots of the ee of the starting material as a function of conversion. As can be seen, the slope of the curve increases as the k_{rel} increases. Interestingly, the physical manifestation of a k_{rel} = 25 is very close to the theoretical maximum. A typical benchmark for the performance of a kinetic resolution is k_{rel} = 10, since this will provide recovered starting material with 90% ee at about 60% conversion and ee of >99% at about 72% conversion.

[2] This figure was reproduced from Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

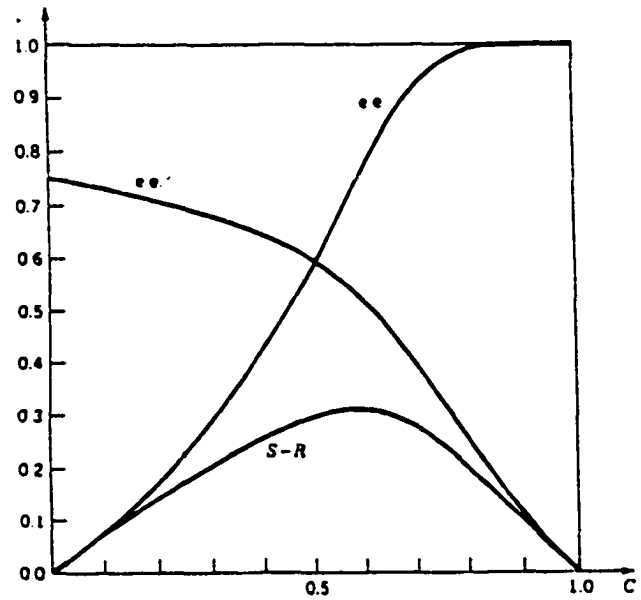

Figure 3.1 Ee of starting material and product for a k_{rel} of 7.

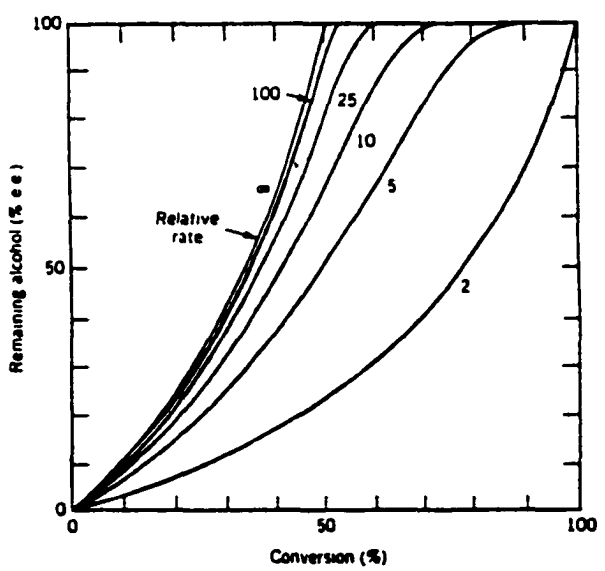

Figure 3.2 Ee of recovered starting material for a variety of k_{rel} values.

3.A.2. Existing Methods

The first chemical kinetic resolution was reported in 1899 when the partial esterification of (-)-mandelic acid with (-)-menthol was observed.[3] The first detailed kinetic study was performed on the alkaloid-mediated asymmetric decarboxylation of camphorcarboxylic acid in the early 20th century.[4] In spite of its early recognition, progress in kinetic resolutions mediated or catalyzed by chiral nonracemic chemicals was elusive compared to those that employ enzymatic processes.[5] However, transition metal catalyzed kinetic resolutions have made tremendous progress since the early 1980's, and the kinetic resolution of chiral olefins has enjoyed much success.

Sharpless and coworkers reported the first highly efficient chemical kinetic resolution of acyclic secondary allylic alcohols using a titanium tartrate complex.[6] They later achieved catalytic activity of the metal complex, and a k_{rel} of up to 700 can be achieved with this system (eq. **3.11**).[7] Except for a few cases, the process is general for acyclic secondary allylic alcohols, and either antipode of the starting material can be obtained since both antipodes of the tartrate ligand are readily available. Unfortunately, cyclic alcohols are resolved poorly by this system because coordination of the alcohol to

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[3] Marckwald, W.; McKenzie, A. *Chem. Ber.* **1899**, *32B*. 2130.

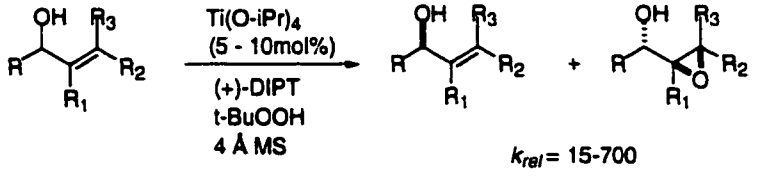
[4] Bredig, G.; Fajans, K.*Ber. Dtsch. Chem. Ges.* **1908**, *41*, 752. (b) Fajans, K. *Z. Phys. Chem.* **1910**, *73*, 25.

[5] (a) For some examples, see: Sih, C.J.; Wu, S.-H. *Topics Stereochem.;* Eliel, E.L. and Wilen, S.H. Eds.; John Wiley & Sons: New York, **1989**, 63. (b) Chen, C.S.; Sih, C.J.; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695. (c) Klibanov, A.M. *Acc. Chem. Res.* **1990**, *23*, 114. (d) Drueckhammer, D.G.; Hennan, W.J.; Pederson, R.L.; Barbas, C.F. III, Gautheron, C.M.; Krach, T.; Wong, C.H. *Synthesis* **1991**, 499. (e) Heraldsson, G.G. In *The Chemistry of Functional Groups, Suppl. B: The Chemistry of Acid Derivatives*; Patai, S.; Ed.; John Wiley & Sons: Chichester, **1992**, 1395.

[6] See ref 2. For a review of this chemistry, see Katsuki, T.; Martin, V.S. *Org. Rxn.* **1996**, *48*, 1.

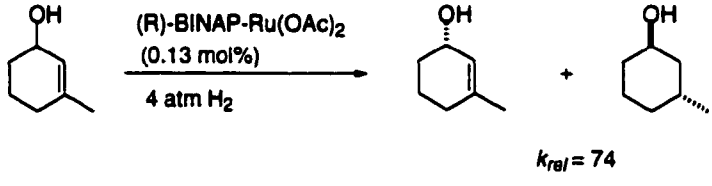
[7] (a) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Kitano, Y.; Matsumoto, T.; Sato, F. *J. Chem. Soc. Chem. Commun.* **1986**, 1323. (c) Kitano, Y.; Matsumoto, T.; Takeda, Y.; Sato, F. *J. Chem. Soc. Chem. Commun.* **1986**, 1732.

the titanium center reduces the stereochemical communication between these olefins and the chiral element.



(eq. **3.11**)

Alternatively, the kinetic resolution of some cyclic alcohols proceeds well via hydrogenation with Noyori's Ruthenium (BINAP) catalyst.[8] This system relies on catalyst pre-coordination to the alcohol in order to direct reduction *syn* to the alcohol, and therefore results in the *trans* alcohol product. An example of its high resolution efficiency is given in equation **3.12**. As in the previous case, both enantiomers of the alcohol can be made since both enantiomers of the binaphthyl ligand are available.

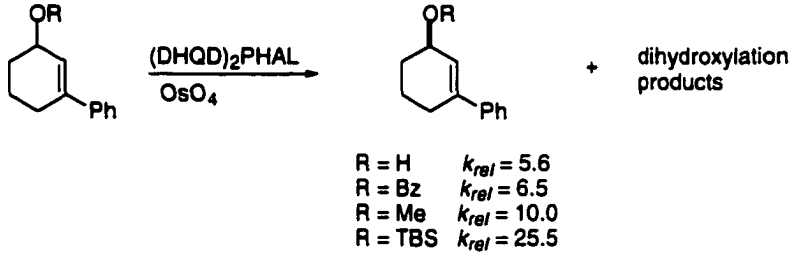


(eq. **3.12**)

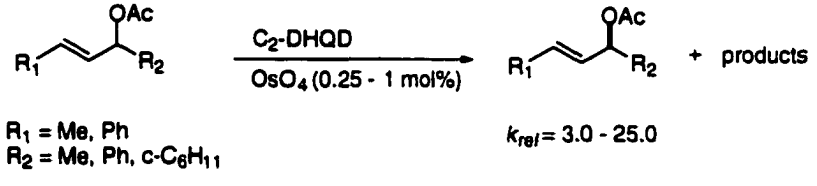
Other systems that efficiently resolve certain classes of olefinic substrates have also been discovered.[9] For example, Sharpless's cinchona-alkaloid-mediated asymmetric dihydroxylation reaction resolves two separate olefinic systems with useful levels of selectivity. First, 1,3-disubstituted cyclohexene derivatives can be resolved effectively if

[8] Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 710.
[9] Hoveyda, A.H.; Didiuk, M.T. *Curr. Org. Chem.* **1998**, *2*, 489.

the 1-substituent is a phenyl group (eq. **3.13**).[10] The size of the protecting group on the alcohol significantly influences the selectivity, with the larger group giving better results. The use of (dihydroquinidine)$_2$phthalazine as the chiral source leads to the recovery of the (*R*) enantiomer of the olefin. Secondly, acyclic allylic acetates are also good substrates if the chiral source is made C_2 symmetric by replacing the phthalazine unit by a 1,4-bisbenzoic acid molecule (eq. **3.14**).[11] One drawback is that the use of dihydroquinine ligands, which gives reaction with the opposite sense of steroinduction, has not been reported to date.



(eq. **3.13**)



(eq. **3.14**)

Cyclic allylic ethers are efficiently resolved using Hoveyda's titanium catalyzed carbomagnesation protocol. Dihydrofuran,[12] dihydropyran[13] (eq. **3.15**), and their seven

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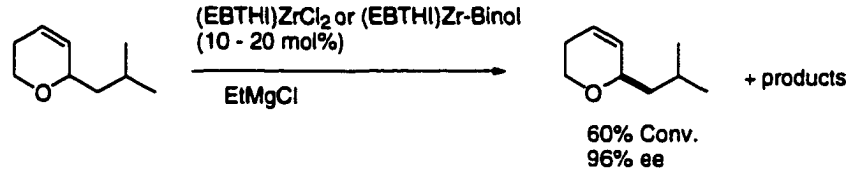
[10] For kinetic resolution of related systems using asymmetric dihydroxylation see: Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, pp2503.

[11] Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* **1993**, *34*, 3911.

[12] Visser, M.S.; Hoveyda, A.H. *Tetrahedron*, **1995**, *51*, 4383.

[13] Morken, J.P.; Didiuk, M.T.; Visser, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1994**, *116*, 3123.

membered ring counterparts[14] are resolved well in many cases. In addition, cyclohexenol, cycloheptenol, and cyclooctenol derivatives are also resolved well.[15] The significance here lies in the fact that not many resolution processes can be extended beyond 5 and 6-membered rings, and so this would be the method of choice for the efficient chemical resolution of these molecules.



(eq. **3.15**)

One final method for the resolution of olefins involves the molybdenum catalyzed asymmetric ring-closing metathesis developed by Hoveyda, Schrock and coworkers.[16] When 1,6-dienes are used as substrates, and the reaction is stopped at partial conversion to the cyclopentene product, k_{rel}'s of up to 58 are observed (eq. **3.16**). This case is unique in the fact that the olefin is the product rather than starting material, but this is not important since control of conversion enables one to access either starting material or product in high optical purity in any efficient resolution. The process is not as efficient for the formation of six membered rings, as k_{rel}'s of 4 and 11 have been reported in those cases, but theses values can still be synthetically useful.

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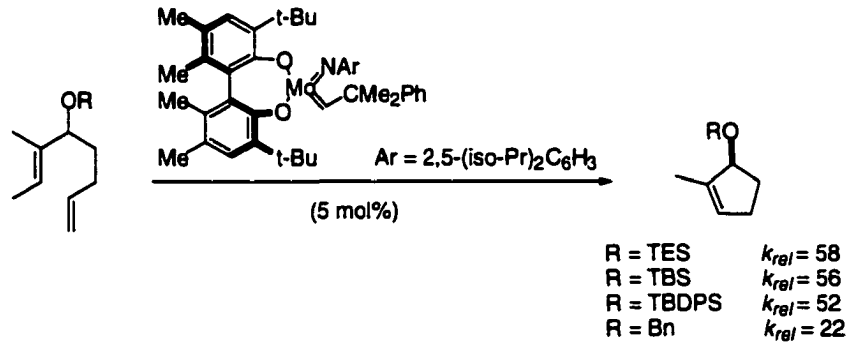
[14] See ref 8.

[15] For the resolution of a cycloheptenol derivative, and its application to the synthesis of (*S,R,R,R*)-Nebivolol, see: Harrity, J.P.A.; Visser, M.S.; Gleason, J.D.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1997**, *119*, 1488. Also see ref 8.

[16] Alexander, J.B.; La, D.S.; Cefalo, D.R.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.



(eq. **3.16**)

Overall, great progress in the area of kinetic resolution of chiral olefins has been achieved. Acyclic allylic alcohols are available through Sharpless asymmetric epoxidation, and to a lesser extent the Sharpless Asymmetric Dihydroxylation. Cyclic olefins can be accessed either with Sharpless Asymmetric Dihydroxylation, Noyori's asymmeric hydrogenation, or Hoveyda's zirconium catalyzed carbomagnesation. However, even though progress has been brisk in this area, there is still a wide range of olefins (and other types of racemic molecules) that elude resolution with the existing methods. Therefore, there is an impetus for additional research in this area.

We thought that an efficient kinetic resolution process via chiral dioxiranes might be feasible using fructose-derived ketone **1-28** as catalyst and Oxone as oxidant. The epoxidation proceeds primarily through a well-ordered spiro transition state **A** (Figure 3.3). Since dioxiranes are expected to be sensitive to sterics, an existing chiral center adjacent to the double bond provides the possibility for kinetic resolution.[17] The following details the studies that have been undertaken in this area.

[17] (a) Vander Velde, S.L.; Jacobsen, E.N. *J. Org. Chem.* **1995**, *60*, 5380. (b) Noguchi, Y.; Irie, R.; Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, 37, 4533. see also, references 4-7.

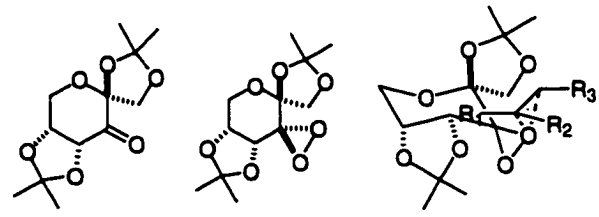


Figure 3.3 Favored Spiro transition state for fructose derived ketone **1-28**.

3.B. RESULTS AND DISCUSSION

3.B.1. 1,6-Disubstituted Cyclohexenes

The initial studies focused on cyclic olefins with the chiral center at the allylic position. The rigid conformation and proximity of the chiral center to the olefin make them promising candidates for kinetic resolution (Figure 3.4). Transition states **B** and **C** represent the spiro transition states for the epoxidation of each enantiomer. Transition state **C** is expected to be disfavored compared to transition state **B** due to the steric interaction between R_2 and one of the dioxirane oxygens. Therefore, 1,6-disubstituted cyclohexenes were intensively studied, and the synthesis of these starting materials is shown in Scheme 3.1.

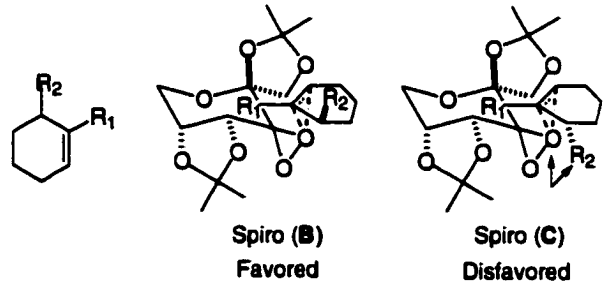
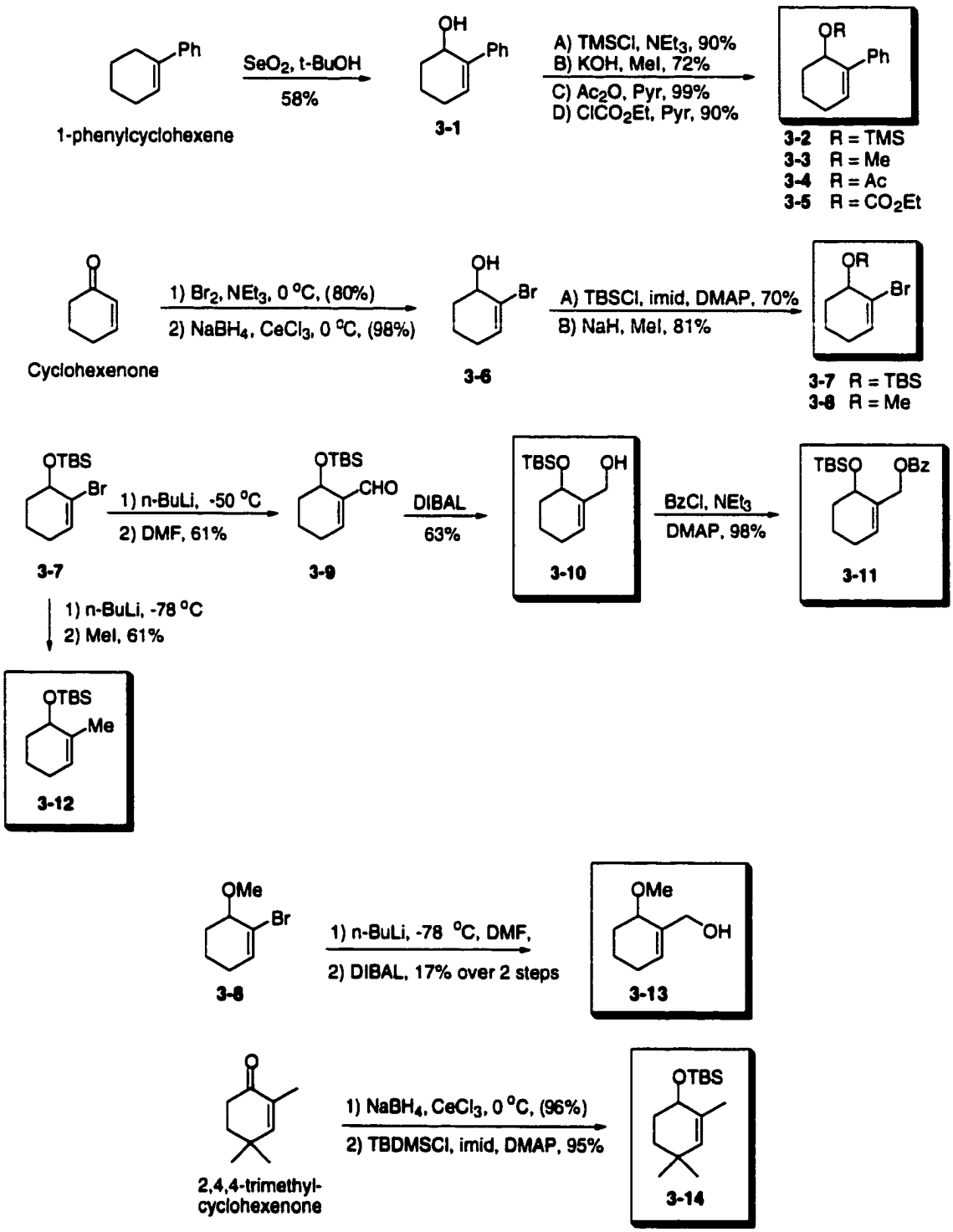


Figure 3.4 Spiro transition states for 1,6-disubstituted cyclohexenes.



Scheme 3.1

Cyclic olefins with a small group at the R_1 position (Figure 3.4) accommodate the spiro transition state very well and hence give high enantioselectivity in the epoxidation (ie. 1-phenylcyclohexene gives 97% ee). Therefore, placing a chiral center at the allylic position of this scaffold provides a good origin for investigation; so phenyl substituted derivatives **3-2 – 3-5** were synthesized from 1-phenylcyclohexene by allylic oxidation with SeO_2[18] followed by protection of the resulting alcohol, all in good yield. Alternatively, vinyl bromides **3-7** and **3-8** were prepared from cyclohexenone by bromination,[19] Luche reduction,[20] and protection, all in good to high yield. These intermediates were prepared with the idea that the bromide could be used as a handle to prepare derivatives with a variety of substituents at the R_1 position. The TBS derivative was subjected to lithium-halogen exchange followed by reaction with DMF to give the unsaturated aldehyde **3-9**, and methylated with MeI to give **3-12**. The aldehyde was reduced to give alcohol **3-10** and then protected as the benzoate **3-11**. The methoxy derivative was also formylated and reduced to the alcohol to give **3-13**. Lastly, 2,4,4-trimethylcylohexenone was reduced and protected to test the effect of a bulkier group (vs. **3-12**) at the 4 position. It was anticipated that the gem-dimethyl group would disfavor the competing planar transition state and hence increase resolution efficiency. Many of these derivatives proved to be good substrates in the kinetic resolution (Table 3.1).

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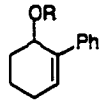
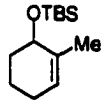
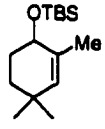
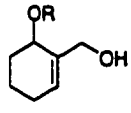
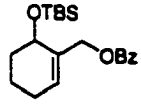
[18] Mousseron, M.; Jacquier, R. *Bull. Chim. Soc. Fr.* **1952**, 467.

[19] Smith, A. B., III; Branca, S.J.; Pilla, N.N.; Guaciaro, M.A. *J. Org. Chem.* **1982**, *47*, 1855.

[20] Gemal, A.L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Table 3.1. Kinetic Resolution of Representative 1,6-Disubstituted Cyclohexenes by Ketone **1-28** Catalyzed Asymmetric Epoxidation[a]

Entry	Substrate	temp (°C)	Conv. (%)[j]	Recovered S.M ee (%)[l]	Epoxide ee (%)	Epoxide (trans/cis)[u]	k_{rel}[w] (k_f/k_s)
							
1[b]	R = TMS	-10	49	96[m] (S)[q]	95[m]	>20	>100
2[c]	R = Me	-10	65	99[n] (S)	85[t]	6	15
3[d]	R = COMe	0	54	96[n] (S)	88[o]	12	43
4[e,f]	R = COOEt	-10	51	94[m] (S)	97[n]	>20	79
5[g]		0	71[k]	89[p] (S)[q]	ND	6[v]	6
6[h]		0	56	89[p] (S)[r]	ND	6	16
							
7[i]	R = Me	0	55	24[m] (S)	ND	ND	2
8[b]	R = TBS	0	70	81[s] (S)	ND	>20	5
9[i]		0	34	30[m] (S)	ND	ND	2

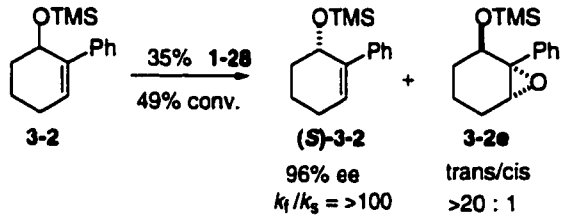
[a] All reactions were carried out with substrate (1eq), ketone (0.20-1.0 eq), Oxone (2.3 – eq), and K_2CO_3 (9.5 eq) in CH_3CN-DMM-0.05 M $Na_2B_4O_7 \cdot 10\ H_2O$ in aqueous EDTA ($4x10^{-4}$ M) solution (1:2:2, v/v/v). Oxone was added over 2.5 h. [b] 0.35 eq ketone used. [c] 0.45 eq ketone used. [d] 0.50 eq ketone used. 0.40 eq ketone used. [e] 0.60 eq ketone used. [f] 2.8 eq Oxone used. [g] 0.20 eq ketone used. [h] 1.0 eq ketone used. [i] 0.30 eq ketone used. [j] Conversion was determined by ^1H NMR of the crude reaction mixture after work-up. In cases where the ee of the epoxide was determined and one diastereomer of the epoxide

was formed predominately (Entries 1 and 4), the conversion was cross-checked applying the ee's of the olefin and epoxide to the following equation: ee(olefin) / ee(epoxide) = C / (1-C). In these cases the measured conversion was consistent with the calculated conversion. [k] The conversion was determined by GC (Restec Corporation RTX-5). [l] The absolute configuration was tentatively assumed based on the spiro reaction mode unless otherwise noted. [m] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [n] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [o] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. [p] Enantioslectivity was determined by chiral GC (Chiraldex G-TA) after conversion to the acetate. [q] The configuration was determined by comparing the measured optical rotation of the known alcohol after desilylation (see experimental). [r] The configuration was determined by comparing the measured optical rotation of the corresponding acetate (see experimental). [s] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) of the corresponding benzoate. [t] Enantioselectivity was determined by ^{1}H NMR shift analysis using Eu(hfc)$_3$. [u] The ratio of *trans* and *cis* epoxides was determined by ^{1}H NMR. [v] The ratio of diastereomers was determined by GC (Restec Corporation RTX-5). [w]The relative rate was calculated using the equation $k_{rel} = k_f/k_s = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where C is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref. 1).

When the epoxidation of **3-2** was carried out with 35% ketone **1-28** at –10 °C for 2.5 h, a 49% conversion was obtained as judged by ^{1}H NMR assay of the crude reaction mixture (equation **3.13**). The ^{1}H NMR spectrum showed the *trans* epoxide was formed predominantly (*trans/cis* >20).[21] Analysis of the unreacted substrate using HPLC on a chiral support (Chiralcel OD) showed a 96% ee. When these values are substituted into eq. **3.8** a k_{rel} of over 100 results. Furthermore, when eq. **3.10** is used to cross-check the NMR conversion, a C of 50.1% is the result. Therefore, the accuracy of the NMR

[21] The *trans* configuration of the major isomer was based on the following comparison: The epoxide was desilylated with TBAF, and the ^{1}H NMR was taken of the epoxy alcohol. This NMR matched that of the resulting epoxy alcohol of the epoxidation of 2-phenyl-2-cyclohexenol with *m*-CPBA. It is known that the epoxidation of the allylic alcohol with *m*-CPBA gives the *cis* epoxide as the major product due to the directing effect of the hydroxy group. For a leading reference on this subject, see: Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1994**, *94*, pp 2503.

conversion is close to the true conversion of the reaction. The fact that the major epoxide was *trans* and the recovered olefin was enriched in the (*S*) isomer supports the transition state analysis.



3-2 (*S*)-3-2 3-2e

96% ee trans/cis

k_f/k_s = >100 >20 : 1

(eq. 3.13)

The ability of the phenyl group to accommodate the spiro transition state is evident with other derivatives as well (Entries 2-4), and the high facial selectivity for the epoxidation translates into high selectivity for the kinetic resolution. It is apparent from these results that "small" groups must usually occupy the R_1 position to obtain high k_{rel} values. For instance, when R_1 is a methyl group (Entry 5) the k_{rel} value is reduced to 6. However, the effect can be reversed when other directing groups are present in the molecule. For example, when a gem dimethyl group is placed at the 3-position (Entry 6) the planar transition state is disfavored and the k_{rel} increased to 16. Other groups such as the hydroxymethyl (Entries 7,8) and the corresponding benzoate (Entry 9) are too large to accommodate the spiro transition state well. Overall, these initial studies show that great success in the kinetic resolution of cyclic olefins is possible with suitably designed substrates.

3.B.2. 1,3-Disubstituted Cyclohexenes

The feasibility of the kinetic resolution of 1,6-disubstituted cyclohexenol derivatives led to the investigation of the closely related 1,3-disubstituted cyclohexenes

(Figure 3.5) In this case the kinetic resolution efficiency would be dependent on the energy difference between repulsive interactions **a** and **b**.

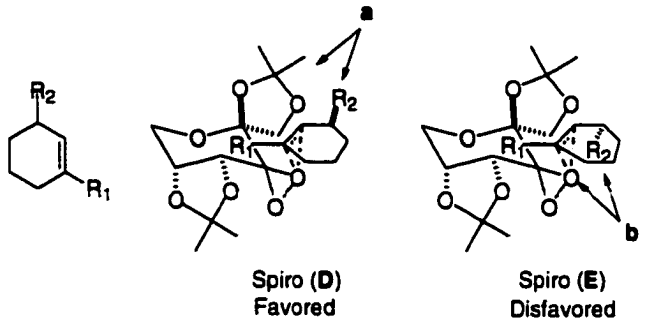


Figure 3.5 Spiro transition states for 1,3-disubstituted cyclohexenes.

Therefore, a variety of 1,3-disubstituted cyclohexenes with structural features similar to the 1,6-derivatives were prepared (Scheme 3.2). 1-Phenyl derivatives **3-18 – 3-20** were prepared from 1,3-cyclohexanedione by exchange with ethanol[22] followed by displacement of the ethoxy group with phenyl magnesium bromide[23] in high yield to give **3-16**. Luche reduction followed by protection gave the various 1-phenyl-3-protected derivatives smoothly. In addition, a carbon substituted derivative **3-21** was prepared using allylic alkylation of carbonate **3-20** with dimethylmalonate in the presence of palladium(0).[24] The methyl substituted derivative **3-23** was prepared from **3-16** by reaction with MeLi, Luche reduction, and protection. **3-24**, which was synthesized from isophorone by reduction followed and protection, has a similar skeleton. The gem-dimethyl group was designed to increase resolution efficiency by disfavoring the competing planar transition state. Since conjugated enynes are good substrates for the epoxidation with **1-26**, 1,3-disubstituted enyne **3-26** was also prepared from the

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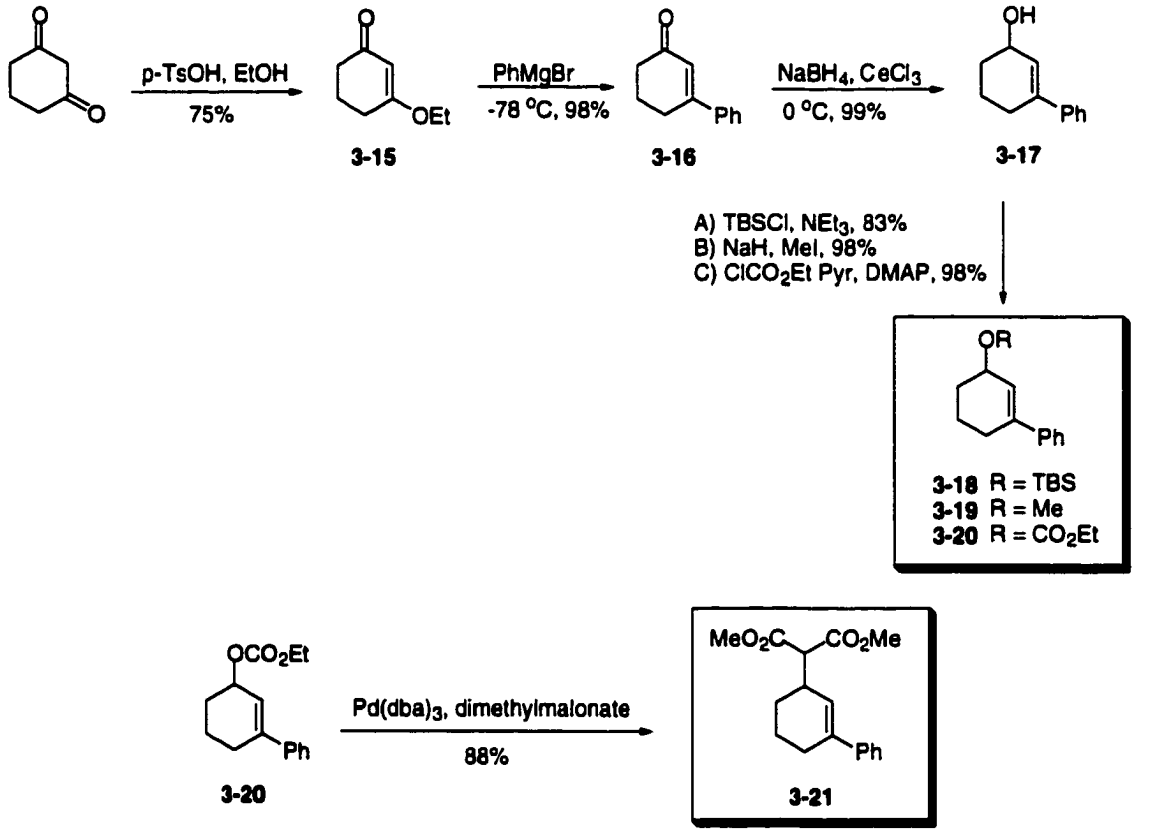
[22] Gannon, W.F.; House, H.E. *Org. Synth. Collected Volume V* **1973**, 539.
[23] Woods, G.F.; Tucker, I.W. *J. Am. Chem. Soc.* **1948**, *70*, 2174.
[24] For a review, see: Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173.

vinylagous ester. Enol ester derivatives are also good substrates for the epoxidation,[25] and a variety of enol pivaloates and acetates **3-29 – 3-36** were prepared. **3-29 – 3-31** were made from 1,3-cyclohexanedione by formation of the vinylagous anhydride,[26] 1,2-reduction with DIBAL at low temperature,[27] and protection. **3-32 – 3-36** were prepared via higher order organocuprates[28] by one-pot conjugate addition/O-alkylation. Enolbenzoate derivatives **3-39 – 3-40** were synthesized in the same way as **3-29 – 3-31**. Results with these olefins are summarized in Table 3.2.

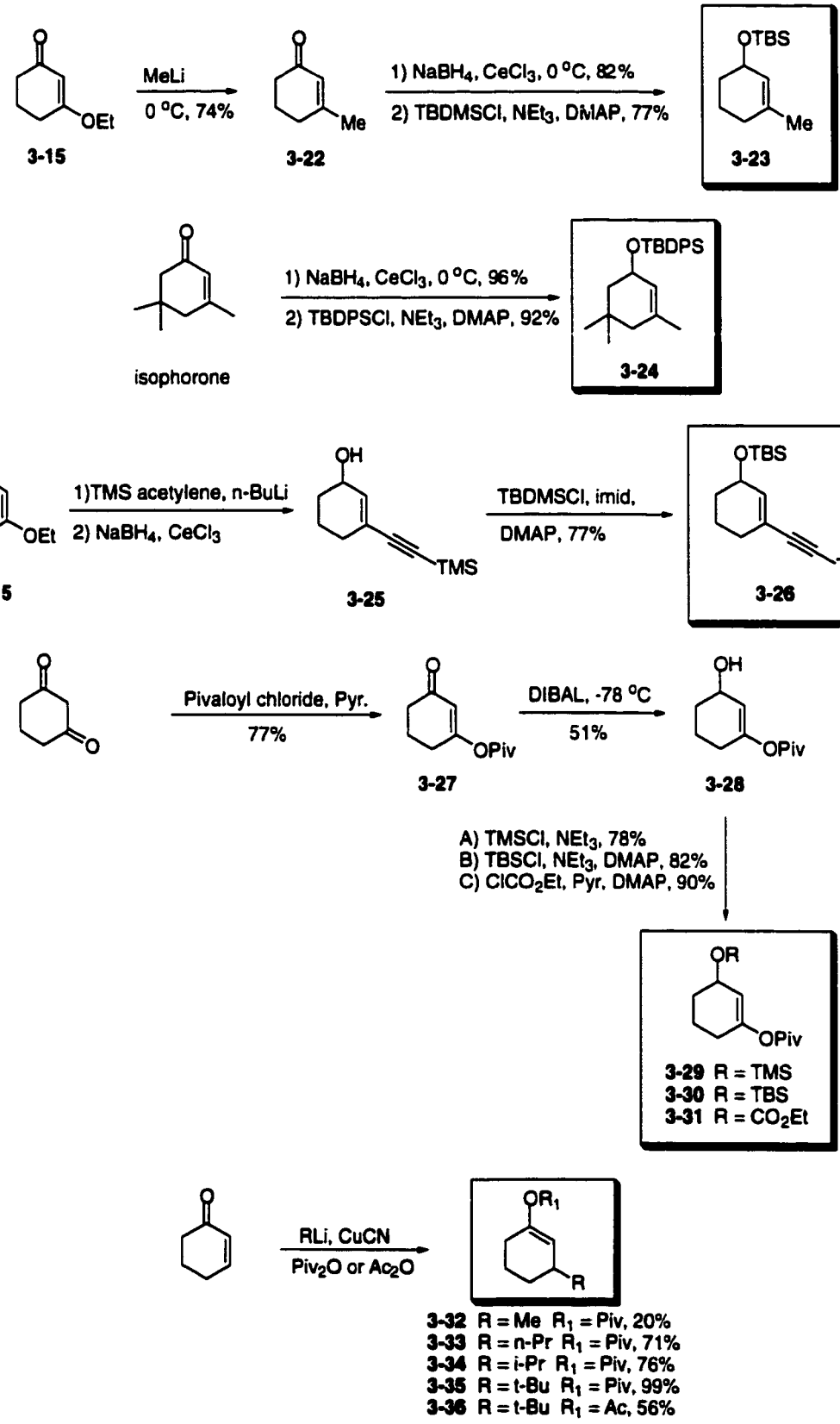


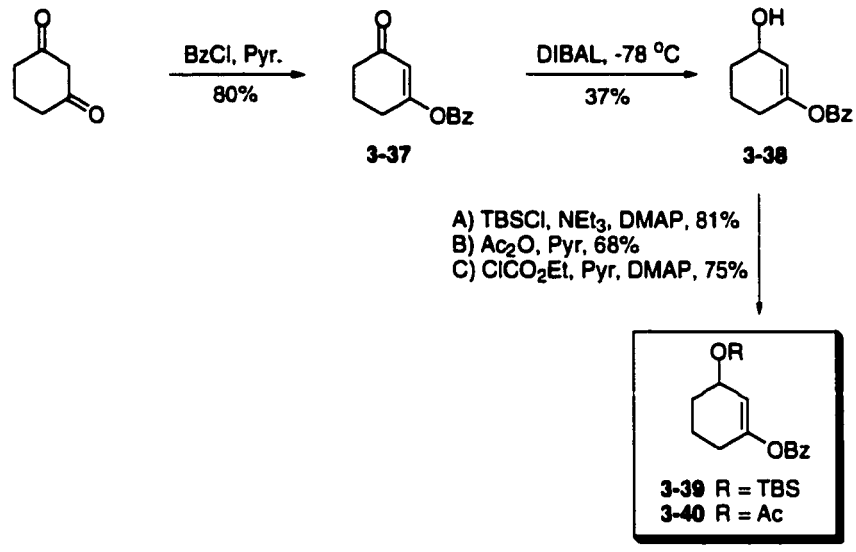
[25] Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.

[26] Akhrem, A.A.; Lakhvich, F.A.; Budai, S.I.; Khlebnicova, T.S.; Petrusevich, I.I. *Synthesis* **1978**, 925.

[27] Wilson, K.E.; Seidner, R.T.; Masamune, S. *Chem. Commun.* **1970**, 213.

[28] Lipshutz, B.H.; Wilhelm, R.S. *J. Am. Chem. Soc.* **1982**, *104*, 4696.





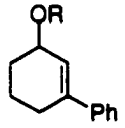
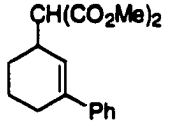
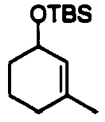
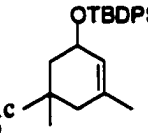
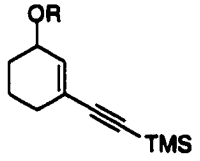
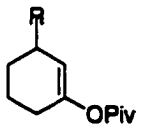
Scheme 3.2

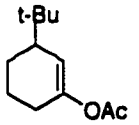
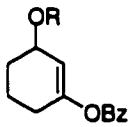
Subjecting the TBS ether of 1-phenyl-2-cyclohexenol **3-18** to the epoxidation (40 mol% ketone **1-28** at –10 °C for 1.5 h) led to 67% conversion of the substrate (Entry 1). The product was a 4/1 mixture of *trans* and *cis* epoxides favoring the *trans* isomer. The enantiomeric excess of the unreacted substrate was determined to be 99%. This result demonstrates that transition state **D** is favored over **E** in Figure 3.4.

Although the absolute configuration for most of the substrates was not obtained, the unreacted substrates are likely to have the *R* configuration based on the transition state analysis in Figure 3.4. To confirm the configuration, the pivaloate in entry 14 was converted to 3-*t*-butylcyclohexanone by hydrolysis (NaOMe-MeOH). The resulting ketone was determined to indeed have the (*R*) configuration by comparing the measured optical rotation with the reported value.[29]

[29] Dieter, R.K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040.

Table 3.2. Kinetic Resolution of Representative 1,3-Disubstituted Cyclohexenes by Ketone **1-28** Catalyzed Asymmetric Epoxidation[a]

Entry	Substrate	temp (°C)	Conv. (%)[k]	Recovered S.M ee (%)[l]	Epoxide ee (%)	Epoxide (trans/cis)	k_{rel}[w] (k_f/k_s)
							
1[b]	R = TBS	-10	67	99[m] (R)	81[s]	4	19
2[c]	R = Me	-10	61	95[m] (R)	ND	6	14
							
3[c]		0	72	81[n] (R)	ND	1.7	4
							
4[c]		0	63	31[o] (R)	37[p]	>20	4
							
5[c]		0	48	32[p] (R)	ND	8	3
							
6[c]	R = TBS	-10	49	75[q] (R)	ND	13	18
7[c]	R = TBS	20	66	96[q] (R)	ND	8	11
							
8[d]	R = OTMS	-10	62	91[r] (R)	76[u]	4	11
9[e]	R = OTBS	-10	55	76[m] (R)	76[u]	9	10
10[f]	R = OCO_2Et	-10	42	35[r] (R)	ND	5	4

11[c]	R = Me	-10	41	37[n](R)	90[u]	3	5
12[b]	R = n-Pr	-10	45	50[n](R)	91[u]	4	4
13[g]	R = ^{i}Pr	-10	59	93[n] (R)	85[u]	8	15
14[h]	R = ^{t}Bu	-10	54	99[n] (R)[t]	84[u]	>20	60
15[i]		0	60	85[n](R)	60[u]	>20	11
16[j]	 R = TBS	0	56	57[r](R)	49[n]	>20	5
17[f]	R = Ac	0	58	51[r](R)	42[r]	>20	4

[a] All reactions were carried out with substrate (1eq), ketone (0.25-0.75 eq), Oxone (2.3 eq), and K_2CO_3 (9.5 eq) in CH_3CN-DMM-0.05 M $Na_2B_4O_7 \cdot 10\ H_2O$ in aqueous EDTA ($4x10^{-4}$ M) solution (1:2:2, v/v/v). Oxone was added over 2.5 h. [b] 0.40 eq ketone used. [c] 0.25 eq ketone used. [d] 0.60 eq ketone used. [e] 0.90 eq. ketone used. [f] 1.0 eq ketone used. [g] 0.75 eq ketone used. [h] 0.45 eq ketone used, 2.8 eq Oxone used. [i] 0.35 eq ketone used. [j] 0.50 eq ketone used. [k] Conversion was determined by ^{1}H NMR of the crude reaction mixture after work-up. In cases where the ee of the epoxide was determined and one diastereomer of the epoxide was formed predominately (entries 4, 14-17), the conversion could be cross-checked applying the ee's of the olefin and epoxide to the following equation: ee(olefin) / ee(epoxide) = C / (1-C). In these cases the measured conversion was consistent with the calculated conversion. [l] The absolute configuration was tentatively assumed based on the spiro reaction mode unless otherwise noted [m] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [n] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. [o] Enantioselectivity was determined by chiral HPLC (Chiralcel OB) after conversion to the benzoate. [p] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after conversion to the benzoate. [q] Enantioselectivity was determined by chiral HPLC (Chiralcel AD) after exhaustive desilylation and conversion of the alcohol to the benzoate. [r] Enantioselectivity

was determined by chiral HPLC (Chiralcel AD). [s] Enantioselectivity was determined by chiral HPLC (Chiralcel AD) after conversion to the benzoate. [t] The configuration was determined by comparing the measured optical rotation with the known ketone after hydrolysis (see experimental). [u] Enantioselectivity was determined by ^{1}H NMR shift analysis using Eu(hfc)$_3$. [v] The ratio of *trans* and *cis* epoxides was determined by ^{1}H NMR. [w] The relative rate was calculated using the equation $k_{rel} = k_f/k_s = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where C is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref. 1).

Table 3.2 shows the results with this class of substrates, in general, parallel those observed with the 1,6-disubstituted case. The size of the group at the allylic position substantially effects resolution efficiency (Entries 1 vs. 2) and substitution of the phenyl group with a methyl group at R_1 reduces resolution efficiency (Entries 4 and 5). Conjugated enynes are also resolved well (Entry 6 and 7). Surprisingly, enol pivaloates are also good substrates in some cases (Entries 8-14). The large pivaloate group is expected to reduce the facial selectivity of the epoxidation by disfavoring the spiro transition state, so one would also expect the kinetic resolution to be poor. However, it appears that the ester is able to adopt a favorable conformation for the epoxidation, since the seven membered ring enol pivaloate gives <10% conversion under identical reaction conditions. The enol acetate, which also has a somewhat large acetate group at R_1 is also resolved well, with a k_{rel} of 11 (Entry 15). On the other hand, enol benzoates, which were expected to be good substrates since the benzoate is flat, are resolved less efficiently (Entries 16 and 17).

3.B.3. Exocyclic and Miscellaneous Cyclic Olefins

Encouraged further by these results, a variety of exocyclic and some miscellaneous cyclic olefins were prepared and subjected to the kinetic resolution. The directing elements present in the spiro transition states for (*E*) exocyclic olefins are presented in Figure 3.6.

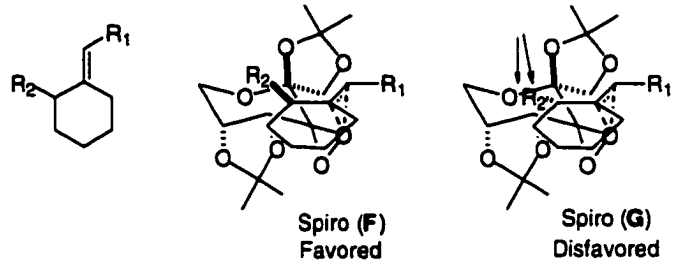


Figure 3.6 Spiro transition states for exocyclic cyclohexenes.

Spiro (**F**) is reasonable well accommodated, with R_2 directed away from the catalyst, while Spiro (**G**) shows severe repulsive interactions between R_2 and the pyran ring of the catalyst. Thus, these olefins were also envisioned to be good candidates for the kinetic resolution. Synthesis of these and other miscellaneous olefins is presented in Scheme 3.3. Three (*E*) exocyclic olefins **3-47 – 3-49** were prepared from cyclohexanone by base-catalyzed aldol condensation[30] followed by Luche reduction and protection as the TMS ether. Exocyclic olefin **3-51** was prepared by Peterson olefination to test the resolution of a (*Z*) olefin.[31] Upon chromatographic separation a low yield o fproduct with a high Z/E ratio was obtained.

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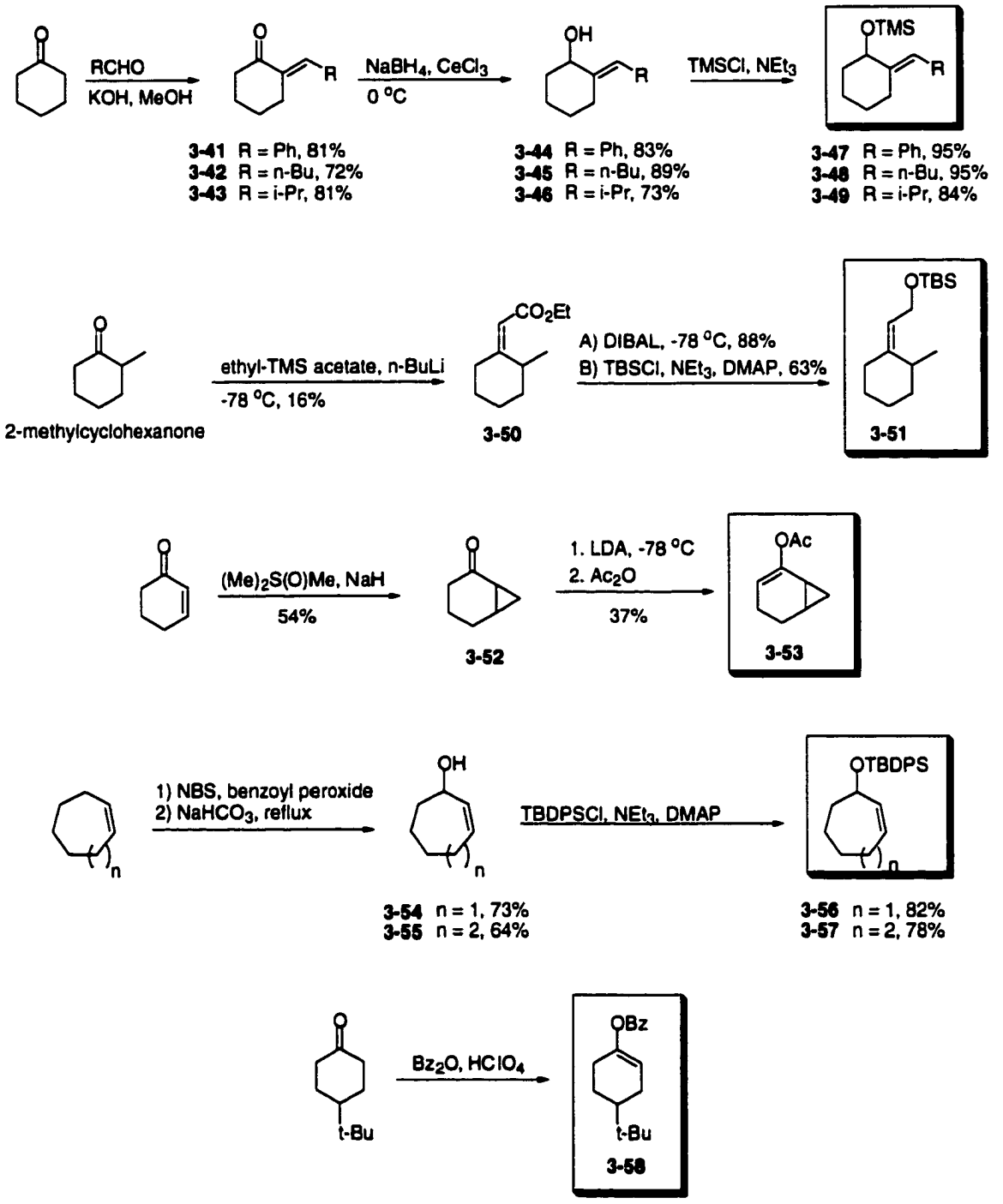
[30] Zair, T.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686.

[31] (a) Visnick, M.; Strekowski, L.; Battiste, M.A. *Synthesis*, **1983**, 284. (b) Strekowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* **1984**, *25*, 5603.



Scheme 3.3

Cyclopropyl derivative **3-54** was prepared in order to test the effect of tying back the chiral center into a cyclopropyl ring. It was prepared from cyclohexenone by

cyclopropanation with dimethylsulfonium methylide[32] followed by enolate formation with LDA and trapping with acetic anhydride. In addition, two *cis* olefins were also prepared. Since *cis* olefins are not good substrates for the epoxidation, the large *tert*-butyldiphenylsilyl (TBDPS) group was installed as directing group. Allylic bromination followed by substitution under basic conditions gave the allylic alcohols. Protection as the silyl ether proceeded smoothly to give **3-56** and **3-57**. Finally, enol benzoate **3-58** was prepared by reaction of the ketone with benzoic anhydride in the presence of $HClO_4$.[33] Results of the kinetic resolution with these substrates is shown in Table 3.3.The k_{rel} for the these substrates were modest compared to the earlier substrates tested.

Interestingly, the (*E*) exocyclic olefins gave the reverse trend than would be expected by the spiro mode of reaction (Entries 1-3). Larger R_1 groups on these substrates should discourage the planar transition state and lead to a higher k_{rel}. However, as R_1 was changed from phenyl to isopropyl, the k_{rel} went from 5 to 1. It was possible that the planar transition state is favored for these substrates; however, when the recovered starting material was desilylated and the optical rotation taken, the absolute configuration was confirmed as (*S*) by comparison to the literature data. In addition, the *cis* olefins and the enol benzoate were also not good substrates. Overall, the substrates shown in Table 3.3 are not promising templates for resolution using ketone **1-28** as the chiral source.

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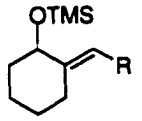
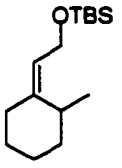
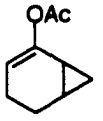
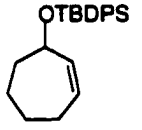
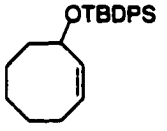
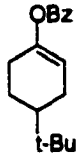
[32] Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
[33] House, H.O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362.

Table 3.3. Kinetic Resolution of Representative Exocyclic and Miscellaneous Olefins by Ketone **1-28** Catalyzed Asymmetric Epoxidation[a]

Entry	Substrate	temp (°C)	Conv. (%)[f]	Recovered S.M ee (%)	Epoxide ee (%)	Epoxide (trans/cis)[o]	k_{rel}[p] (k_f/k_s)
							
1[b]	R =Ph	0	42	41[h] (S)[l]	ND	4	5
2[c]	R = n-Bu	-10	53	42[j] (S)	ND	ND	2
3[b]	R = i-Pr	0	35	4[j] (S)	2[m]	6	1
							
4[d]		0	73	66[k] (R)	ND	ND	3
							
5[e]		0	56	48[h] (5S,6S)	ND	5	4
							
6[c]		0	59	3[h] (S)	23[n]	3	1
							
7[c]		0	55	15[l] (S)	ND	>20	2
							
8[c]		0	78	55[h] (R)	ND	ND	2

[a] All reactions were carried out with substrate (1eq), ketone (0.20-1.0 eq), Oxone (2.3 eq), and K_2CO_3 (9.5 eq) in CH_3CN-DMM-0.05 M $Na_2B_4O_7 \cdot 10\ H_2O$ in aqueous EDTA (4×10^{-4} M) solution (1:2:2, v/v/v). [b] 1.0 eq ketone, 2.8 eq Oxone, 12.4 eq. K_2CO_3 was used. [c] 0.25 eq ketone used. [d] 0.20 eq ketone used. [e] 0.30 eq ketone used. [f] Conversion was determined by ^1H NMR of the crude reaction mixture after work-up. [g] The absolute configuration was tentatively assumed based on the spiro reaction mode unless otherwise noted. [h] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [i] The configuration was determined by comparing the measured optical rotation with the known alcohol after desilylation (see experimental). [j] Enantioselectivity was determined by ^1H NMR shift analysis using $Eu(hfc)_3$ after desilylation with TBAF. [k] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. [l] Enantioselectivity was determined by chiral HPLC (Chiralcel AD). [m] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) of the corresponding benzoate. [n] Enantioselectivity was determined by chiral GC (Chiraldex G-TA) after desilylation with TBAF. [o] The ratio of *trans* and *cis* epoxides was determined by ^1H NMR. [p] The relative rate was calculated using the equation $k_{rel} = k_f/k_s = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where C is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref. 1).

3.B.4. Acyclic Olefins

The final class of substrates tested in the kinetic resolution was acyclic olefins. Transition state analysis of these substrates indicates that the prospect of efficient resolution is tenuous at best (Figure 3.7). Depending on the conformation of the olefin, the (*R*) or (*S*) enantiomer can be envisioned to react competitively through separate spiro modes. Spiro (**I**) also has the disadvantage of $A_{1,3}$ strain imposed on the methyl groups, and so Spiro (**H**) is expected to be favored.

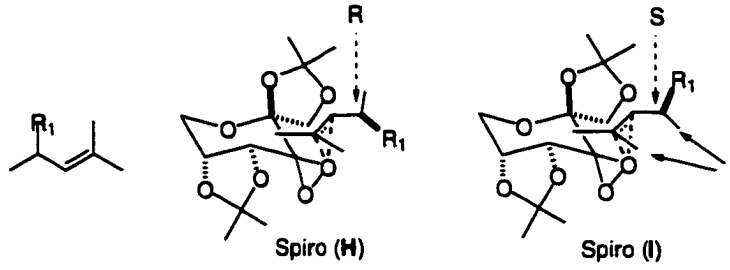
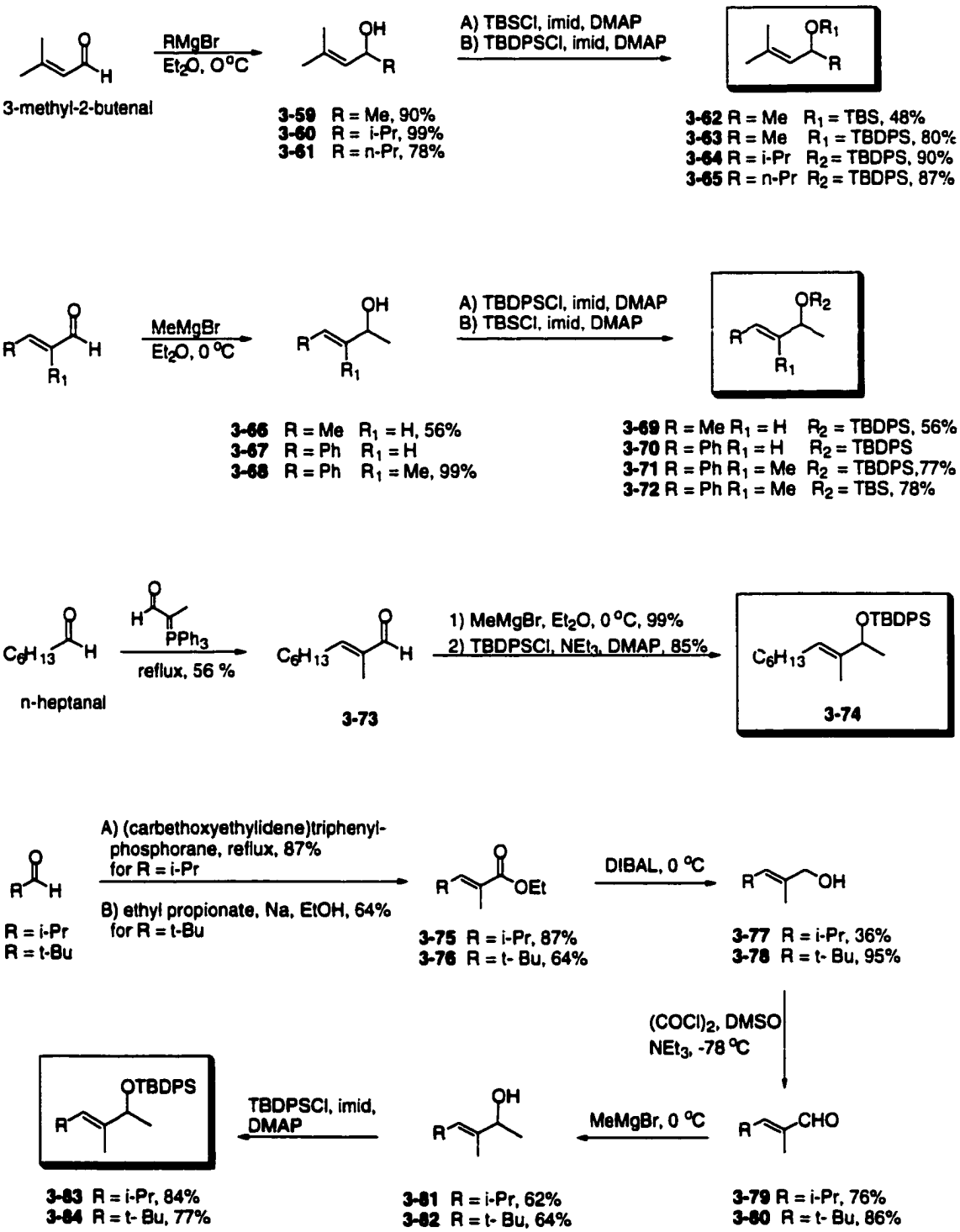


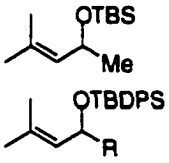
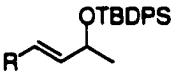
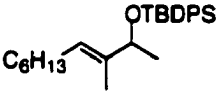
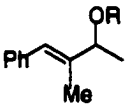
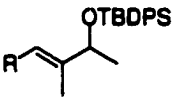
Figure 3.7 Spiro transition states for trisubstituted acyclic olefins.

Initial results with **3-62** and **3-63** were interesting (*vide infra*), and so a full complement of acyclic structures were prepared (Scheme 3.4). The acyclic substrates **3-62 - 3-65** were made by 1,2-addition of Grignard reagents to 3-methyl-2-butenal followed by protection as either the TBS ether or the larger TBDPS ether. A similar strategy was taken with *trans*-crotonal, *trans*-cinnamaldehyde, and α-methyl-*trans*-cinnamaldehyde to make **3-69 – 72.** The aliphatic trisubstituted olefin **3-74** was synthesized from n-heptanal by reaction with 2-(triphenylphosphoranylidene)propionaldehyde, chain extension with methyl Grignard, and protection. Finally, the branched analogues **3-83** and **3-84** were prepared by olefination (either by the aldol or Wittig reaction), reduction to the aldehyde by a reduction/oxidation sequence, addition of methyl Grignard, and protection of the alcohol. The results of kinetic resolution of these substrates is summarized in Table 3.4.



Scheme 3.4

Table 3.4. Kinetic Resolution of Representative Acyclic Olefins by Ketone **1-28** Catalyzed Asymmetric Epoxidation[a]

Entry	Substrate	Conv. (%)[d]	Recovered S.M ee (%)[f]	Epoxide ee (%)	Epoxide (trans/cis)[m]	k_{rel}[p] (k_f/k_s)
1[b]		38[e]	0	82/97[g]	1.1[e]	1
2[c]	R =Me	67	73[g] (S)[h]	74/92[g]	3[n]	4
3[c]	R =n-Pr	27	20[i] (S)	87/92[g]	6	5
4[c]	R =i-Pr	7	ND	ND	ND	ND
5[c]	 R =Me	37	9[j] (S)	93/91[g]	2	2
6[c]	R = Ph	43	21[k] (S)	93/67[k]	2[o]	2
7[c]		78	33[l](S)	87/93[g]	1.4	2
8[c]	 R = TBS	NR	ND	ND	ND	ND
9[c]	R = TBDPS	NR	ND	ND	ND	ND
10[c]	 R = i-Pr	NR	ND	ND	ND	ND
11[c]	R = t-Bu	NR	ND	ND	ND	ND

[a] Reactions were carried out with substrate (1 eq), ketone (0.30-1.0 eq), Oxone (4.1 eq), and K_2CO_3 (9.5 eq) in CH_3CN-DMM-0.05 M $Na_2B_4O_7 10\ H_2O$ in aqueous EDTA ($4x10^{-4}$ M) solution (1:2:2, v/v/v) at 0 °C. Oxone was added over 2.5 h. [b] 0.30 eq ketone

used. [c] 1.0 eq ketone, 4.7 eq Oxone, 20.1 eq. K_2CO_3 was used. [d] Conversion was determined by ^1H NMR of the crude reaction mixture after work-up unless otherwise noted. [e] Conversion and diastereoselectivity was determined by GC (Varian RTX-5 column). [f] The absolute configuration was tentatively assumed based on the stereochemical study done for entry 2, unless otherwise noted. [g] The enantioselectivity was determined by chiral GC (Chiraldex G-TA) after desilylation with TBAF. [h] The absolute configuration was determined by comparison of the alcohol after desilylation to an authentic sample of the (*R*) alcohol prepared by Sharpless kinetic resolution. [i] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ) of the corresponding benzoate. [j] Enantioselectivity was determined by chiral HPLC (Chiralcel OD) of the corresponding benzoate. [k] The enantioselectivity was determined by chiral HPLC (Chiralcel OD) after desilylation with TBAF. [l] Enantioselectivity was determined by ^1H NMR shift analysis using $Eu(hfc)_3$ after desilylation with TBAF. [m] The ratio of *trans* and *cis* epoxides was determined by ^1H NMR, unless otherwise noted. [n] The *trans* and *cis* epoxides were verified by comprison of the ^1H NMR to the literature data. [o] The *trans* isomer was verified as the major diastereomer after desilylation and comparison to the published spectra. [p] The relative rate was calculated using the equation $k_{rel} = k_f/k_s = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where C is the conversion and ee is the percent enantiomeric excess of the recovered starting material (ref. 1).

Kurihara and coworkers described a highly diastereoselective racemic epoxidation of the TBDPS protected olefin **3-63** with 2-phenylcyclohexanone as dioxirane precursor,[34] so it was thought that this skeleton would be a good starting point for the investigation. When the TBS protected olefin **3-62** was resolved with 30 mol% catalyst at 0 °C with 4.7 eq Oxone, a 38% conversion of essentially racemic starting material resulted (Entry 1). Surprisingly, however, the isolated epoxides were present in high optical purity after desilylation and analysis by chiral GC (Chiraldex G-TA). In addition, when 1 eq ketone was used to epoxidize **3-63**, a 67% conversion to two epoxides in a 3.8/1 diastereomeric ratio occurred (Entry 2). The recovered starting material was

recovered in only 73% ee. However, the ee's of the epoxides were high, with the *trans* giving a 74% ee and the *cis* giving a 92% ee. Similar results were obtained with the other acyclic olefins tested (Entries 2,3,5-7). The k_{rel} values were not particularly high in any of these cases, but the ee's of the isolated epoxides were typically in the high 80 to low 90% range. These results suggest that the enantiomers of the starting material react at similar rates, but each with high diastereoselectivity.

To fully delineate the modes of reaction for **3-63**, the absolute stereochemistry of the recovered olefin and the two epoxides was determined. Desilylation of the crude reaction mixture with TBAF provided the corresponding alcohols, which were purified and analyzed by chiral GC (Chiraldex G-TA).[35] Comparison of the chiral GC traces (Chirladex G-TA column) for the allylic alcohol, *cis*, and *trans* epoxy alcohols with authentic samples showed that the kinetic resolution provided the (*S*) allylic alcohol and the (*R*)-*trans* epoxide predominantly (Figure 3.5). Thus, Spiro (**J**) and Spiro (**K**) were the major modes of reaction, with Spiro (**J**) predominating.

Although these substrates were poorly resolved, the above results suggest the possibility of a highly diastereoselective epoxidation protocol if the starting olefin were stereodefined. To explore this possibility, (***R***)-**3-63** and (***R***)-**3-70** were prepared in >99% ee via Sharpless kinetic resolution and protection. These olefins were then epoxidized with **1-28** and **ent-1-28** as shown in Scheme 3.6.

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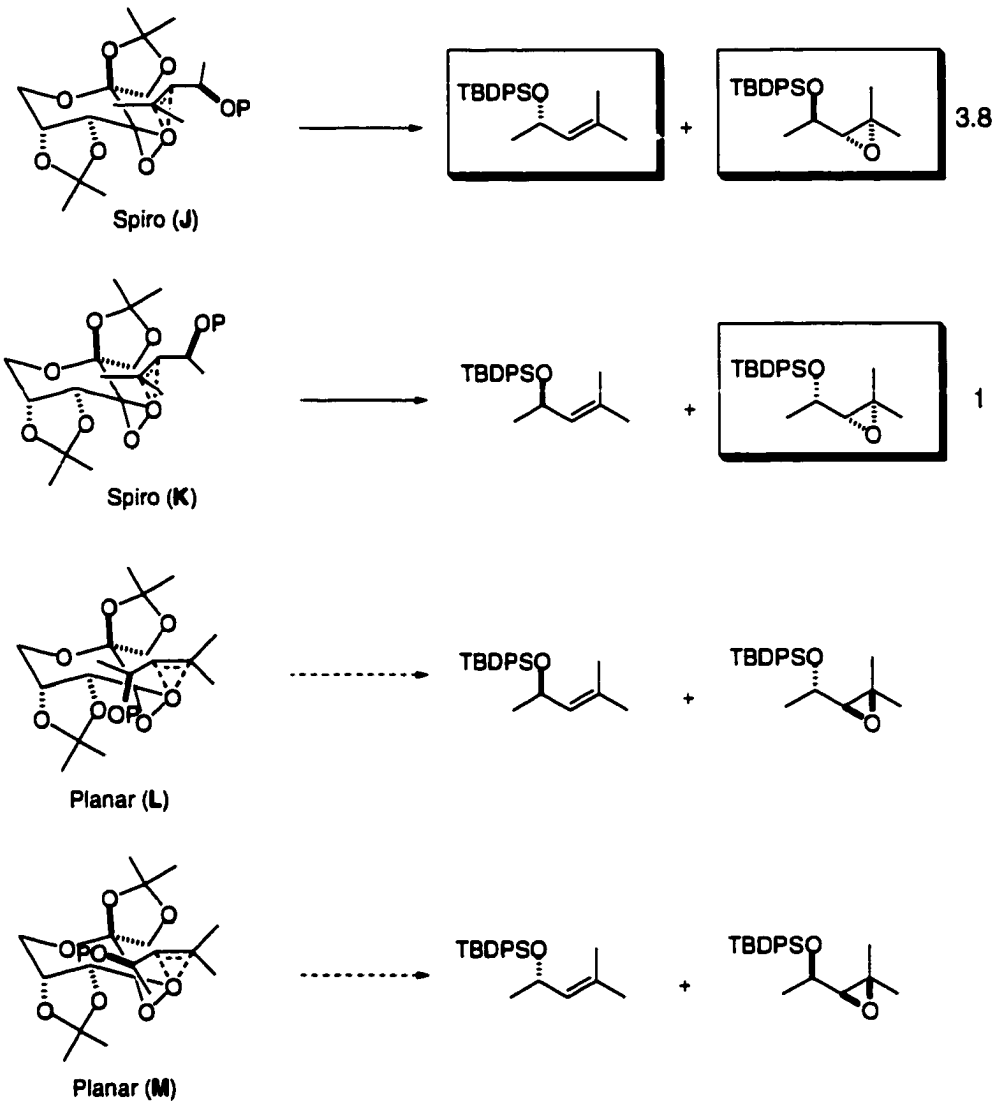
[34] Kurihara, M.; Ishii, K.; Kasahara, Y.; Kameda, M.; Pathak, A.K.; Miyata, N. *Chem. Lett.* **1997**, 1015. The racemic epoxidation with 1,3-dichloroacetone, gave a 3.4/1 dr.

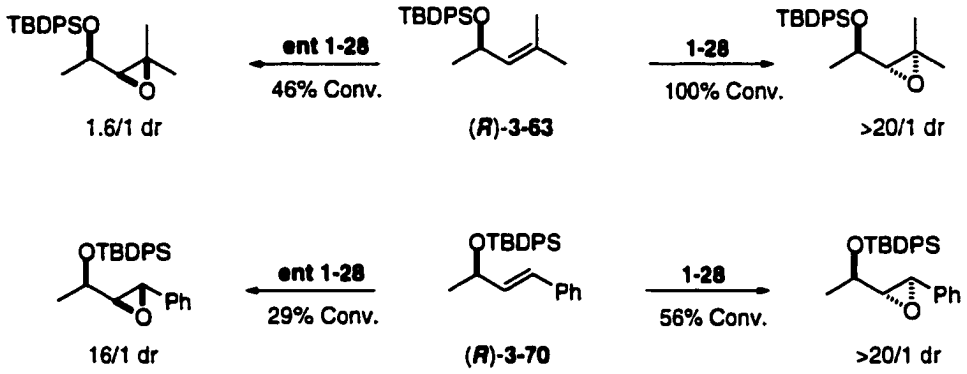
[35] Authentic samples of the allylic alcohol and epoxy alcohols were obtained by kinetic resolution of alcohol **3-59** via Sharpless asymmetric epoxidation with (+)-diethyltartrate as ligand, which gives enrichment of the (*R*) allylic alcohol.



Scheme 3.5

As can be seen, the sense of asymmetric induction is controlled by the catalyst. In addition, the reactivity and selectivity are highly dependent on the ability of the reaction to go through a transition state similar to Spiro (**J**). Reaction of (***R***)-**3-63** with **1-28**, which accommodates Spiro (**J**) well, gave complete conversion to a single diastereomer of the *trans* epoxide as determined by ^{1}H NMR integration. On the other hand, reaction with **ent 1-28** resulted in a low diastereoselectivity for the *cis* epoxide. Presumably, there was a competition between Spiro (**N**) and Planar (**O**) in this case, which translates into

the low diastereoselectivity (Figure 3.8). This reaction can be viewed as a matched/mismatched diastereoselective reaction in which Spiro (**J**) is the dominant transition state when **1-28** is used.



Scheme 3.6

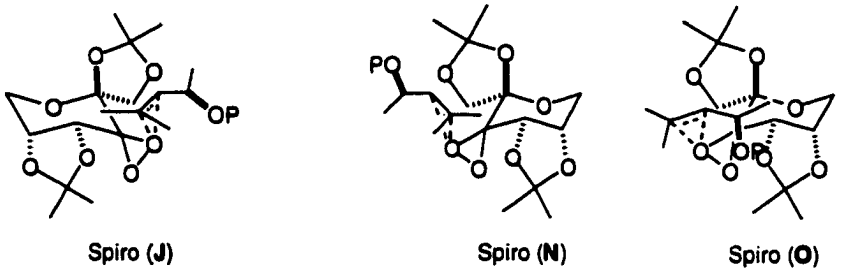
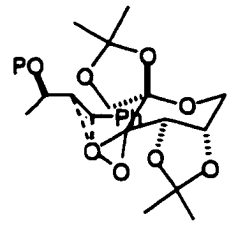


Figure 3.8 Competing transition states for **ent 1-28**.

The reactivity pattern for *trans*-disubstituted olefin (***R***)-**3-70** is also interesting. Results with **1-28** mirrored those with (***R***)-**3-63**, but reaction with **ent 1-28** also gave high selectivity for the *cis* product. Apparently, the favored spiro transition state in this case (Spiro (**P**), Figure 3.9) was more favored than Spiro (**N**) because of the absence of $A_{1,3}$ strain, which translates into a high diastereoselectivity.



Spiro (**P**)

Figure 3.9 Spiro transition state for **ent 1-28** and a *trans* disubstituted acyclic olefin.

These results offer the intriguing possibility of a diasteroeselective epoxidation with optically-enriched acyclic olefins. Acyclic allylic alcohols can be epoxidized with high diastereoselectivity with mCPBA,[36] V(acac) in some cases,[37] and Sharpless conditions.[5] However, if there is no allylic alcohol present the selectivity suffers in all these cases. Furthermore, achiral dioxiranes usually give modest diastereoselectivity whether an alcohol is present or not.[38] Therefore, a general diastereoselective epoxidation of acyclic olefins is of general interest and warrants investigation. While this possibility has not been fully explored at the present time, it is currently left open for further experimentation to fully assess the steric requirements for high selectivity.

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[36] These epoxidations are selective for the *cis* product when the olefin contains high $A_{1,3}$strain, and the *trans* product when there is a large group at the chiral center. See: Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1993**, *93*, 1307 for a review.

[37] (a) Sharpless, K.B.; Verhoeven, T.R. *Aldrichim. Acta* **1979**, *12*, 63. (b) Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203. (c) Jorgensen, K.A. *Chem. Rev.* **1989**, *89*, 431.

3.C. CONCLUSIONS

This study further validates the spiro reaction mode as an invaluable predictive tool for the ketone catalyzed asymmetric epoxidation and kinetic resolution. The kinetic resolution of 1,6- and 1,3-disubstituted cyclohexenes can proceed with high resolution efficiency in many cases, particularly when the R_1 group is small. In cases where the diastereoselectivity is high, the method also provides a route towards stereodefined *trans* epoxides, which can be difficult to prepare otherwise. Of the two, the 1,6-disubstituted case is resolved better than the 1,3-case. In cases where other kinetic resolution methods are competitive with our own, this method offers the advantage of simple reaction procedure and the exclusion of potentially toxic transition metals. The resolution of exocyclic and acyclic olefins met with less success. However, the possibility of a highly diastereoselective epoxidation of optically active acyclic olefins remains a possibility that requires further exploration.

2.D. EXPERIMENTAL

Representative Kinetic Resolution Procedure (Table 1, Entry 3). To a vigorously stirred solution of 1-phenyl-6-acetoxycyclohexene (0.108 g, 0.50 mmol), ketone **1-28** (0.064 g, 0.25 mmol) and tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) in dimethoxymethane (10 mL), acetonitrile (5 mL), and buffer (0.05 M, $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA, 10 mL) were added Oxone (0.76 g, 1.24 mmol) in aq. Na_2EDTA (in 4 x 10^{-4} M, 9.8 mL) and a solution of K_2CO_3 (0.76 g, 5.5 mmol) in H_2O (9.8 mL) separately at a rate of 4 mL per hour (via syringe pump) at 0 °C over 2.5 h. The reaction

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[38] For lead references, see: (a) Adam, W.; Brunker, H.-G.; Kumar, A.S.; Peters, E.-M.; Peters, K.; Schneider, U.; Georg, H.; von Schnering, H.G. *J. Am. Chem. Soc.* **1996**, *118*, 1899. (b) Adam, W.; Degen, H.-G.; Saha-Moller, C.R. *J. Org. Chem.* **1999**, *64*, 1274. Also see ref. 34.

mixture was quenched with H_2O, extracted with pentane, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography [the silica gel was buffered with 1% NEt_3 in hexane, hexane/ethyl acetate (60/1 v/v) was used as eluent] to give recovered starting material (0.046 g, 43%) as a colorless oil and the *trans* epoxide (0.037 g, 32%) as a colorless oil.

(Table 3.1, Entry 1)

1-Phenyl-6-hydroxycyclohexene (3-1)(MF1911). SeO_2 (5.22 g, 47.0 mmol) was dissolved in t-BuOH (8 mL) by stirring at room temperature for 2 h. 1-phenylcyclohexene (7.5 mL, 47.0 mmol) was added and the mixture was stirred under nitrogen for 2 d. The reaction was quenched with H_2O (10mL) and extracted with Et_2O (3 X 20 mL). The combined organics were washed with H_2O (1 X 20 mL), brine (1 X 20 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a yellow oil. The oil was purified by flash column chromatography (1/1 Hexanes/Et_2O) to give the alcohol as a slightly yellow oil (4.75 g, 58.0%). IR (NaCl): 3378, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.20 (m, 5H), 6.14 (dd, J = 4.6, 3.3 Hz, 1H), 4.68 (m, 1H), 2.30 – 2.11 (m, 2H), 1.95 – 1.65 (m, 5H); ^{13}C (75 MHz, $CDCl_3$) δ 140.3, 139.3, 128.8, 128.7, 127.2, 126.2, 65.59, 31.73, 26.22, 17.49.

(*S*)-1-Phenyl-6-(trimethylsilyloxy)cyclohexene (3-2)(MF1913). To a solution of 6-hydroxy-1-phenylcyclohexene (0.62 g, 3.50 mmol) in THF (15 mL) was added TMSCl (0.58 g, 5.30 mmol) and NEt_3 (1.06 g, 10.5 mmol) and the solution was stirred overnight. The reaction was quenched with H_2O (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organics were washed with brine (1 X 20 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the off white oil was purified by flash chromatography on silica gel

(hexanes) to give the silyl ether as a colorless oil (0.77 g, 89.8%). Kinetic resolution: 49.4% conversion, 43.0% yield, 95.5% ee, $[\alpha]^{25}_{D}$ = -101.1° (*c* 0.44 in $CHCl_3$); IR (NaCl): 1731, 1600, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H), 6.09 (dd, J = 4.2, 3.3 Hz, 1H), 4.75 (dd, J = 3.6 Hz, 1H), 2.40 – 2.20 (m, 2H), 2.00 – 1.70 (m, 4H), 0.68 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 141.7, 139.8, 128.6, 127.9, 126.6, 126.5, 66.68, 32.60, 25.94, 17.12, 0.37. Anal Calcd for $C_{25}H_{22}OSi$: C, 73.11; H, 9.00. Found: C, 73.40; H, 9.19.

The olefin was desilated with TBAF and the optical rotation of the alcohol was measured to determine the absolute configuration: $[\alpha]^{25}_{D}$= -59.0° (*c* 1.0, $CHCl_3$); lit.[39] showed the (+)-enantiomer to have (*R*) stereochemistry.

Epoxide (MF2119). (*trans*) colorless oil; 41.6% yield, 95.3% ee, $[\alpha]^{25}_{D}$ = -11.6° (*c* 0.12, $CHCl_3$); IR (NaCl): 1447, 1251, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.60 (m, 3H), 7.70 – 7.60 (m, 3H), 4.57 (t, J = 4.5 Hz, 1H), 3.67 (d, J = 3.3 Hz, 1H), 2.45 – 2.30 (m, 2H), 2.30 – 2.00 (m, 2H), 1.90 – 1.70 (m, 1H), 1.40 – 1.20 (m, 1H), 0.20 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 139.8, 128.0, 127.5, 127.4, 69.27, 63.48, 59.97, 29.20, 23.51, 14.12, -0.43. Anal Calcd for $C_{15}H_{22}O_2Si$: C, 68.65; H, 8.45. Found: C, 68.75; H, 8.40.

(Table 3.1, Entry 2)

(*S*)-1-Phenyl-6-methoxycyclohexene (3-3)(MF1918). To a heterogeneous mixture of KOH (1.16 g, 20.6 mmol) in DMSO (15 mL) was added of 6-hydroxy-1-phenylcyclohexene (898 mg, 5.16 mmol) and MeI (1.46 g, 10.3 mmol) and the resulting light yellow solution was stirred at room temperature for 2 h. The reaction was then diluted with H_2O (15 mL) and the mixture was extracted with AcOEt (3 X 15 mL). The combined organics were washed with brine (1 X 20 mL) and dried (Na_2SO_4). After

[39] Allen, J.V.; Williams, J.M.J. *Tetrahedron Lett.* **1996**, *37*, 1859.

removal of the solvent under reduced pressure, the off white oil was purified by flash chromatography on silica gel (20/1 hexanes/Et_2O) to give the methyl ether as a colorless oil (0.69 g, 71.8%). Kinetic resolution: 62.0% conversion, 98.7% ee, $[\alpha]^{25}_D$ = -79.9° (*c* 0.38 in $CHCl_3$); IR (NaCl): 1644, 1598, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 5H), 6.18 (m, 1H), 4.16 (m, 1H), 3.33 (s, 3H), 2.40 – 2.10 (m, 4H), 1.90 – 1.60 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 141.4, 137.4, 129.5, 128.2, 126.6, 125.7, 74.25, 56.21, 26.23, 26.03, 16.89. Anal Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.80; H, 8.63.

Epoxide (MF2117). (*trans* and *cis* mixture) colorless oil; (*trans*): 85.0% ee; IR (NaCl) 1494, 1448, 1196 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.35 – 7.23 (m, 3H), 3.79 (t, J = 3.9 Hz, 1H), 3.29 (m, 1H), 3.16 (s, 3H), 2.05 – 1.98 (m, 2H), 1.86 – 1.74 (m, 1H), 1.73 – 1.58 (m, 2H), 1.42 – 1.32 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 139.7, 127.9, 127.5, 127.3, 78.20, 61.64, 60.47, 57.58, 23.92, 23.19, 14.13. Anal Calcd for $C_{13}H_{16}O_2$ (*trans* and *cis* mixture): C, 77.75; H, 7.46. Found: C, 77.61; H, 8.03.

(Table 3.1, Entry 3)

(*S*)-1-Phenyl-6-(acetoxy)cyclohexene (3-4)(MF1914). To a solution of 6-hydroxy-1-phenylcyclohexene (620 mg, 3.56 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added acetic anhydride (436 mg, 4.27 mmol) and pyridine (512 mg, 6.47 mmol) and the solution was stirred overnight with gradual warming to room temperature. The reaction was quenched with H_2O (15 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 15 mL), the combined organics were washed with brine (1 X 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (50/1 hexanes/AcOEt) to give the acetate as a colorless oil (765 mg, 99.4%). Kinetic resolution: 53.6% conversion,

42.7% yield, 96.1% ee, $[\alpha]^{25}_D$ = -156.6° (*c* 0.57 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$)[40] δ 7.40 – 7.20 (m, 5H), 6.34 (dd, J = 4.8, 3.3 Hz, 1H), 5.94 (dd, J = 3.6 Hz, 1H), 2.40 – 2.15 (m, 2H), 2.10 – 1.70 (m, 4H), 1.94 (s, 3H). Anal Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.69.

Epoxide (MF2120, 2125). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 32.1% yield, 88.4% ee (*trans*); IR (NaCl): 1735, 1378, 1235 cm^{-1}; (*trans*): IR (NaCl): 1735, 1378, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 7.35 – 7.25 (m, 3H), 5.42 (t, J = 4.2 Hz, 1H), 3.37 (s, 1H), 2.10 – 2.02 (m, 2H), 1.96 – 1.85 (m, 1H), 1.82 (s, 3H), 1.69 – 1.54 (m, 2H), 1.52 – 1.40 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 169.6, 138.2, 127.9, 127.6, 125.5, 70.13, 61.45, 59.44, 25.68, 23.30, 20.83, 14.65. Anal Calcd for $C_{14}H_{16}O_3$ (*trans* and *cis* mixture): C, 72.39; H, 6.94. Found: C, 72.39; H, 6.97.

(Table 3.1, Entry 4)

(*S*)-1-Phenyl-6-(ethoxycarbonyloxy)cyclohexene (3-5)(MF1915). To a solution of 6-hydroxy-1-phenylcyclohexene (0.80 g, 4.59 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added ethyl chloroformate (1.49 g, 13.8 mmol) and pyridine (1.09 g, 13.8 mmol) and the solution was stirred overnight with gradual warming to room temperature. The reaction was quenched with H_2O (10 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (2 X 15 mL), the combined organics were washed with brine (1 X 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (50/1 hexanes/AcOEt) to give the acetate as a colorless oil (1.02 g, 90.3%). Kinetic resolution: 51.0% conversion, 45.1% yield, 93.7% ee, $[\alpha]^{25}_D$ = -98.8° (*c* 1.13 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$)[41] δ 7.40 – 7.20 (m, 5H), 6.32 (dd, J = 4.8, 3.3 Hz, 1H), 5.78 (m, 1H), 4.14

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[40] Hansson, S.; Heumann, A.; Rein, T.; Akermark, B. *J. Org. Chem.* **1990**, *55*, 975.

[41] Iwamatsu, S.-I.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, 9625.

(qd, J = 7.2, 0.6 Hz, 2H), 2.40 – 2.10 (m, 3H), 2.00 – 1.70 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H). HRMS Calcd (M^++1) for $C_{15}H_{18}O_3$: 2447.1334. Found: 247.1332.

Epoxide (MF2118, 2133). (*trans*) colorless oil; Kinetic resolution: 47.8% yield, 97.8% ee (*trans*); IR (NaCl): 1746, 1372, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.30 – 7.20 (m, 3H), 5.28 (t, J = 4.2 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 3.37 (s, 1H), 2.09 –2.03 (m, 2H), 1.96 (tt, J = 12.0, 3.6 Hz, 1H), 1.75 – 1.60 (m, 2H), 1.51 – 1.40 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 154.1, 137.8, 127.9, 127.5, 73.99, 63.84, 61.16, 59.61, 25.54, 23.08, 14.40, 14.05. HRMS Calcd (M^++1) for $C_{15}H_{18}O_4$: 263.1283. Found: 263.1285.

(Table 3.1, Entry 5)

1-Bromo-6-(*tert*-butyldimethylsilyloxy)cyclohexene (3-6)(MF1607, 1617). To a solution of cyclohexenone (10.3 ml, 105 mmol), in CCl_4 (70 mL) at 0 °C was added Br_2 (5.75 mL, 112 mmol) in CCl_4 (20 mL) over 45 m and the solution was stirred for 5 h, then NEt_3 (11.33 g, 112 mmol) was added dropwise as a solution in CCl_4 (40 mL) at 0 °C over 1 h. The resulting gray suspension was stirred vigorously for 1 h and the solid was filtered off. The resulting filtrate was washed with 1 N HCl (50 mL), H_2O (50 mL), brine (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure (and recycled) to give crude product (14.90 g, 80.0%, which was taken directly to the next step.[42]

To a solution of the crude enone (14.9 g, 85.1 mmol) in MeOH (30 mL) at 0 °C was added $CeCl_3 7 H_2O$ (31.7 g, 85.1 mmol) and it was stirred until all of the cerium dissolved. To this solution was added $NaBH_4$ (3.22 g, 85.1 mmol) portionwise over 30 m. The suspension was then stirred over 2 h with gradual warming to room temperature,

[42] (a) Sato, K.; Inoue, S.; Kuranami, S.I.; Ohashi, M.; *J. Chem. Soc. Perkin Trans., I* **1977**, 1666. (b) Smith, A.B., III; Brance, S.J.; Prilla, N.W.; Graciano, M.A. *J. Org. Chem.* **1995**, 599.

taken back to 0 °C, and quenched by the dropwise addition of H_2O (2 mL). The MeOH was then removed under reduced pressure, the white residue was taken up in H_2O (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 X 30 mL). The combined organics were washed with brine (1 X 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced to give the alcohol as a slightly colorless oil (14.74 g, 97.6%).[43] This crude product was again taken on as produced.

To a solution of crude 1-bromo-6-hydroxycyclohexene (8.46 g, 47.8 mmol) in dry DMF (18 mL) was added *tert*-butyldimethylsilyl chloride (TBDMSCl) (8.64 g, 57.4 mmol), imidazole (7.81 g, 114.7 mmol), and 4-dimethylamino pyridine (0.10 g) and the solution was stirred for 24 h. The reaction was then quenched with H_2O (30 mL) and extracted with hexanes (3 X 30 mL). The combined organics were washed with brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on silica gel (hexanes) to give TBS ether **3-7** as a colorless oil (9.75 g, 70.1%). IR (NaCl): 1645, 1472, 1362, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (dd, J = 4.6, 3.7 Hz, 1H), 4.15 (m, 1H), 2.15 – 1.90 (m, 2H), 1.82 – 1.65 (m, 2H), 1.55 (m, 2H), 0.89 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); 131.9, 125.8, 70.60, 33.74, 27.78, 25.82, 18.13, 17.20, -4.47, -4.67.

(*S*)-1-Methyl-6-(*tert*-butyldimethylsilyloxy)cyclohexene (3-12)(MF2644). To a solution of 1-bromo-6-(*tert*-butyldimethylsiloxy)cyclohexene (2.91 g, 10.0 mmol) in THF (15 mL) at –78 °C was added n-BuLi (4.8 mL, 12 mmol, 2.5 M in hexanes) and the solution was stirred at –78 °C for 2.5 h, and then MeI (1.70 g, 12 mmol) was added. The reaction was stirred overnight with warming to room temperature and the reaction was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The combined organics were washed with brine (1 X 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a

[43] Bentley, T.W.; Narman, S.J.; Kemmer, R.; Christl, M. *Liebigs. Ann. Chem.* **1995**, 599.

yellow oil, which was purified by flash column chromatography (50/1 hexanes/AcOEt) to give the methyl ether as a colorless oil (1.52 g, 67.2%). Kinetic resolution: 71.4% conversion, 27.4% yield, 88.7% ee, $[\alpha]^{25}_{D}$ = -24.3° (*c* 0.40, $CHCl_3$); IR (NaCl): 3387, 1670, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[44] δ 5.48 (s, 1H), 4.03 (s, 1H), 2.05 – 1.89 (m, 2H), 1.78 – 1.59 (m, 2H), 1.68 (s, 3H), 1.53 – 1.46 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). The recovered olefin was converted to the alcohol in order to determine the absolute configuration: $[\alpha]^{25}_{D}$= -94.9° (*c* 0.13, $CHCl_3$); lit.[45] $[\alpha]^{20}_{D}$= +130° (*c* 1.39, $CHCl_3$ for (*R*)-enantiomer).

The recovered olefin was converted to the acetate in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1H), 5.19 (t, J = 4.5, 1H), 2.04 (s, 3H), 2.10 – 1.90 (m, 2H), 1.77 (t, J = 4.5 Hz, 1h), 1.74 (t, J = 4.8 Hz, 1H), 1.63 (s, 3H), 1.62 – 1.51 (m, 2H).

Epoxide (MF2647). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 64.7% yield; IR (NaCl): 1472, 1257, cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (t, J = 4.8 Hz, 1H), 2.98 (s, 1H), 1.85 – 1.80 (m, 2H), 1.70 – 1.60 (m, 2H), 1.28 (s, 3H), 1.30 – 1.20 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 69.65, 60.64, 59.87, 29.39, 25.81, 23.97, 20.37, 18.05, 14.55, -4.44, -4.88. Anal Calcd for $C_{13}H_{26}O_2$ (*trans* and *cis* mixture): C, 66.14; H, 10.23. Found: C, 66.32; H, 10.48.

(Table 3.1, Entry 6)

1,3,3-Trimethyl-6-hydroxycyclohexene. The compound was made according to the Luche procedure for **3-6** (1.00 g, 96.0%). ^1H NMR (300 MHz, $CDCl_3$)[46] δ 5.24 (br s, 1H),

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[44] Zhu, S.S.; Cefalo, D.R.; La, D.S.; Jamieson, J.Y.; Davis, W.M.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **1999**, *121*, 8251.

[45] Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* **1985**, *33*, 52.

[46] Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1991**, 1053.

3.93 (t, J = 5.0 Hz, 1H), 1.74 (d, J = 1.0 Hz, 3H), 2.10 – 1.30 (m, 5H), 1.00 (s, 3H), 0.92 (s, 3H).

(*S*)-1,3,3-Trimethyl-6-(*tert*-butyldimethylsilyloxy)cyclohexene (3-14). The compound was made according to the procedure for **3-7** to give the TBS ether as a colorless oil (1.20 g, 95.0%). Kinetic resolution: 55.5% conversion, 43.6% yield, 88.6% ee, $[\alpha]^{25}_{D}$ = -21.5 (*c* 0.62, $CHCl_3$); IR(NaCl): 1650, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, J = 0.9 Hz, 1H), 3.98 (t, J = 6.0 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.70 –1.50 (m 2H), 1.66 (s, 3H), 1.40 – 1.30 (m, 1H), 0.98 (s, 3H), 0.91 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 134.9, 134.3, 70.06, 34.15, 32.29, 30.36, 29.97, 29.56, 20.88, 18.40, -4.07, -4.47. Anal Calcd for $C_{15}H_{30}OSi$: C, 70.86; H, 11.80. Found: C, 70.88; H, 11.95.

The recovered olefin was converted to the acetate to determine absolute configuration and enantiomeric excess: $[\alpha]^{25}_{D}$= -90.2° (*c* 0.23, MeOH); lit[21] $[\alpha]^{21}_{D}$= -97.9° (*c* 1.07, MeOH) for (*S*)-enantiomer. (*trans* acetate): ^1H NMR (300 MHz, $CDCl_3$)[46] δ 5.38 (s, 1H), 5.16 (d, J = 5.0 Hz, 1H), 2.07 (s, 3H), 1.62 (s, 3H), 2.0 – 1.35 (m, 4H), 1.02 (s, 3H), 0.95 (s, 3H).

Epoxide (MF2548). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 18.4% yield; IR (NaCl): 1472, 1362, 1256 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (t, J = 4.5 Hz, 1H), 2.57 (s, 1H), 1.70 – 1.59 (m, 1H), 1.31 – 1.20 (m, 2H), 1.28 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 1.09 – 1.00 (m, 1H), 0.87 (s, 9H), 0.57 (s, 3H), 0.03 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 69.62, 69.11, 61.51, 29.87, 29.76, 27.16, 26.03, 25.85, 20.45, 18.08, -4.38, -4.86. Anal Calcd for $C_{15}H_{30}O_2Si$ (*trans* and *cis* mixture): C, 66.67; H, 11.10. Found: C, 66.49; H, 11.02.

The epoxides were converted to the corresponding acetate to determined the enantiomeric excess: (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, J = 5.1 Hz, 1H), 2.66 (s, 1H), 2.09 (s, 3H), 1.77 (tq, J = 9.9, 4.2 Hz, 1H), 1.48 – 1.38 (m, 1H), 1.29 (s, 3H), 1.25 – 1.16 (m, 2H), 1.07 (s, 3H), 1.03 (s, 3H).

(Table 3.1, Entry 7)

1-Bromo-6-methoxycyclohexene (3-8)(MF1618). A 100 mL roundbottom flask was charged with NaH (786 mg, 19.7 mmol, 60% dispersion in mineral oil) and the gray solid was washed with pentane (3 X 5 mL) and taken up in distilled THF (30 mL). 1-Bromo-6-hydroxycyclohexene (2.90 g, 16.4 mmol) was added as a solution in THF (15 mL) and the orange suspension was stirred for 30 m. MeI (18.6 g, 131 mmol) was added, the reaction was stirred for 2 h, it was quenched with H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 X 15 mL). The combined organics were washed with brine (1 X 10 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure to give a yellow oil. The oil was purified by flash chromatography on silica gel (3/1 hexanes/ Et_2O) to give the methyl ether as a colorless oil (2.54 g, 81.1 %). IR (NaCl): 1643, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, J = 4.8, 3.6 Hz, 1H), 3.75 (t, J = 3.6 Hz, 1H), 3.45 (s, 3H), 2.20 – 2.00 (m, 2H), 1.80 – 1.55 (m, 2H), 1.40 – 1.20 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 133.5, 122.5, 78.47, 57.23, 28.27, 27.68, 16.82.

6-(Methoxy)cyclohexene-1-carboxaldehyde (MF1621). To a solution of 1-bromo-6-methoxycyclohexene (2.54 g, 13.3 mmol) in distilled THF (25 mL) at –78 °C was added n-BuLi (5.85 mL, 14.6 mmol, 2.5 M in hexanes) and the solution was stirred at –78 °C for 2 h, at which time DMF (4 mL) was added dropwise and the solution was stirred for 30 m with gradual warming. The reaction was quenched with H_2O (10 mL) and the pH adjusted to about 2 with 1 N HCl. Et_2O (25 mL) was added, the layers were separated, and the aqueous solution was extracted with Et_2O (2 X 20 mL). The combined organics were washed with brine (1 X 20 mL), dried (Na_2SO_4), and the solvent removed under

reduced pressure to give a yellow oil (1.60 g, 85.9% crude) which was taken directly to the next step.

(*S*)-6-(Methoxy)cyclohexene-1-methanol. (3-13)(MF1622). To a solution of crude 1-carboxaldehyde-6-methoxycyclohexene (1.50 g, 10.7 mmol) in distilled Et_2O (20 mL) at 0 °C was added DIBAL (11.8 mL, 11.8 mmol, 1.0 M in hexanes) and the solution was stirred for 2 h with gradual warming to room temperature. The reaction was quenched with saturated NH_4Cl (5 mL) at 0 °C, and the aluminum salts were filtered through a sintered glass funnel. The filtrate was then extracted with Et_2O (3 X 20 mL). The combined organics were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (1/1 hexane/Et_2O) to give the methyl ether as a light yellow oil (300 mg, 20%, 17% over two steps). 23.4% ee, $[\alpha]^{25}_D$= -49.7° (*c* 0.30, CH_2Cl_2); IR (NaCl): 3387, 1670, 1191 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (dt, J = 4.5, 1.2 Hz, 1H), 4.16 (d, J = 11.4 Hz, 1H), 4.07 (dd, J = 11.4, 7.5 Hz, 1H), 3.86 (t, J = 3.6 Hz, 1H), 3.40 (s, 3H), 2.40 = 2.30 (m, 1H), 2.20 – 1.50 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 136.9, 128.8, 76.02, 66.40, 56.29, 26.42, 25.07, 18.21.

(Table 3.1, Entry 8)

6-(*tert*-Butyldimethylsilyloxy)cyclohexene-1-carboxaldehyde (3-9)(MF1544). To a solution of 1-bromo-6-(*tert*-butyldimethylsiloxy)cyclohexene (871 mg, 3.0 mmol) in distilled THF (3 mL) at –78 °C was added n-BuLi (1.3 mL, 3.3 mmol, 2.5 M in hexanes) and the solution was stirred at –78 °C for 5 h, at which time DMF (4 mL) was added dropwise and the solution was stirred for 30 m with gradual warming. The reaction was quenched with H_2O (10 mL), and the pH adjusted to about 7 with 1 N HCl *carefully*. (The acid must be added dropwise very slowly. It was found that fast addition caused a severe reduction of yield, presumably due to elimination of the formyl group) Et_2O (15 mL) was

added, the layers were separated, and the aqueous solution was extracted with Et_2O (2 X 10 mL). The combined organics were washed with brine (1 X 10 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure to give the aldehyde as a colorless oil. (438 mg, 61.0% crude). IR (NaCl): 1692, 1644, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 6.82 (ddd, J = 4.8, 2.7, 0.6 Hz, 1H), 4.62 (t, J = 3.3 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.30 – 2.18 (dddd, J = 10.5, 6.3, 3.0, 1.2 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.90 – 1.80 (m, 1H), 1.75 – 1.60 (m, 1H), 1.51 (tt, J = 13.5, 3.0 1H), 0.87 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 193.0, 152.4, 142.7, 59.91, 30.99, 26.69, 25.86, 18.08, 16.41, -4.60, -4.93.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)cyclohexene-1-methanol. (3-10)(MF1548). The compound was reduced with DIBAL according to the procedure for **3-13** (466 mg, 62.7%). Kinetic resolution: 69.6% conversion, 27.7% yield, 80.9% ee; IR (NaCl): 3331, 1669, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (t, J = 3.6 Hz, 1H), 4.36 (t, J = 5.4 Hz, 1H), 4.13 (d, J = 11.7 Hz, 1H), 4.03 (dd, J = 11.7, 8.4 Hz, 1H), 2.30 – 1.50 (m, 7H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 139.1, 127.5, 68.73, 65.91, 32.75, 25.72, 25.15, 19.36, 18.01, -4.08, -4.81. Anal Calcd for $C_{13}H_{26}O_2Si$: C, 64.40; H, 10.80. Found: C, 64.36; H, 10.66.

Epoxide (MF1606). (*trans*, isolated as a mixture with ketone **1-26**) colorless oil; IR (NaCl): 1490, 1472, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (br s, 1H), 3.85 (d, J = 12.3 Hz, 1H), 3.62 (d, J = 12.3 Hz, 1H), 3.27 (d, J = 1.2 Hz, 1H), 2.03 – 1.70 (m, 4H), 1.40 – 1.20 (m, 2H), 0.91 (s, 9H), 0.13 (s, 3H), 0.98 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 68.53, 63.32, 61.25, 57.53, 30.04, 25.88, 23.80, 18.30, 14.75, -4.47, -5.18. HRMS Calcd for $C_{13}H_{26}O_3Si$: 259.1730. Found: 259.1729.

(Table 3.1, Entry 9)

(*S*)-6-Methoxycyclohexene-1-methylbenzoate (3-11)(MF 1703) To a solution of 6-*tert*-alcohol **3-10** (0.70 g, 2.90 mmol) in CH_2Cl_2 (10 mL) was added benzoyl chloride (0.45 g, 3.20 mmol) and triethylamine (1.47 g, 14.5 mmol), and 4-dimethylaminopyridine (0.02 g) and the solution was stirred overnight. The reaction was quenched with H_2O (10 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (2 X 15 mL), the combined organics were washed with brine (1 X 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (50/1 hexanes/AcOEt) to give the benzoate as a colorless oil (0.98 g, 97.6%). Kinetic resolution: 34.2% conversion, 56.9% yield, 30.1% ee; IR (NaCl): 1721, 1602, 1451, 1271 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.60 – 7.53 (m, 1H), 7.48 – 7.42 (m, 2H), 5.94 (dt, J = 3.6, 0.9 Hz, 1H), 5.91 (dd, J = 12.3, 1.5 Hz, 1H), 4.76 (d, J = 12.3 Hz, 1H), 4.37 (t, J = 4.8 Hz, 1H), 2.15 – 2.05 (m, 2H), 1,85 – 1.70 (m, 2H), 1.65 – 1.55 (m, 2H), 0.91 (s, 9H), 0.10 (s, 3H), 0.86 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 166.4, 135.3, 132.8, 130.5, 129.6, 129.2, 128.3, 66.29, 65.71, 32.54, 25.82, 25.28, 18.56, 18.04, -4.26, -4.90.

Epoxide (MF1727). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 20.1% yield; IR (NaCl): 1724, 1451, 1274 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.7 Hz, 2H), 7.57 (tt, J = 7.5, 4.2 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.82 (d, J = 12.0 Hz, 1H), 4.35 (t, J = 4.5 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.28 (t, J = 2.1 Hz, 1H), 1.95 – 1.90 (m, 2H), 1.80 – 1.60 (m, 2H), 1.45 – 1.25 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 166.3, 133.0, 130.0, 129.7, 128.3, 66.41, 65.38, 59.86, 57.01, 28.70, 25.76, 23.19, 17.95, 14.27, -4.37, -5.08.

(Table 3.2, Entry 1)

3-Ethoxy-2-cyclohexene-1-one (3-15)(MF1916). To a solution of 1,3-cyclohexanedione (47.05 g, 420 mmol) in benzene (900 mL) was added absolute EtOH (250 mL) and *p*-TsOH (2.3 g) and the heated to remove the benzene/EtOH azeotrope (59 °C) at about 100 mL/hour. When the temperature of the distillate reached 74 °C it was cooled and the red syrup was extracted with 1 N NaOH (4 X 100 mL). The organic solvent was then removed under reduced pressure and the resulting red syrup was distilled (70–75 °C/1 mmHg) to give the vinylagous ester as a colorless oil (44.02 g, 74.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.41 (t, J = 6.3 Hz, 2H), 2.35 (t, J = 6.0 Hz, 2H), 1.98 (dt, J = 6.3, 6.0 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

3-Phenyl-2-cyclohexene-1-one (3-16)(MF1917). To a solution of PhMgBr (71 mL, 214 mmol, 3.0 M in Et_2O) in Et_2O (150 mL) at –78 °C was added 3-ethoxy-2-cyclohexen-1-one (10.0 g, 41.4 mmol) as a solution in Et_2O (100 mL) over 3 h. The resulting light brown suspension was stirred for an additional 2 h at –78 °C then warmed to –10 °C over 2 h. Glacial acetic acid (12 mL) and H_2O (40 mL) were added in succession at –10 °C and the resulting lemon yellow solution was extracted with AcOEt (3 X 100 mL). The combined organics were washed with saturated $NaHCO_3$ (1 X 100 mL), H_2O (1 X 100 mL), brine (1 X 100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (8/1 hexanes/AcOEt) to give the ketone as a colorless oil (12.1 g, 98.1%). ^{1}H NMR (300 MHz, $CDCl_3$)[47] δ 7.60 – 7.30 (m, 5H), 6.42 (s, 1H), 2.78 (td, J = 6.0, 1.2 Hz, 2H), 2.49 (t, J = 6.9 Hz, 2H), 2.16 (tt, J = 6.9, 6.0 Hz, 2H).

1-Phenyl-3-hydroxycyclohexene (3-17)(MF1919). The Luche reduction was done according to the procedure provided for **3-6** (3.33 g, 99.0%). ^{1}H NMR (300 MHz,

[47] House, H.E.; Wilkins, J.M. *J. Org. Chem.* **1978**, *43*, 2443.

$CDCl_3$)[48] δ 7.45 – 7.20 (m, 5H), 6.13 (ddd, J = 3.6, 1.8, 1.8 Hz, 1H), 4.39 (m, 1H), 2.55 – 2.30 (m, 2H), 2.0 – 1.85 (m, 2H), 1.80 – 1.60 (m, 3H).

(*R*)-1-Phenyl-3-(*tert*-butyldimethylsilyloxy)cyclohexene (3-18)(MF1924). To a solution of 1-Phenyl-3-hydroxycyclohexene (503 mg, 2.9 mmol) in dry CH_2Cl_2 (10 mL) was added TBDMSCl (1.06 g, 7.0 mmol) and NEt_3 (731 mg, 7.2 mmol), and the solution was stirred for 24 h. The reaction was then quenched with H_2O (10 mL) and extracted with hexanes (3 X 10 mL). The combined organics were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on silica gel (100/1 hexanes/AcOEt) to give the silyl ether as a colorless oil (687 mg, 82.5%). Kinetic resolution: 99.4% ee, $[\alpha]^{25}_D$ = + 28.4° (*c* 0.94, $CHCl_3$); IR (NaCl): 1644, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 5H), 6.03 (ddd, J = 6.3, 1.5, 1.5 Hz, 1H), 4.44 (m, 1H), 2.55 – 2.30 (m, 2H), 2.05 – 1.90 (m, 2H), 1.80 – 1.60 (m, 2H), 0.96 (m, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 141.7, 138.6, 128.2, 127.1, 125.4, 67.61, 32.19, 27.39, 25.98, 20.15, 18.32, -4.44, -4.50. Anal Calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 74.85; H, 9.75.

Epoxide (MF2116). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 80.6% ee (*trans*); IR (NaCl): 1472, 1257, 1095 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.48 (m, 5H), 4.29 (dd, J = 8.7, 6.0 Hz, 1H), 3.27 (d, J = 0.9 Hz, 1H), 2.56 – 2.45 (m, 1H), 2.38 (dt, J = 14.7, 4.8 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.92 – 1.82 (m, 1H), 1.75 – 1.63 (m, 1H), 1.60 – 1.50 (m, 1H), 1.16 (s, 9H), 0.36 (s, 6H). Anal Calcd for $C_{18}H_{28}O_2Si$ (*trans* and *cis* mixture): C, 74.94; H, 9.78. Found: C, 74.85; H, 9.75.

The epoxide was converted to the benzoate to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 6.0 Hz, 2H), 7.70 – 7.30 (m, 8H), 6.22 (br s, 1H), 5.72 (m, 1H), 2.65 – 2.55 (m, 1H), 2.50 – 2.40 (m, 1H), 2.20 – 1.50 (m, 4H).

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[48] Reich, H.J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.

(Table 3.2, Entry 2)

(*R*)-3-Methoxy-1-phenylcyclohexene (3-19)(MF1925). The methyl ether was prepared according to the procedure given for **3-8** (0.54 g, 98.3%). 95% ee; $[\alpha]^{25}_{D}$ = +52.0° (*c* 0.15, $CHCl_3$); IR (NaCl): 1643, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.30 – 7.15 (m, 3H), 6.15 (ddd, J = 5.1, 1.5, 1.5 Hz, 1H), 3.92 (m, 1H), 3.41 (s, 3H), 2.50 – 2.30 (m, 2H), 1.95 – 1.85 (m, 2H), 1.75 – 1.65 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 141.5, 140.4, 128.1, 127.2, 125.3, 124.2, 74.83, 55.76, 27.62, 27.43, 19.56. Anal Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.93; H, 8.37.

Epoxide (MF2115). (*trans* and *cis* mixture) colorless oil: IR (NaCl): 1495, 1448, 1101 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 3.57 (dd, J = 9.0, 6.0 Hz, 1H), 3.45 (s, 3H), 3.10 (s, 1H), 2.21 (dd, J = 10.2, 5.4 Hz, 1H), 2.14 (dt, J = 14.1, 3.9 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.67 – 1.56 (m, 1H), 1.43 (ddd, J = 10.2, 5.1, 2.4 Hz, 1H), 1.26 (dq, J = 8.1, 3.9 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 141.2, 128.3, 127.5, 125.4, 75.71, 63.23, 61.30, 56.93, 28.56, 27.10, 15.84. Anal Calcd for $C_{13}H_{16}O$ (*trans* and *cis* mixture): C, 76.44; H, 7.90. Found: C, 76.23; H, 7.66.

(Table 3.2, Entry 3)

1-Phenyl-3-(ethoxycarbonyloxy)cyclohexene (3-20)(MF1926). The carbonate was prepared according to the procedure provided for **3-5** (1.17 g, 98.4%). IR (NaCl): 1733, 1644, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.35 – 7.20 (m, 3H), 6.14 (ddd, J = 5.7, 1.5, 1.5 Hz, 1H), 5.31 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.55 – 2.30 (m, 2H), 1.95 – 1.75 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 154.9, 142.9, 140.9, 128.2, 127.6, 125.4, 121.4, 72.33, 63.69, 27.84, 27.33, 19.03, 14.23.

(*R*)-[bis(methoxycarbonyl)methyl]-1-phenylcyclohexene (3-21)(MF2206). To a solution of NaH (178 mg, 4.46 mmol, 60% dispersion in mineral oil), in dry THF (15

mL) was added dimethylmalonate (536 mg, 4.06 mmol) and $Pd(dba)_3{\cdot}CHCl_3$ (462 mg, 0.4 mmol) the solution was stirred for 30 m. 3-Ethoxycarbonyloxy-1-phenylcyclohexene (1.0 g, 4.06 mmol) and the red solution was heated to reflux for 4 h, then cooled. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with Et_2O (3 X 15 mL), the combined organics were washed with brine (1 X 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (50/1 to 15/1 hexanes/AcOEt) to give the product as a colorless oil (1.03 g, 88.0%). Kinetic resolution: 80.6% ee, $[\alpha]^{25}_D$ = -23.9° (*c* 0.65, $CHCl_2$); IR (NaCl): 1737, 1598, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H), 5.85 (m, 1H), 3.69 (s, 6H), 3.40 (d, J = 9.6 Hz, 1H), 3.17 (m, 1H), 2.40 – 2.25 (m, 2H), 1.95 (m, 1H), 1.70 – 1.55 (m, 2H), 1.34 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 172.3, 172.1, 142.4, 139.3, 128.4, 127.1, 125.4, 125.1, 57.48, 52.77, 14.11, 27.57, 24.17, 22.78, 16.56. Anal Calcd for $C_{17}H_{20}O_4$: C, 70.80; H, 6.99. Found: C, 70.89; H, 6.90.

Epoxide (MF2209). (*trans* and *cis* mixture) colorless oil; IR (NaCl): 1754, 1739, 1436 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 3.74 (s, 6H), 3.56 (d, J = 6.0 Hz, 1H), 3.05 (s, 1H), 2.68 (dt, J = 11.7, 6.0 Hz, 1H), 2.21 – 2.14 (m, 2H), 1.70 – 1.10 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 168.6, 168.5, 141.6, 128.2, 127.4, 125.4, 62.94, 61.28, 54.75, 52.60, 52.49, 35.39, 28.91, 25.17, 18.35. Anal Calcd for $C_{17}H_{20}O_5$ (*trans* and *cis* mixture): C, 67.09; H, 6.62. Found: C, 66.88; H, 6.61.

(Table 3.2, Entry 4)

3-Methyl-2-cyclohexene-1-one (3-22)(MF2426). To a solution of MeLi (14 mL, 19.6 mmol, 1.4 M in pentane) in Et_2O (30 mL) at –78 °C was added 3-ethoxy-2-cyclohexen-1-one (2.1 g, 15.0 mmol) as a solution in Et_2O (15 mL) over 30 m. The solution was stirred for an additional 5 h at –78 °C , warmed to –10 °C over 2 h, and glacial acetic acid (2.6 mL) and H_2O (10 mL) were added in succession at –10 °C. The resulting lemon yellow

solution was extracted with AcOEt (3 X 25 mL). The combined organics were washed with saturated $NaHCO_3$ (1 X 30 mL), H_2O (1 X 30 mL), brine (1 X 30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (9/1 hexanes/AcOEt) to give the ketone as a colorless oil (1.22 g, 73.9%). IR (NaCl): 1667, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[49] δ 5.88 (s, 1H), 2.35 (t, J = 6.3 Hz, 2H), 2.29 (t, J = 6.0 Hz, 2H), 1.99 (septet, J = 6.3 Hz, 2H), 1.96 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 199.5, 162.7, 126.4, 36.90, 30.87, 24.40, 22.48.

(*R*)-1-Methyl-3-(*tert*-butyldimethylsilyloxy)cyclohexene (3-23)(MF2434, 2438). The alcohol was prepared according to the Luche procedure provided for **3-6** to give the alcohol as a light yellow oil (1.33 g, 82.4%) that was taken on.

The TBS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (2.06 g, 76.5%). Kinetic resolution: 63.1% conversion, 13.0% yield, 30.9% ee, $[\alpha]^{25}_D$ = -9.4° (*c* 0.11, $CHCl_3$); IR (NaCl): 1672, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.20 (s, 1H), 1.95 – 1.70 (m, 4 H), 1.64 (s, 3H), 1.53 – 1.42 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 136.8, 125.6, 67.36, 32.36, 29.97, 26.04, 23.64, 19.97, 18.42, -4.44, -4.54. Anal Calcd for $C_{13}H_{26}OSi$: C, 69.02; H, 11.49. Found: C, 69.21; H, 11.36.

The recovered olefin was converted to the benzoate in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (tt, J = 7.2, 1.5 Hz, 2H), 7.59 (t, J = 6.0 Hz, 2H), 7.47 (t, J = 8.4 Hz, 1H), 5.52 (d, J = 6.3 Hz, 1H), 3.98 (d, J = 6.3 Hz, 1H), 1.98 (s, 3H), 2.0 – 1.50 (m, 6H).

Epoxide (MF2520). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 55.5% yield, 36.5% ee (*trans*); IR (NaCl): 1472, 1257, 1007 cm^{-1}; (*trans*): ^1H NMR (300 MHz,

[49] Chong, B.-D.; Ji, Y. Il; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323.

$CDCl_3$) δ 3.89 (dd, J = 8.4, 6.0 Hz, 1H), 2.82 (s, 1H), 1.89 – 1.80 (m, 1H), 1.78 – 1.69 (m, 1H), 1.78 – 1.69 (m, 1H), 1.65 – 1.58 (m, 1H), 1.47 – 1.38 (m, 1H), 1.30 (s, 3H), 1.25 – 1.10 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.66 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 67.69, 64.17, 58.85, 30.75, 29.65, 25.92, 23.39, 18.28, 15.94, -4.60, -4.79.

The isolated epoxide was converted to the benzoate in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H), 7.55, (tt, J = 7.2, 1.5 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 5.26 (t, J = 6.0 Hz, 1H), 3.05 (s, 1H), 2.10 – 1.90 (m, 2H), 1.80 – 1.70 (m, 1H), 1.60 – 1.20 (m, 3H), 1.38 (s, 3H).

(Table 3.2, Entry 5)

1,5,5-Trimethyl-3-(*tert*-butyldiphenylsilyloxy)cyclohexene. The TBDPS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (1.12 g, 82.1% yield). Kinetic resolution: 48.0% conversion, 40.1% yield, 31.9% ee, $[\alpha]^{25}_D$ = +17.2°; (*c* 0.36, $CHCl_3$); IR (NaCl): 1673, 1589, 1407 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 4H), 7.45 – 7.32 (m, 6H), 5.33 (s, 1H), 4.25 (m, 1H), 1.79 (d, J = 17.7 Hz, 1H), 1.61 (s, 3H), 1.51 (d, J = 17.7 Hz, 1H), 1.45 – 1.30 (m, 2H), 1.07 (s, 9H), 0.92 (s, 3H), 0.65 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 136.1, 135.1, 134.9, 129.7, 127.7, 124.4, 68.54, 45.01, 44.30, 31.31, 31.03, 27.28, 26.76, 23.85. 19.39. The recovered olefin was converted to the benzoate in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 5.4 Hz, 2H), 7.53 (tt, J = 7.2, 1.5 Hz, 1H), 7.42 (t, J = 7.2 Hz, 2H), 5.59 (s, 1H), 5.23 (s, 1H), 1.89 (m, 1H), 1.85 (d, J = 6.3 Hz, 1H), 1.73 (s, 3H), 1.60 (d, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 1H), 1.07 (s, 3H), 1.00 (s, 3H).

Epoxide (MF2428). (*trans* and *cis* mixture) colorless oil: Kinetic resolution: 41.5% yield; IR (NaCl): 1590, 1472, 1111 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 4H), 7.45 – 7.32 (m, 6H), 4.17 (t, J = 5.4 Hz, 1H), 2.91 (s, 1H), 1.63 (d, J = 15.0 Hz, 1H), 1.50 (d, J = 15.0 Hz, 1H), 1.35 – 1.20 (m, 2H), 1.30 (s, 3H), 1.10 (s, 9H), 1.00

(s, 3H), 0.75 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.7, 133.9, 133.7, 129.6, 127.6, 67.51, 62.74, 58.97, 42.73, 41.70, 31.18, 29.46, 27.05, 26.97, 24.42, 19.24.

(Table 3.2, Entry 6,7)

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilylethynyl)cyclohexene (3-27) (MF1923). The TBS ether was prepared from alcohol **3-15** according to the procedure provided for **3-6** to give product as a colorless oil (2.06 g, 76.5%). IR (NaCl): 2148, 1627, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (ddd, J = 4.8, 1.8, 1.5 Hz, 1H), 4.22 (m, 1H), 2.15 – 2.00 (m, 2H), 1.85 – 1.70 (m, 2H), 1.60 – 1.40 (m, 2H), 0.88 (s, 9H), 0.16 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 138.3, 122.5, 106.2, 92.59, 66.48, 31.58, 29.15, 25.88, 19.47, 18.17, 0.01, -4.65. HRMS Calcd for (M^+-1) for $C_{17}H_{32}OSi_2$: 307.1913. Found: 307.1921.

The recovered olefin was exhaustively desilated and the free alcohol was then converted to the benzoate in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.60 (tt, J = 7.2, 2.1 Hz, 1H), 7.56 – 7.45 (m, 2H), 6.31 (dt, J = 1.8, 1.5 Hz, 1H), 5.60 (d, J = 3.9 Hz, 1H), 2.99 (s, 1H), 2.40 – 2.20 (m, 2H), 2.05 – 1.70 (m, 4H).

Epoxide (MF2113). (*trans* and *cis* mixture) colorless oil; IR (NaCl): 2172, 1472, 1251 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (dd, J = 8.4, 6.6 Hz, 1H), 3.23 (s, 1H), 2.13 (dt, J = 15.3, 4.3 Hz, 1H), 2.02 (m, 1H), 1.74 (td, J = 6.3, 6.0 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.20 – 1.10 (m, 2H), 0.91 (s, 9H), 0.17 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 104.8, 87.58, 66.88, 64.59, 51.68, 29.98, 29.29, 25.81, 18.16, 15.16, -0.23, -4.78, -4.93. Anal Calcd for $C_{17}H_{32}O_2Si$ (*trans* and *cis* mixture): C, 62.90; H, 9.94. Found: C, 63.01; H, 10.05.

(Table 3.2, Entry 8)

3-Pivalyloxy-2-cyclohexene-1-one (3-27)(MF1950). To a dry 500 mL roundbottom flask was added distilled 1,2-dichloroethane (150 mL), 1,3-cyclohexanedione (5.0 g, 44.6 mmol), trimethylacetyl chloride (5.37 g, 44.6 mmol), and pyridine (3.53 g, 44.6 mmol) and the solution was stirred for 1 h. It was quenched with H_2O (75 mL) and the organic layer was washed with HCl/H_2O (50 mL, 1/1 v/v), saturated $NaHCO_3$ (50 mL), saturated $CuSO_4$ (50 mL), brine (50 mL), and dried ($NaSO_4$). The organics were concentrated under reduced pressure and the resulting oil was purified by flash chromatography on silica gel (2/1hexanes/AcOEt) to give the enone as a colorless oil (2.06 g, 76.5%). IR (NaCl): 1755, 1681, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (dd, J = 1.2 Hz, 1H), 2.52 (td, J = 6.0, 1.2 Hz, 2H), 2.41 (t, J = 6.0 Hz, 2H) 2.06 (quintet of doublets, J = 6.0, 1.2 Hz, 2H), 1.28 (s. 9H); ^{13}C (75 MHz, $CDCl_3$) δ 199.4, 175.1, 170.3, 117.4, 39.24, 36.07, 28.15, 16.81, 21.21.

1-Pivalyloxy-2-cyclohexene-1-ol (3-28)(MF2007). The alcohol was prepared by DIBAL reduction at –78 °C according to the procedure provided for **3-13** to give product as a light yellow oil (3.68 g, 50.8%). IR (NaCl): 3428, 1745, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, J = 2.7, 1.2 Hz, 1H), 4.36 (m, 1H), 2.20 – 2.10 (m, 2H), 1.95 – 1.65 (m, 4H), 1.24 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 176.9, 151.7, 116.6, 65.03, 31.05, 26.95, 26.91, 18.37, 14.12.

(*R*)-1-Pivalyloxy-3-(trimethylsilyloxy)cyclohexene (3-29)(MF2011). The TMS ether was prepared according to the procedure given for **3-2** to give product as a colorless oil (761 mg, 77.6%). Kinetic resolution: 91.2% ee, $[\alpha]^{25}_D$ = +24.0° (*c* 0.25, $CHCl_3$); IR (NaCl): 1747, 1686, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (dt, J = 3.9, 1,5 Hz, 1H), 4.37 (m, 1H), 2.13 – 2.05 (m, 2H), 1.85 – 1.50 (m, 4H), 1.20 (s, 9H), 0.10 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 176.7, 151.0, 117.2, 65.85, 38.81, 31.64, 27.02, 26.65, 18.91, 0.16. Anal Calcd for $C_{14}H_{26}O_3Si$: C, 62.22; H, 9.62. Found: C, 62.20; H, 9.47.

Epoxide (MF2226): (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 77.0% ee (*trans*); IR (NaCl): 1748, 1466, 1132 cm $^{-1}$; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (dd, J = 7.8, 4.8 Hz, 1H), 3.11 (s, 1H), 2.31 (dt, J = 14.4, 5.4, 1H), 1.97 (ddd, J = 14.4, 9.3, 5.7 Hz, 1H), 3.84 (dd, J = 7.8, 4.8 Hz, 1H), 3.11 (m, 1H), 1.72 – 1.52 (m, 2H), 1.16 (s, 9H), 0.12 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 176.8, 99.91, 83.10, 67.05, 61.84, 38.70, 29.82, 26.80, 16.34, -0.01. HRMS Calcd for (M^++1) for $C_{14}H_{26}O_4Si_2$: 287.1679. Found: 287.1678.

(Table 3.2, Entry 9)

(*R*)-1-Pivalyloxy-3-(*tert*-butyldimethylsilyloxy)cyclohexene (3-30)(MF2012). The TBS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (1.01 g, 81.9%). Kinetic resolution: 76.3% ee, $[\alpha]^{25}_D$ = + 10.2° (*c* 0.22 $CHCl_3$); IR (NaCl): 1748, 1686, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (dt, J = 3.6, 1.5 Hz, 1H), 4.40 (m, 1H), 2.15 – 2.05 (m, 2H), 1.90 – 1.75 (m, 2H), 1.70 – 1.55 (m, 2H), 1.23 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 176.80, 150.70, 117.5, 66.21, 38.82, 31.80, 27.04, 26.66, 25.90, 18.92, 18.20, -4.62.

Epoxide (MF2225). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 75.8% ee (*trans*); IR (NaCl): 1755, 1463, 1259, 1128 cm $^{-1}$; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (dd, J = 7.5, 4.5 Hz, 1H), 3.05 (s, 1H), 2.27 (dt, J = 14.4, 5.4 Hz, 1H), 1.95 (dd, J = 11.4, 5.4 Hz, 1H), 1.65 – 1.55 (m, 2H), 1.30 – 1.20 (m, 2H), 1.12 (s, 9H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 176.8, 83.14, 67.36, 61.84, 38.72, 29.75, 26.96, 26.83, 25.78, 18.11, 16.21, -4.76, 4.91.

(Table 3.2, Entry 10)

(*R*)-1-Pivalyloxy-3-(ethoxycarbonyloxy)cyclohexene (3-31)(MF2013). The carbonate was prepared according to the procedure provided for **3-5** to give the product as a

colorless oil (1.01 g, 90.1%). Kinetic resolution: 34.9% ee, $[\alpha]^{25}_D$ = + 13.3° (*c* 0.36, $CHCl_3$); IR (NaCl): 1743, 1686, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (dt, J = 5.7, 1.5 Hz, 1H), 5.29 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.25 – 2.15 (m, 2H), 1.95 – 1.75 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H), 1.26 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 176.3, 154.7, 154.5, 112.0, 71.39, 63.75, 38.82, 27.46, 26.95, 26.71, 18.33, 14.22.

Epoxide (MF2013). (*trans* and *cis* mixture) colorless oil; IR (NaCl): 1747, 1464, 1131 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (ddd, J = 7.5, 5.1, 0.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.30 (s, 1H), 2.35 (dt, J = 14.4, 5.7 Hz, 1H), 2.07 (ddd, J = 19.8, 8.1, 6.0 Hz, 1H), 1.85 – 1.80 (m, 2H), 1.75 – 1.50 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.19 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 177.1, 154.7, 82.63, 71.95, 64.63, 58.80, 39.04, 27.11, 25.76, 18.28, 16.28, 14.54.

(Table 3.2, Entry 11)

(*R*)-1-Pivalyloxy-3-methylcyclohexene (3-32)(MF2306). To a suspension of CuCN (5.37 g, 60.0 mmol) in Et_2O (120 mL) at –78 °C under argon was added MeLi (44.3 mL, 62 mmol, 1.4 M in hexanes) and the suspension was stirred for 15 m. 2-Cyclohexene-1-one (1.92 g, 20.0 mmol) was then added dropwise and the resulting lemon yellow solution was stirred for 1 h at –78 °C at which time the trimethylacetyl chloride (13.97 g, 70.5 mmol) was added. The resulting suspension was stirred for 2 h with gradual warming to room temperature and the solids were filtered. The filtrate was washed with H_2O (100 mL), dried (Na_2SO_4), the organics were removed under reduced pressure, and the oil was purified by flash column chromatography (10/1 hexanes/Et_2O) to give the enol pivaloate as a colorless oil (779 mg, 20.0%).

Note: If the excess pivaloyl anhydride and product have similar chromatographic properties, the anhydride can be removed by treating the crude product with $NaBH_4$ before purification. Kinetic resolution: 37.2% ee, $[\alpha]^{25}_D$ = -7.1° (*c* 0.46 $CHCl_3$); IR

(NaCl): 1745, 1687, 1137 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (s, 1H), 2.40 – 2.30 (br s, 1H), 2.15 – 2.04 (m, 2H), 1.85 – 1.58 (m, 3H), 1.23 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.1, 148.3, 119.6, 38.76, 30.50, 29.43, 27.10, 26.57, 21.59, 21.37.

Epoxide (MF2318). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 89.6% ee (*trans*); IR (NaCl): 1739, 1459, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (d, J = 0.9 Hz, 1H), 2.30 – 2.10 (m, 1H), 2.05 – 1.95 (m, 2H), 1.62 – 1.25 (m, 3H), 1.19 (s, 9H), 1.14 (d, J = 7.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.4, 83.51, 64.04, 38.88, 30.00, 28.62, 27.04, 26.17, 20.31, 18.65.

(Table 3.2, Entry 12)

(*R*)-1-Pivalyloxy-3-(n-propyl)cyclohexene (3-33)(MF2338). The n-Pr derivative was prepared according to the above procedure with n-propyl magnesium bromide to give the enol pivaloate as a colorless oil (1.58 g, 71.0%). Kinetic resolution: 50.2% ee, $[\alpha]^{25}_D$ = -7.9° (*c* 0.33, $CHCl_3$); IR (NaCl): 1745, 1687, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.25 (s, 1H), 2.27 – 2.17 (m, 1H), 2.17 – 2.05 (m, 2H), 1.85 – 1.60 (m, 4H), 1.40 – 1.25 (m, 4H), 1.24 (s, 9H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.4, 148.7, 118.6, 39.07, 38.75, 34.60, 28.75, 27.42, 27.14, 21.81, 20.38, 14.51.

Epoxide (MF2339). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 90.6% ee (*trans*); IR (NaCl): 1740, 1461, 1139 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.00 (d, J = 0.6 Hz, 1H), 2.22 (dtt, J = 14.1, 3.9, 0.6 Hz, 1H), 2.05 – 1.92 (m, 2H), 1.87 – 1.70 (m, 1H), 1.62 – 1.35 (m, 7H), 1.19 (s, 9H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.5, 83.69, 63.62, 30.92, 35.62, 35.25, 27.54, 27.16, 26.88, 20.46, 19.12, 14.40.

(Table 3.2, Entry 13)

(*R*)-1-Pivalyloxy-3-(isopropyl)cyclohexene (3-34)(MF2310). The i-Pr derivative was prepared according to the above procedure with *iso*-propyl magnesium bromide to give the enol pivaloate as a colorless oil (1.70 g, 76.0%). Kinetic resolution: 93.1% ee, $[\alpha]^{25}_{D}$ = -26.1° (*c* 0.85, $CHCl_3$); IR (NaCl): 1745, 1687, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1H), 2.22 – 1.95 (m, 3H), 1.92 – 1.80 (m, 2H), 1.75 – 1.53 (m, 3H), 1.24 (s, 9H), 0.91 (d, J = 3.1 Hz, 3H), 0.89 (d, 3.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.1, 148.8, 117.0, 41.13, 28.73, 27.08, 26.78, 25.05, 22.01, 19.67. Anal Calcd for $C_{14}H_{25}O_2$: C, 75.02; H, 10.71. Found: C, 74.88; H, 10.54. Anal Calcd for $C_{14}H_{24}O_2$: C, 75.02; H, 10.71. Found: C, 74.88; H, 10.54.

Epoxide (MF2317). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 84.8% ee (*trans*); IR (NaCl): 1740, 1461, 1139 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (dddd, J = 13.5, 3.6, 2.4, 1.2 Hz, 1H), 1.98 (ddd, J = 17.4, 11.7, 5.7 Hz, 1H), 1.78 (septet, J = 6.3 Hz, 1H), 1.65 – 1.55 (m, 2H), 1.40 – 1.25 (m, 3H), 1.19 (s, 9H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 177.4, 84.03, 62.88, 42.34, 31.91, 30.83, 27.20, 23.66, 20.72, 20.39, 19.78, 19.73. HRMS Calcd (M^++1) for $C_{14}H_{24}O_3$: 241.1804. Found: 241.1801.

(Table 3.2, Entry 14)

(*R*)-1-Pivalyloxy-3-(*tert*-butyl)cyclohexene (3-35)(MF2303). The t-Bu derivative was prepared according to the above procedure with *tert*-butyllithium to give the enol pivaloate as a colorless oil (4.71 g, 99.0%). Kinetic resolution: 99.1% ee, $[\alpha]^{25}_{D}$ = -30.4° (*c* 0.28, $CHCl_3$); IR (NaCl): 1747, 1686, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (s, 1H), 2.21 – 1.55 (m, 7H), 1.24 (s, 9H), 0.89 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 177.1, 149.3, 115.8, 45.36, 38.72, 32.89, 27.24, 27.08, 26.63, 23.68, 22.57. Anal Calcd for $C_{15}H_{26}O_2$: C, 75.65; H, 10.92. Found: C, 75.49; H, 10.75.

The recovered enol ester was hydrolyzed (NaOH, MeOH) to give 3-*tert*-butylcyclohexanone in order to determine the absolute configuration by optical rotation. $[\alpha]^{25}_{D}$ = +22.0° (*c* 0.09, $CHCl_3$); lit[50] $[\alpha]_D$ = +27.5° (*c* 0.09, $CHCl_3$) for (*R*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (dtd, J = 13.2, 3.6, 2.1 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.25 (ddd, J = 13.2, 6.3, 1.2 Hz, 1H), 2.11 (dq, J = 13.2, 3.3, Hz, 1H), 2.08 (d, J = 13.2 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.51 (qdd, J = 13.2, 3.0, 1.2 Hz, 1H), 1.31 (ddd, J = 24.6, 12.6, 3.3 Hz, 1H), 0.89 (s, 9H).

Epoxide (MF2311). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 84.0% ee (*trans*); IR (NaCl): 1740, 1476, 1142 cm $^{-1}$; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 1H), 2.19 (dd, J = 14.4, 4.5 Hz, 1H), 1.97 (td, J = 12.6, 5.4 Hz, 1H), 1.67 – 1.54 (m, 2H), 1.48 (dd, J = 11.7, 5.4 Hz, 1H), 1.41 – 1.13 (m, 2H), 1.19 (s, 9H), 0.99 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 172.4, 79.38, 64.66, 56.86, 41.90, 34.19, 27.71, 22.87, 22.37, 17.88, 15.31. HRMS Calcd (M^++1) for $C_{15}H_{26}O_3$: 255.1961. Found: 155.1669.

(Table 3.2, Entry 15)

(*R*)-1-Acetoxy-3-(*tert*-butyl)cyclohexene (3-36). The t-Bu derivative was prepared according to the above procedure with *tert*-butyllithium followed by trapping with acetic anhydride to give the enol pivaloate as a colorless oil (2.20 g, 56.1%). Kinetic resolution: 85.3% ee, $[\alpha]^{25}_{D}$ = -31.2° (*c* 0.99, $CHCl_3$); IR(NaCl): 1757, 1684, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H), 2.12 (s, 3H), 2.10 – 1.50 (m, 7H), 0.88 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 169.5, 149.2, 116.3, 45.29, 32.89, 27.22, 26.79, 23.61, 22.55, 21.10.

Epoxide (MF2143). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 60.4% ee (*trans*); IR (NaCl): 1750, 1371, 1238 cm $^{-1}$; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 1H), 2.21 (d, J = 4.5 Hz, 1H), 2.02 (s, 3H), 1.60 – 1.45 (m, 2H), 1.45 – 1.40 (m, 1H),

[50] Zweig, J.S.; Luche, J.L.; Crabbe, P. *Tetrahedron Lett.* **1975**, 2355.

1.30 – 1.00 (m, 3H), 0.95 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) 169.2, 83.86, 61.30, 46.20, 32.22, 27.29, 26.68, 22.33, 21.16, 19.77.

(Table 3.2, Entry 16)

3-Benzoyloxy-2-cyclohexene-1-one (3-37)(MF1938). The enol benzoate was prepared according to the procedure provided for **3-27** using benzoyl chloride to give product as a colorless oil (10.06 g, 80.0%). IR (NaCl): 1741, 1678, 1644, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 – 8.05 (m, 2H), 7.70 – 7.60 (m, 1H), 7.55 – 7.45 (m, 2H), 6.05 (t, J = 1.2 Hz, 1H), 2.69 (td, J = 6.0, 1.2 Hz, 2H), 2.47 (t, J = 6.0 Hz, 2H), 2.13 (tt, J = 6.0 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 199.4, 170.1, 163.1, 134.0, 130.1, 128.6, 128.5, 117.8, 36.73, 28.36, 21.29.

3-Benzoyloxy-2-cyclohexene-1-ol (3-38)(MF2019) . Ketone **3-37** was reduced according to the procedure provided for **3-28** to give the product as a colorless oil (3.53 g, 37.4%). IR (NaCl): 3412, 1731, 1686, 1269 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 2H), 7.65 – 7.55 (m, 1h), 7.50 – 7.40 (m, 2H), 5.66 (dt, J = 4.2, 1.2 Hz, 1H), 4.44 (m, 1H), 2.35 – 2.22 (m, 2H), 2.00 – 1.65 (m, 5H); ^{13}C (75 MHz, $CDCl_3$) δ 164.8, 151.8, 133.4, 129.9, 129.5, 128.4, 117.3, 65.14, 31.05, 27.05, 18.49.

(*R*)-1-Benzoyloxy-3-(*tert*-Butyldimethylsilyloxy)cyclohexene (3-39)(MF2015). The TBS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (1.12 g, 80.8%). Kinetic resolution: 57.0% ee, $[\alpha]^{25}_D$ = +11.0° (*c* 0.50, $CHCl_3$); IR (NaCl): 1733, 1686, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.65 – 7.55 (m, 1H), 7.50 – 7.40 (m, 2H), 5.52 (dt, J = 3.6, 1.5 Hz, 1H), 4.47 (m, 1H), 2.30 –2.20 (m, 2H), 2.00 – 1.80 (m, 2H), 1.80 – 1.60 (m, 2H), 0.91 (s, 9H), 0.09 (s,

6H); ^{13}C (75 MHz, $CDCl_3$) δ 164.7, 150.7, 133.3, 129.9, 129.8, 128.4, 118.2, 66.24, 31.79, 26.95, 25.89, 19.01, 18.21, -4.61.

Epoxide (MF2111). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 42.3% ee (*trans*); IR (NaCl): 1733, 1452, 1275 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.4, 1.2 Hz, 2H), 7.50 (tt, J = 7.5, 1.5 Hz, 1H), 7.36 (tt, J = 8.4, 1.5 Hz, 2H), 3.89 (dd, J = 6.9, 3.9 Hz, 1H), 3.23 (s, 1H), 2.38 (dt, J = 14.1, 5.4 Hz, 1H), 2.15 (dd, J = 9.0, 5.7 Hz, 1H), 1.70 – 1.55 (m, 2H), 1.42 – 1.20 (m, 2H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 164.8, 133.4, 129.8, 129.5, 128.5, 83.73, 67.30, 61.98, 29.74, 27.23, 25.77, 18.11, 16.26, -4.76, -4.91.

(Table 3.2, Entry 17)

(*R*)-1-Benxoyloxy-3-(acetoxy)cyclohexene (3-40)(MF2016). To a solution of 3-hydroxy-1-(benzoyl)cyclohexene (1.50 g, 6.88 mmol) in CH_2Cl_2 (20 mL) was added acetic anhydride (772 mg, 7.60 mmol) and pyridine (816 mg, 10.3 mmol) and the solution was stirred overnight. The reaction was quenched with H_2O (10 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (2 X 15 mL), the combined organics were washed with brine (1 X 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (3/1 hexanes/AcOEt) to give the acetate as a colorless oil (1.22 g, 68.2%). Kinetic resolution: 51.3% ee, $[\alpha]^{25}_D$ = +18.3° (*c* 0.10, $CHCl_3$); IR (NaCl): 1733, 1687, 1239 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.2, 1.5 Hz, 2H), 7.59 (tt, J = 5.2, 1.5 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 5.66 (dt, J = 6.0, 1.5 Hz, 1H), 5.45 (m, 1H), 2.38 – 2.31 (m, 2H), 2.06 (s, 3H), 1.95 – 1.78 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 170.6, 164.4, 153.9, 133.4, 129.9, 129.5, 128.5, 113.2, 67.86, 27.58, 27.00, 21.31, 18.70.

Epoxide (MF2123). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 41.8% ee (*trans*); IR (NaCl): 1732, 1452, 1276 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.59 (tt, J = 7.2, 1.2 Hz, 1H), 7.44 (tt, J = 7.8, 1.2 Hz, 2H), 5.03 (dd, J = 7.2, 5.7 Hz, 1H), 3.40 (s, 1H), 2.44 (dd, J = 14.1, 5.7 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.13 (s, 3H), 1.94 – 1.70 (m, 2H), 1.60 – 1.40 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 170.2, 164.9, 133.6, 129.8, 129.0, 128.4, 82.97, 68.15, 59.12, 27.05, 25.51, 21.03, 16.16.

(Table 3.3, Entry 1)

(*E*)-α-Benzylidenecyclohexanone (3-41). To a solution of cyclohexanone (29.4 g, 300 mmol) and benzaldehyde (10.6 g, 100 mmol) in MeOH (30 mL) was added 15% KOH (1.87 mL, 5 mmol) and the reaction was stirred at room temperature for 3 h. The mixture was quenched with H_2O, extracted with CH_2Cl_2 (3 X 30 mL), and the combined organics were washed with brine (1 X 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was distilled (b.p. = 80 °C/1 mm Hg) to give the desired enone as a yellow oil (5.5 g, 81.0%) based on recovered starting material. IR (NaCl): 1689, 1602, 1256 cm^{-1}.

(*E*)-α-Benzylidene-1-cyclohexanol. (3-44). The alcohol was prepared by Luche reduction according to the procedure provided for **3-6** to give product as a yellow oil (4.5 g, 83.1%). ^1H NMR (300 MHz, $CDCl_3$)[51] δ 7.30 (m, 5H), 6.52 (br s, 1H), 4.30 (br s, 1H), 2.81 (m, 1H), 2.25 – 1.88 (m, 3H), 1.80 – 1.46 (m, 5H).

(*E*)-α-Benzylidene-1-(trimethylsilyloxy)cyclohexane (3-47)(MF2425). The silyl ether was prepared according to the procedure provided for **3-2** to give product as a colorless oil (657 mg, 94.5%). Kinetic resolution: 42.2% conversion, 46.1% yield, 40.7% ee,

[51] Peijnenburg, W.J.G.M.; Buck, H.M. *Tetrahedron* **1988**, *44*, 4927.

$[\alpha]^{25}_D$ = -24.1° (*c* 1.00, $CHCl_3$); IR (NaCl): 1599, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.20 (m, 5H), 6.58 (s, 1H), 4.23 (ddd, J = 4.8, 4.2, 1.5 Hz, 1H), 2.82 (dt, J = 14.1, 4.8 Hz, 1H), 1.72 – 1.35 (m, 4H), 2.18 – 1.85 (m, 3H), 0.24 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 144.4, 138.4, 129.1, 128.2, 126.2, 120.6, 74.25, 37.93, 27.65, 27.61, 23.97, 0.37.

The recovered starting material was converted to the alcohol to determine the absolute configuration: $[\alpha]^{25}_D$ = -12.0° (*c* 1.0, $CHCl_3$); lit[52] $[\alpha]^{20}_D$ = +37.0° (*c* 1.0, $CHCl_3$) for the (R) enantiomer.

Epoxide (MF2431). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 35.1% yield; IR (NaCl): 1449, 1251 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.52 (m, 5H), 4.53 (s, 1H), 4.07 (dd, J = 9.6, 4.5 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.17 – 1.97 (m, 3H), 1.92 – 1.50 (m, 3H), 1.46 – 1.36 (m, 1H), 0.48 (s, 9H). Anal Calcd for $C_{15}H_{24}O_2Si$ (*trans* and *cis* mixture): C, 68.18; H, 9.08. Found: C, 68.38: H, 8.89.

(Table 3.3, Entry 2)

(*E*)-α-(Pentylidene)cyclohexanone (3-42)(ZXM150). The enone was prepared by aldol condensation of cyclohexanone with valeraldehyde according to the procedure provided for **3-42** to give product as a colorless oil (12.0 g, b.p. = 160–170 °C/20 mmHg, 75% based on recovered starting material).[53]

(*E*)-α-Pentylidene-1-cyclohexanol (3-45). The alcohol was prepared by Luche reduction according to the procedure provided for **3-6** to give product as a light yellow oil (6.20 g, 89.0%) IR (NaCl): 3352, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 1H), 4.08 (m, 1H), 2.40 (m, 1H), 2.07 – 1.90 (m, 3H), 1.86 – 1.72 (m, 2H), 1.60 – 1.41 (m, 5H),

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[52] Fuganti, C.; Grasselli, P.; Mendozza, M.; Servi, S.; Zucchi, G. *Tetrahedron* **1997**, *53*, 2617.

[53] Mitsudo, T.-a.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230.

1.35 – 1.22 (m, 4H), 0.90 (m, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 140.84, 121.28, 73.70, 36.09, 32.09, 27.21, 26.42, 25.84, 22.83, 22.26, 13.92.

(*E*)-α-Pentylidene-1-(trimethylsilyloxy)cyclohexane (3-48)(MF2521). The silyl ether was prepared according to the procedure provided for **3-2** to give product as a colorless oil (1.36 g, 95.1%). Kinetic resolution: 53.2% conversion, 41.8% yield, 42.2% ee, $[\alpha]^{25}_D$ = -36.6° (*c* 1.21, $CHCl_3$); IR (NaCl): 1442, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (m, 1H), 3.96 (m, 1H), 2.42 (m, 1H), 2.00 (m, 2H), 1.75 (m, 3H), 1.56 – 1.29 (m, 8H), 0.88 (m, 3H), 0.08 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 140.8, 120.7, 74.26, 37.75, 32.43, 27.60, 26.70, 26.63, 23.76, 22.57, 14.24, 0.33.

Epoxide (MF2550). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 46.3% yield; IR (NaCl): 1455, 1250 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.42 (dd, J = 7.5, 3.3 Hz, 1H), 2.92 (m, 1H), 1.80 – 1.30 (m, 14H), 0.89 (t, J = 7.2 Hz, 3H), 0.64 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 72.51, 64.28, 61.03, 34.18, 28.91, 27.46, 26.48, 24.42, 22.64, 22.29, 14.09, 0.29.

(Table 3.3, Entry 3)

(*E*)-α-(isopropylidene)cyclohexanone (3-43). The enone was prepared by aldol condensation of cyclohexanone with isobutyraldehyde according to the procedure provided for **3-41** to give product as a colorless oil (24.5 g, b.p. = 125–130 °C/20 mmHg, 81.4 %).[54]

(*E*)-α-isopropylidene-1-cyclohexanol (3-46). The alcohol was prepared by Luche reduction according to the procedure provided for **3-6** to give product as light yellow oil (10.0 g, 73.0%).^1H NMR (300 MHz, $CDCl_3$)[55] δ 5.12 (d, J = 8.7, 1H), 4.00 (m, 1H), 2.56

[54] For characterization data, see: Paterson, I. *Tetrahedron* **1988**, *44*, 4207.

[55] Kelkar, S.V.; Arbale, A.A.; Joshi, G.S.; Kulkarni, G.H. *Synth. Commun.* **1990**, *20*, 839.

(m, 1H), 2.42 (m, 1H), 1.95 (m, 1H), 1.81 (m, 2H), 1.62 – 1.40 (m, 5H), 0.96 (d, J = 3.1 Hz, 3H), 0.94 (d, J = 3.1 Hz, 3H).

(*E*)-α-isopropylidene-1-(trimethylsilyloxy)cyclohexane (3-49)(MF2424). The silyl ether was prepared according to the procedure provided for **3-2** to give product as a colorless oil (1.14 g, 84.3%). Kinetic resolution: 35.2% conversion, 55.3% yield, 3.8% ee; IR (NaCl): 1672, 1472, 1462, 1357 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 8.7 Hz, 1H), 3.96 (m, 1H), 2.56 (m, 1H), 2.44 (m, 1H), 1.82 – 1.70 (m, 3H), 1.54 – 1.33 (m, 4H), 0.97 (d, J = 3.1 Hz, 3H), 0.95 (d, J = 3.1 Hz, 3H), 0.10 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 138.6, 128.3, 74.05, 37.42, 27.61, 26.57, 25.96, 23.46, 23.38, 0.09.

Epoxide. (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 20.6% yield, 1.8% ee (*trans*); IR (NaCl): 1453, 1251 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (dd, J = 7.5, 3.3 Hz, 1H), 2.59 (d, J = 9.3 Hz, 1H), 1.85 – 1.56 (m, 5H), 1.54 – 1.32 (m, 4H), 1.04 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 72.60, 67.18, 64.96, 34.06, 27.04, 26.72, 24.55, 22.15, 20.26, 19.13, 0.31.

The epoxides were converted to the benzoate for determination of the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.4, 1.8 Hz, 2H), 7.56 (tt, J = 7.8, 0.9 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 4.76 (dd, J = 5.7, 3.3 Hz, 1H), 2.81 (d, J = 9.6 Hz, 1H), 2.10 – 1.20 (m, 9H), 1.07 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H).

(Table 3.3, Entry 4)

(Z)-Ethyl-2-(2-methylcyclohexylidene)acetate (3-50)(MF2604). To a solution of diisopropylamine (4.01 g, 39.7 mmol) in THF (60 mL) at 0 °C was added n-BuLi (17.5 mL, 43.8 mmol, 2.5 M in hexanes) and the solution was stirred for 10 m at 0 °C , then taken to –78 °C and ethyl trimethylsilylacetate (6.36 g, 39.7 mmol) was added and the solution was stirred at that temperature for 45 m, at which time 2-methylcyclohexanone (4.45 g, 39.7 mmol) was added dropwise. The reaction was stirred at 2.5 h, warmed to

room temperature, quenched with saturated NH_4Cl (30 mL), extracted with Et_2O (3 X 50 ml), and the combined organics were washed with brine (1 X 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (97/3 hexanes/AcOEt) to give the acetate as a colorless oil (1.18 g, 16.4%, >19/1 *Z/E*). IR (NaCl): 1715, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (d, J = 1.8 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.39 (tdd, J = 13.2, 4.8, 1.8 Hz, 1H), 2.06 (d of mult., J = 13.2 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.68 – 1.48 (m, 5H), 1.38 (tt, J = 12.0, 2.7 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 183.7, 167.4, 166.4, 59.40, 33.24, 33.11, 32.94, 30.77, 28.27, 20.38, 18.36, 14.35.

(*Z*)-2-(2-Methylcyclohexylidene)ethanol (MF2605) The ester was reduced with 2.0 eq DIBAL according to the procedure provided for **3-13** to give the alcohol as a light yellow oil (795 mg, 88.2%). IR (NaCl): 3320, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (td, 6.9, 2.1 Hz, 1H), 4.24 (ddd, J = 12.0, 6.9, 0.9 Hz, 1H), 4.15 (ddd, J = 12.0, 6.9, 2.1 Hz, 1H), 2.94 (m, 1H), 2.38 – 2.24 (m, 1H), 2.07 – 1.98 (m, 1H), 1.87 – 1.77 (m, 1H), 1.68 – 1.50 (m, 4H), 1.47 – 1.25 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 147.9, 120.3, 58.28, 33.26, 32.38, 30.51, 28.34, 20.80, 18.70.

(*Z*)-2-(2-Methylcyclohexylidene)-1-(*tert*-butyldimethylsilyloxy)ethane (3-51)(MF2607). The TBS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (851 mg, 62.6%). Kinetic resolution: 73.3% conversion, 25.0% yield, 65.7% ee, $[\alpha]^{25}_D$ = +41.3° (*c* 0.29, $CHCl_3$); IR (NaCl): 1655, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (td, J = 6.6, 1.8 Hz, 1H), 4.22 (ddd, J = 12.6, 6.6, 1.2 Hz, 1H), 4.13 (ddd, J = 12.6, 6.6, 2.1 Hz, 1H), 2.85 – 2.73 (m, 1H), 2.22 (tdd, J = 13.8, 4.5, 2.1 Hz, 1H), 1.96 (d of mult., J = 13.5 Hz, 1H), 1.77 = 1.68 (m, 1H), 1.59 – 1.42 (m, 4H), 1.32 – 1.21 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz,

$CDCl_3$) δ 145.0, 121.3, 59.21, 33.05, 32.29, 30.65, 28.25, 26.09, 20.86, 18.49, 18.39, -4.91, -4.95. Anal Calcd for $C_{14}H_{30}OSi$: C, 69.42: H, 12.38. Found: C, 69.64; H, 12.60.

Epoxide (MF1612). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 65.9% yield; IR (NaCl): 1472, 1256 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (m, 2H), 2.85 (t, J = 5.7 Hz, 1H), 2.04 (m, 1H), 1.83 – 1.70 (m, 1H), 1.67 – 1.30 (m, 6H), 1.06 (d, J = 6.9 Hz, 3H), 1.00 – 0.91 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 65.39, 61.76, 31.67, 30.88, 29.92, 26.05, 25.89, 19.55, 18.27, 14.26, -5.26, -5.35. Anal Calcd for $C_{15}H_{30}OSi$ (*trans* and *cis* mixture): C, 70.86; H, 11.80. Found: C, 70.71; H, 11.78.

(Table 3.3, Entry 5)

Bicyclo[4.1.0]heptane-2-one (3-52)(MF1541). A 250 mL flame dried flask was charged with NaH (1.80 g, 45.0 mmol, 60% dispersion in mineral oil) and the NaH was washed with pentane (3 X 10 mL). The gray solid was taken up in dry DMSO (65 mL) and trimethylsulfoxonium chloride (5.79 g, 45 mmol) was added and the suspension was stirred for 45 m. To this mixture was added cyclohexenone (3.58 g, 37.2 mmol) and the solution was stirred at room temperature for 2 h, then 1 h at 50 °C, cooled, and quenched with H_2O (50 mL). The mixture was then extracted with Et_2O (3 X 50 mL), and the combined organics were washed with brine (1 X 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting yellow oil was filtered through a plug of silica gel (10/1 hexanes/Et_2O) and distilled (85 °C/ 10 mmHg) to give the product as a colorless oil (2.20 g, 53.7%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (dt, J = 18.0, 3.9 Hz, 1H), 2.10 – 1.50 (m, 7H), 1.20 – 1.00 (m, 2H).

Bicyclo[4.1.0]hept-2-en-2-yl acetate (3-53)(MF1549). To a solution of diisopropylamine (445 mg, 4.4 mmol) in THF (15 mL) at 0 °C was added n-BuLi (1.75 mL, 4.4 mmol, 2.5 M in hexanes) and the reaction was stirred for 10 m and taken to –78

°C. **3-52** was added dropwise and the solution was stirred for 30 m. Acetic anhydride (2.04 g, 20 mmol) was added and the solution was warmed to room temperature and stirred there for 1 h. The reaction was quenched by the addition of H_2O (10 mL) and the mixture was extracted with AcOEt (3 X 15 mL). The combined organics were washed with brine (1 X 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting oil was filtered through a plug of silica gel (50/1 hexanes/Et_2O to give the enol acetate as a colorless oil (226 mg, 37.1%). Kinetic resolution: 55.7% conversion, 36.8% yield, 48.3% ee; IR (NaCl): 1758, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (dt, J = 6.9, 2.4 Hz, 1H), 2.14 (s, 3H), 2.15 – 2.00 (m, 1H), 1.95 – 1.80 (m, 2H), 1.70 – 1.60 (m, 1H), 1.50 – 1.40 (m, 1H), 1.25 – 1.15 (m, 1H), 0.85 – 0.70 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ 169.2, 149.9, 107.4, 20.96, 19.24, 18.23, 14.82, 11.79, 9.95.

Epoxide (MF1605). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 32.4% yield; IR (NaCl): 1750, 1371, 1230 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (dt, 1.8, 0.9 Hz, 1H), 2.08 (s, 3H), 2.00 – 1.60 (m, 6H), 1.00 – 0.95 (qd, J = 5.1, 0.6Hz, 1H), 0.71 (ddd, J = 8.4, 8.0, 5.3 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 169.2, 82.89, 58.61, 23.77, 21.18, 20.21, 16.49, 12.40, 6.93.

(Table 3.3, Entry 6)

(*Z*)-2-Cycloheptene-1-ol (3-54)(MF2443, 2444). To a solution of cycloheptene (4.33 g, 35 .0 mmol) in CCl_4 (50 mL) was added N-bromosuccinimide (5.34 g, 30 mmol) and benzoyl peroxide (29 mg, 0.012 mmol), and the solution was heated to reflux for 2 h, cooled, and filtered to remove the succinimide byproduct. The mixture was washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). The organics were removed under reduced pressure to give crude product (8.88 g) that was taken directly to the next step.

To a solution of the allylic bromide (6.22 g, 35.7 mmol) in acetone/H_2O (50 mL, 1/1 v/v) was added $NaHCO_3$ and the solution was heated to reflux for 2 h, cooled, and the

acetone was removed under reduced pressure. The remaining aqueous solution was extracted with Et_2O (3 X 25 mL) and organics were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil that was purified by flash column chromatography (1/1 hexanes/Et_2O) to give the product as a colorless oil (2.92 g, 72.9% over two steps). ^1H NMR (300 MHz, $CDCl_3$)[56] δ 5.78 (m, 1H), 4.41 (d, J = 8.1 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.05 – 1.50 (m, 8H), 1.40 – 1.25 (m, 1H).

(*Z*)-1-(*tert*-Butyldiphenylsilyloxy)cycloheptene (3-56)(MF2446). The TBDPS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (2.34 g, 82.1%). Kinetic resolution: 59.3% conversion, 48.9% yield, 2.9% ee; IR (NaCl): 1428, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 4H), 7.45 – 7.30 (m, 6H), 5.81 (dt, J = 11.4, 2.7 Hz, 1H), 5.64 (m, 1H), 4.39 (m, 1H), 2.10 (dt, J = 15.9, 8.1 Hz, 1H), 1.94 – 1.75 (m, 2H), 1.75 – 1.61 (m, 2H), 1.52 (m, 1H), 1.35 – 1.23 (m, 2H), 1.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 139.0, 135.8, 129.4, 129.1, 127.4, 73.33, 36.49, 28.50, 27.05, 26.88, 26.66, 19.26.

The silyl ether was converted to the benzoate for determination of enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.4, 1.5 Hz, 2H), 7.55 (tt, J = 7.5, 1.5 Hz, 1H), 7.45 (tt, J = 7.5, 1.5 Hz, 2H), 5.87 (m, 1H), 5.78 (dddd, J = 9.6, 3.0, 1.5, 1.2 Hz, 1H), 5.65 (d of mult., J = 9.6 Hz, 1H), 2.29 (ddd, J = 16.2, 7.2, 0.9 Hz, 1H), 2.20 – 2.13 (m, 1H), 2.05 – 1.95 (m, 2H), 1.85 – 1.60 (m, 3H), 1.55 – 1.40 (m, 1H).

Epoxide (MF2503). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 53.0% yield, 23.0% ee (*trans*); IR (NaCl): 1427, 1142 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 4H), 7.45 – 7.30 (m, 6H), 3.98 (dt, J = 9.3, 5.1 Hz, 1H), 3.04 (dt, J = 7.3, 5.1 Hz, 1H), 2.97 (t, J = 5.1 Hz, 1H), 2.22 – 2.04 (m, 1H), 1.70 – 1.20 (m, 9H), 1.08 (d, J = 4.2 Hz, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.8, 135.7, 129.6, 127.5, 73.97, 60.19, 54.65, 34.69, 29.56, 27.02, 25.30, 23.74, 19.35.

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[56] Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401.

The epoxides were converted to the epoxy-alcohol to determine the enantiomeric excess.

(*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (ddd, J = 10.8, 3.6, 0.9 Hz, 1H), 3.28 (d, J = 5.1 Hz, 1H), 3.25 (br s, 1H), 3.07 (q, J = 5.1 Hz, 1H), 2.30 – 2.10 (m, 1H), 1.90 – 1.30 (m, 6H), 0.95 (m, 1H).

(*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (ddd, J = 6.0, 5.7, 3.3 Hz, 1H), 3.25 (br s, 1H), 3.16 (td, J = 5.7, 0.9 Hz, 1H), 3.06 (q, J = 5.7 Hz, 1H), 2.30 – 2.15 (m, 1H), 1.90 – 1.20 (m, 7H).

(Table 3.3, Entry 7)

(*Z*)-2-Cyclooctene-1-ol (3-55)(MF 2509, 2510). The alcohol was prepared according to the procedure provided for **3-54** to give product as a colorless oil (2.42 g, 64.0% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$)[49] δ 5.55 (m, 1H), 5.62 (dt, J = 10.8, 1.5 Hz, 1H), 4.64 (dt, J = 6.0, 4.8 Hz, 1H), 2.20 – 2.00 (m, 2H), 1.91 (t, J = 10.5, 6.3 Hz, 1H), 1.70 – 1.30 (m, 8H).

(*Z*)-1-(*tert*-Butyldiphenylsilyloxy)cyclooctene (3-57)(MF2514). The TBDPS ether was prepared according to the procedure provided for **3-18** to give product as a colorless oil (2.01 g, 77.9%). Kinetic resolution: 54.8% conversion, 40.0% yield, 15.2% ee; IR (NaCl): 1427, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.44 – 7.31 (m, 6H), 5.61 (ddd, J = 10.8, 6.9, 1.2 Hz, 1H), 5.47 (m, 1H), 4.58 (septet of triplets, J = 5.4, 1.2 Hz, 1H), 1.92 - 1.83 (m, 1H), 1.79 – 1.67 (m, 2H), 1.58 – 1.45 (m, 3H), 1.37 – 1.10 (m, 4H), 1.06 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.7, 135.4, 134.7, 134.4, 129.3, 127.3, 70.69, 38.72, 29.25, 27.03, 26.51, 26.30, 23.77, 19.25.

The silyl ether was converted to the benzoate for determination of enantiomeric excess: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.54 (tt, J = 7.5, 1.5 Hz, 1H), 7.43 (tt, J = 7.5, 0.9 Hz, 2H), 5.90 (dt, J = 9.9, 6.6 Hz, 1H), 5.72 (m, 1H), 5.61 (ddd, J = 10.8, 6.6, 0.9

Hz, 1H), 2.40 – 2.27 (m, 1H), 2.21 – 2.10 (m, 1H), 2.08 – 2.00 (m, 1H), 1.80 – 1.40 (m, 6H), 1.50 – 1.45 (m, 1H).

Epoxide (MF2445). (*trans* and *cis* mixture) colorless oil; Kinetic resolution: 53.4% yield; IR (NaCl): 1427, 1111 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 4H), 7.45 – 7.30 (m, 6H), 3.58 (ddd, J = 10.2, 8.1, 5.4 Hz, 1H), 3.01 (dd, J = 8.1, 4.5 Hz, 1H), 2.92 (dt, J = 10.2, 4.5 Hz, 1H), 2.06 (dq, J = 13.8, 3.9 Hz, 1H), 1.71 (m, 3H), 1.52 – 1.10 (m, 4H), 1.09 (s, 9H), 0.92 – 0.82 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 135.8, 129.5, 127.3, 73.38, 60.15, 55.23, 36.35, 27.34, 27.03, 26.48, 25.50, 23.77, 19.38.

(Table 3.3, Entry 8).

(*R*)-1-Benzoyloxy-4-(*tert*-butyl)cyclohexene (3-58).

Kinetic resolution: 77.6% conversion, 20.2% yield, 54.7% ee, $[\alpha]^{25}_D$ = -44.6° (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$)[57] δ 8.08 (d, J = 5.2 Hz, 2H), 7.55 (tt, J = 5.2, 1.5 Hz, 1H), 7.47 (tt, J = 5.2, 1.5 Hz, 2H), 5.48 (dt, J = 6.0, 1.5 Hz, 1H), 2.50 – 2.30 (m, 1H), 2.30 – 2.10 (m, 2H), 2.05 – 1.90 (m, 2H), 1.50 – 1.45 (m, 2H), 0.92 (s, 9H).

Epoxide: (*trans* and *cis* mixture) colorless oil; IR (NaCl): 1726, 1276 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 – 8.10 (m, 2H), 7.58 (tt, J = 7.2, 1.8 Hz, 1H), 7.48 – 7.41 (m, 2H0, 3.48 (t, J = 2.1 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.25 – 2.15 (m, 1H), 1.75 – 1.55 (m, 2H), 1.45 – 1.10 (m, 1H), 0.87 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 165.3, 133.4, 129.7, 129.2, 128.3, 83.55, 61.09, 39.12, 31.83, 29.96, 27.32, 26.51, 22.56. Anal Calcd for $C_{17}H_{22}O_3$ (*trans* and *cis* mixture): C, 74.47; H, 8.02. Found: C, 74.53; H, 8.18.

(Table 3.4, Entry 1)

4-Methyl-3-pentene-2-ol (3-59)(MF2543). To a solution of 3-methyl-2-butenal (2.0 g, 23.8 mmol) in Et_2O (75 mL) at 0 °C was added MeMgBr (9.50 mL, 28.6 mmol, 3.0 M in Et_2O) dropwise via syringe. The solution was stirred for 4 h with gradual warming to room temperature. The solution was then taken back to 0 °C and then quenched with saturated NH_4Cl solution (10 mL). The layers were then separated and the aqueous layer was extracted with Et_2O (2 X 15 mL). The combined organics were washed with brine (1 X 30 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure to give a yellow oil. The oil was purified by flash chromatography on silica gel (1/1 hexanes/ Et_2O) to give the alcohol as a light yellow oil (2.26 g, 94.0 %). ^1H NMR (300 MHz, $CDCl_3$)[58] δ 5.20 (dqq, J = 8.4, 1.5, 1.5 Hz, 1H), 4.56 (dq, J = 8.4, 6.3 Hz, 1H), 1.72 (d, J = 1.5 Hz, 3H), 1.69 (d, J = 1.5 Hz, 3H), 1.35 (s, 1H), 1.23 (d, J = 6.3 Hz, 3H).

4-Methyl-2-(*tert*-butyldimethylsilyloxy)-3-pentene (3-62)(MF2550). The TBS ether was prepared according to the procedure provided for **3-18** to give the silyl ether as a colorless oil (0.62 g, 48.2 %). Kinetic resolution: 38.3% conversion, 33.4% yield; IR (NaCl): 1473, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (ddt, J = 8.4, 1.5, 1.5 Hz, 1H), 4.55 (dq, J = 8.4, 6.3 Hz, 1H), 1.72 (d, J = 1.5 Hz, 3H), 1.66 (d, J = 1.5 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 130.6, 130.1, 66.04, 25.99, 24.82, 25.68, 19.70, 18.80, -4.30, -4.58.

Epoxides (MF2609).[59] Kinetic resolution: 35% yield, (*trans* and *cis* mixture) colorless oil; 82% ee (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (dq, J = 8.0, 6.1 Hz, 1H), 2.63 (d, J = 8.0 Hz, 1H), 1.31 (s, 3H), 1.32 (s, 3H), 1.27 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

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97.6% ee (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (dq, J = 8.1, 6.3 Hz, 1H), 2.61 (d, J = J = 8.1 Hz, 1H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 0.86 (s, 9H), 0.43 (s, 3H), 0.25 (s, 3H).

(Table3.4, Entry 2)

4-Methyl-2-(*tert*-butyldiphenylsilyloxy)-3-pentene (3-63)(MF2550). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (1.33 g, 86.9 %). Kinetic resolution: 66.8% conversion, 28.7% yield, 72.5% ee, $[\alpha]^{25}_D$ = -6.0° (*c* 0.37, $CHCl_3$); IR (NaCl): 1677, 1590, 1369, 1111 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H), 7.42 – 7.30 (m, 6H), 5.22 (m, 1H), 4.47 (dq, J = 8.4, 6.3 Hz, 1H), 1.56 (s, 3H), 1.17 (s, 3H), 1.15 (dd, J = 6.3, 0.6 Hz, 3H), 1.03 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.8, 135.7, 134.7, 134.5, 130.7, 130.0, 129.3, 129.2, 127.3, 127.2, 66.84, 27.00, 25.53, 24.63, 19.25, 17.76.

Epoxides (MF2549). Kinetic resolution: 65.0% yield (*trans* and *cis* mixture) colorless oil; 74.4% ee (*trans*); IR (NaCl): 1473, 1428, 1378, 1112 cm^{-1}; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.67 (m, 4H), 7.55 – 7.38 (m, 6H), 3.57 (dq, J = 7.8, 6.3 Hz, 1H), 2.81 (d, J = 7.8 Hz, 1H), 1.33 (d, J = 6.3 Hz, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.80 (s, 9H) ^{13}C (75 MHz, $CDCl_3$) δ 135.7, 135.6, 134.0, 133.6, 129.7, 129.6, 127.6, 127.5,67.77, 67.38, 59.60, 26.89, 24.46, 19.23, 18.59.

91.0% ee (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.67 (m, 4H), 7.55 – 7.38 (m, 6H), 3.67 (dq, J = 8.1, 6.6 Hz, 1H), 2.92 (d, J = 8.1 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.11 (s, 3H), 1.00 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 136.0, 135.8, 133.6, 129.4, 129.4, 127.4, 69.67, 68.66, 57.70, 26.97, 24.99, 20.59, 19.31, 18.71. Anal Calcd for $C_{22}H_{30}O_2Si$ (*trans* and *cis* mixture): C, 74.58; H, 8.47. Found: C, 74.53; H, 8.32.

The epoxides were converted to the epoxy alcohol in order to determine the enantiomeric excess: ^{1}H NMR (300 MHz, $CDCl_3$) (*trans*): δ 3.75 – 3.60 (m, 1H), 2.64 (d, J = 7.8 Hz, 1H), 1.82 (d, J = 3.9 Hz, 1H), 1.35 (s, 3H), 1.32 (d, J = 7.5 Hz, 3H).

(*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 – 3.60 (m, 1H), 2.70 (d, J = 7.8, 1H), 2.35 (d, J = 2.4 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.25 (d, J = 6.3 Hz, 3H).

(Table 3.4, Entry 3)

2-Methyl-2-heptene-4-ol (3-61) (MF2641). The alcohol was prepared by addition of n-propylmagnesium bromide to 3-methyl-2-butenal according to the procedure provided for **3-59** to give the alcohol as a light yellow oil (1.18 g, 78.0 %). IR (NaCl): 3340, 1676, 1448, 1376 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (d of septets, J = 8.7, 1.5 Hz, 1H), 4.34 (dt, J = 8.7, 6.3 Hz, 1H), 1.72 (d, J = 1.5 Hz, 3H), 1.69 (d, J = 1.5 Hz, 3H), 1.61 – 1.50 (m, 2H), 1.44 – 1.28 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 134.5, 128.2, 68.32, 39.84, 25.71, 18.65, 18.14, 14.02.

2-Methyl-4-(*tert*-butyldiphenylsilyloxy)-2-heptene (3-65) (MF2643). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (1.33 g, 86.9 %). Kinetic resolution: 27.0% conversion; 61.9% yield, 20.6% ee, $[\alpha]^{25}_D$ = -0.55° (*c* 0.37, $CHCl_3$); IR (NaCl): 1957, 1894, 1822, 1676, 1472 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 4H), 7.50 – 7.35 (m, 6H), 5.21 (d of septets, J = 8.7, 1.5 Hz, 1H), 4.42 (m, 1H), 1.62 (d, J = 1.5 Hz, 3H), 1.55 – 1.43 (m, 1H), 1.40 – 1.28 (m, 2H), 1.21 (d, J = 1.5 Hz, 3H), 1.14 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 1.16 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 134.7, 131.8, 129.6, 129.2, 129.1, 128.7, 127.6, 70.34, 40.86, 27.08, 25.59, 19.37, 18.32, 17.94, 14.19.

Thee silyl ether was converted to the benzoate in order to determine the enantiomeric excess: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 7.5 Hz, 2H), 7.51 (tt, J = 7.5, 1.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.72 (dt, J = 9.0, 6.6 Hz, 1H), 5.21 (d of mult., J = 4.0 Hz,

1H), 1.85 – 2.75 (m, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 1.63 (d of quintets, J = 8.7, 6.6 Hz, 1H), 1.39 (sextet, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H.

Epoxides (MF1650). Kinetic resolution: 26.1% yield (*trans* and *cis* mixture) colorless oil; 86.9% ee (*trans*): IR (NaCl): 1962, 1894, 1822, 1472, 1112 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 4H), 7.45 – 7.32 (m, 6H), 3.46 (dt, J = 8.4, 4.8 Hz, 1H), 2.79 (d, J = 8.4 Hz, 1H), 1.65 – 1.20 (m, 4H), 1.10 (s, 3H), 1.08 (s, 3H), 1.04 (s, 9H), 0.83 (t, J = 7.7Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 135.7, 134.1, 129.7, 129.6, 127.5, 127.4, 70.36, 66.65, 59.25, 37.99, 26.94, 24.32, 19.42, 18.66, 17.73, 14.34.

91.6% ee (*cis*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 4H), 7.45 – 7.32 (m, 6H), 3.46 (m, 1H), 2.83 (d, J = 8.4 Hz, 1H), 1.65 – 1.20 (m, 4H), 1.08 (d, J = 0.9 Hz, 3H), 1.06 (d, J = 0.9 Hz, 3H), 1.04 (s, 9H), 0.72 (t, J = 7.7 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) (*cis*) δ 136.1, 135.9, 133.7, 133.4, 129.4, 129.3, 127.3, 127.2, 72.70, 67.83, 58.24, 37.49, 27.08, 26.62, 24.99, 19.63, 17.81, 14.26. Anal Calcd for $C_{24}H_{34}O_2Si$: C, 75.39; H, 8.89. Found: C, 75.22; H, 8.84.

The epoxides were converted to the hydroxy-epoxides in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) (*trans*): δ 3.52 (dt, J = 7.8, 4.2 Hz, 1H), 2.67 (d, J = 7.8 Hz, 1H), 1.72 – 1.40 (m, 5H), 1.39 (s, 3H), 1.35 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H).

(Table 3.4, Entry 4)

2,5-Dimethyl-2-hexen-4-ol (3-60)(MF2613). The alcohol was prepared by the addition of isopropylmagnesium bromide to 3-methyl-2-butenal according to the procedure provided for **3-59** to give the alcohol as a light yellow oil (2.55 g, 98.5 %). ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (d of septets, J = 9.0, 1.5 Hz, 1H), 4.01 (dd, J = 9.0, 6.9 Hz, 1H), 1.70 (d, J = 1.5 Hz, 3H), 1.65 (d, J = 1.5 Hz, 3H), 1.63 (octet, J = 6.9 Hz, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H).

2,5-Dimethyl-4-(*tert*-butyldiphenylsilyloxy)-2-hexene (3-66)(MF2616). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (2.56 g, 89.7 %). IR (NaCl): 1956, 1890, 1820, 1427, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H), 7.40 – 7.27 (m, 6H), 5.10 (doublet of septets, J = 9.3, 1.2 Hz, 1H), 4.11 (dd, J = 9.3, 5.4 Hz, 1H), 1.73 (dsd, J = 6.6, 5.4, 1.2 Hz, 1H), 1.48 (d, J = 1.2 Hz, 3H), 1.07 (d, J = 1.2 Hz, 3H), 1.04 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 131.5, 130.4, 130.3, 128.2, 124.8, 124.6, 122.8, 122.7, 122.6, 121.8, 70.66, 30.94, 22.70, 21.25, 15.11, 14.01, 13.61, 13.17.

(Table 3.4, Entry 5)

(*E*)-3-Pentene-2-ol (3-66)(MF2614). The alcohol was prepared by the addition of methylmagnesium bromide to *trans*-crotonaldehyde according to the procedure provided for **3-59** to give the alcohol as a light yellow oil (1.44 g, 56.0 %). ^1H NMR (300 MHz, $CDCl_3$)[60] δ 5.61 (dqd, J = 15.0, 6.3, 0.9 Hz, 1H), 5.49 (ddd, J = 15.0, 6.3, 1.2 Hz, 1H), 4.22 (dq, J = 6.0, 5.7 Hz, 1H), 1.65 (d, J = 6.3 Hz, 3H), 1.57 (d, J = 2.7 Hz, 1H), 1.21 (d, J = 6.6 Hz, 3H).

(*E*)-4-(*tert*-Butyldiphenylsiloxy)-2-pentene (3-69) (MF2633). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (1.82 g, 56.1 %). Kinetic resolution: 36.5% conversion, 58.9% yield, 9.2% ee, $[\alpha]^{25}_D$ = + 0.52° (*c* 0.52, $CHCl_3$); IR (NaCl): 1957, 1888, 1824, 1675, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H), 7.45 – 7.25 (m, 6H), 5.46 (ddq, J = 15.6, 6.0, 1.5 Hz, 1H), 5.34 (dqd, J = 15.6, 6.3, 0.9 Hz, 1H), 4.23 (dq, J = 6.9, 6.3 Hz, 1H), 1.57 (dt, J = 6.0, 0.9 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 1.05 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9,

[60] Hayashi, T.; Akihiro, Y.; Yoshihiko, I.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

135.8, 135.4, 134.7, 134.3, 129.3, 129.2, 127.3, 127.2, 124.1, 70.29, 27.06, 24.46, 19.30, 17.57. Anal calcd for $C_{21}H_{28}OSi$: C, 77.80; H, 8.60. Found: C, 77.64; H, 8.59.

Thee silyl ether was converted to the benzoate in order to determine the enantiomeric excess: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 8.0 (m, 2H), 7.57 – 7.45 (m, 1H), 7.46 (m, 2H), 5.82 (dq, J = 12.0, 6.0 Hz, 1H), 5.63 (dq, J = 6.6, 1.5 Hz, 1H), 5.56 (dd, J = 12.0, 6.6 Hz, 1H), 1.70 (dd, J = 7.2, 1.5 Hz, 3H), 1.42 (d, J = 6.0 Hz, 3H).

Epoxides (MF2637). Kinetic resolution: 35.0% yield (*trans* and *cis* mixture) colorless oil; 92.8% ee (*trans*); IR (NaCl): 1960, 1890, 1829, 1447, 1112 cm^{-1}; (*trans*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.46 – 7.30 (m, 6H), 3.49 (dq, J = 6.0 Hz, 2.58 (dd, J = 6.0, 2.1 Hz, 1H), 2.43 (qd, J = 5.4, 2.1 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 5.4 Hz, 3H), 1.06 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.8, 135.7, 133.8, 129.6, 127.5, 127.4, 69.63, 62.78, 53.97, 26.94, 20.95, 19.25, 17.29.

91.0% ee (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.46 – 7.30 (m, 6H), 2.81 (dq, J = 5.4, 2.4 Hz, 1H), 2.75 (dd, J = 6.0, 2.4 Hz, 1H), 1.26 (d, J = 5.4 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 135.7, 133.6, 129.5, 127.4, 70.19, 63.81, 51.81, 26.97, 20.05, 19.34, 17.42. Anal Calcd for $C_{21}H_{28}O_2Si$ (*trans* and *cis* mixture): C, 74.12; H, 8.23. Found: C, 73.93: H, 8.33.

The epoxides were converted to the epoxy-alcohols in order to determine the enantiomeric excess. These were not purified due to the small amount obtained (less than 5 mg) and its volatility.

(Table 3.4, Entry 6)

(*E*)-1-Phenyl-3-(*tert*-butyldiphenylsiloxy)-1-butene

Kinetic resolution: 43.1% conversion, 49.0% yield, 20.7% ee, $[\alpha]^{25}_D$ = + 0.52° (*c* 0.36, $CHCl_3$); IR (NaCl): 1590, 1428, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 4H), 7.45 – 7.10 (m, 11H); 6.17 (dd, J = 15.9, 6.0 Hz, 1H), 4.46 (sextet, J = 6.0 Hz,

1H), 1.24 (d, J = 6.0 Hz, 3H), 1.08 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 137.1, 135.9, 135.8, 134.5, 134.0, 129.5, 129.4, 128.4, 128.3, 127.4, 127.1, 126.3, 70.34, 27.10, 24.46, 19.37. Anal Calcd for $C_{26}H_{30}OSi$: C, 80.83; H, 7.76. Found: C, 81.00; H, 7.83.

The silyl ether was converted to the alcohol for determination of enantiomeric excess and absolute configuration: $[\alpha]^{25}_D$ = - 4.97° (*c* 0.79, $CHCl_3$); lit[61] $[\alpha]_D$ = + 24.5° (*c* 3.0, $CHCl_3$) for (*R*) enantiomer.

Epoxides (MF2727). Kinetic resolution: 40.0% yield (*trans* and *cis* mixture) colorless oil; 93.0% ee (*trans*): IR (NaCl): 1962, 1987, 1826, 1472, 1112 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.64 (m, 4H), 7.47 – 7.10 (m, 11H), 3.74 (dq, J = 5.1 Hz, 1H), 3.52 (d, J = 2.1 Hz, 1H), 2.98 (dd, J = 5.1 , 2.1 Hz, 1H), 1.24 (d, J = 5.1 Hz, 3H), 1.06 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 137.1, 135.8, 135.9, 133.4, 129.6, 128.2, 127.9, 127.6, 125.6, 69.16, 65.87, 55.95, 26.95, 20.89, 19.28.

67.6% ee (*cis*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.65 (m, 4H), 7.47 – 7.10 (m, 11H), 3,85 (dq, J = 6.3 Hz, 1H), 3.71 (d, J = 2.4 Hz, 1H), 3.08 (dd, J = 5.4, 2.4 Hz, 1H), 1.15 (d, J = 6.3 Hz, 3H), 1.11 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 137.1, 135.8, 134.2, 133.5, 129.7, 128.3, 128.0, 127.5, 125.5, 69.88, 66.71, 55.95, 27.01, 20.13, 19.39.

The *trans* and *cis* diastereomers were confirmed by desilation with TBAF and comparison to the ^1H NMR spectrum of an authentic sample prepared form *trans*-4-phenyl-3-butene-2-one through epoxidation[62] with $NaOH/H_2O_2$ followed by reduction under Luche conditions[63] (1.7/1 *trans/cis*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H), 4.12 (qd, J = 6.4, 2.1 Hz, 1H), 3.96 (d, J = 2.1 Hz, 1H), 3.10 (t, J = 2.1 Hz, 1H), 1.97 (s, 1H), 1.24 (d, J = 6.4 Hz, 3H). 4.12 (qd, J = 6.4, 2.1 Hz, 1H).

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[61] Stary, I.; Zajicek, J.; Kocovsky, P. *Tetrahedron* **1992**, *48*, 7229.

[62] Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T. *J. Org. Chem.* **1991**, *56*, 1631.

[63] Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* **1992**, *33*, 6569.

(Table 3.4, Entry 7)

(*E*)-2-Methyl-2-nonenal (3-73)(MF2714). To a solution of heptanal (1.39 g, 12.0 mmol) in CH_2Cl_2 (15 mL) was added 2-(triphenylphoranylidene)propionaldehyde (6.64 g, 24.0 mmol) and the reaction was heated to reflux for 2 weeks. The CH_2Cl_2 was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (1/1 hexanes/Et_2O) to give the aldehyde as a yellow oil (1.05 g, 56.8 %). IR (NaCl): 1691, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.45 (td, J = 6.0, 1.5 Hz, 1H), 2.30 (q, J = 6.7 Hz, 2H), 1.70 (d, J= 1.5 Hz, 3H), 1.50 – 1.40 (m, 2H), 1.33 – 1.19 (m, 6H), 0.85 (t, J = 6.7, Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 195.1, 154.9, 139.1, 31.59, 28.99, 28.99, 28.35, 22.55, 14.05, 9.18.

(*E*)-3-Methyl-3-decen-2-ol (MF2740). The alcohol was prepared by the addition of methylmagnesium bromide to according to the procedure provided for **3-73** to give the alcohol as a light yellow oil (454 mg, 99.0 %). IR (NaCl): 3346, 1696, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (tt, J = 7.2, 1.2 Hz, 1H), 4.20 (q, J = 6.3 Hz, 1H), 2.00 (q, J = 6.3 Hz, 3H), 1.62 (d, J = 1.2 Hz, 3H), 1.38 – 1.22 (m, 9H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 138.1, 125.3, 73.41, 31.79, 29.50, 29.03, 27.52, 22.66, 21.59, 14.11, 11.39.

(*E*)-2-*Tert*-butyldiphenylsilyloxy-3-methyl-3-decene (3-74)(MF2743). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the silyl ether as a colorless oil (592 mg, 84.5 %). Kinetic resolution: 78.0% conversion, 21.2% yield, 30.0% ee, $[\alpha]^{25}_D$ = + 7.53° (*c* 1.2, $CHCl_3$); IR (NaCl): 1474, 1427, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.55 (m, 4H), 7.45 – 7.30 (m, 6H), 5.13 (t, J = 6.3 Hz, 1H), 4.17 (q, J = 6.3 Hz, 1H), 1.93 – 1.86 (br s, 2H), 1.60 (s, 3H), 1.30 – 1.18 (m, 6H), 1.13 (d, J = 6.3 Hz, 3H), 1.05 (s, 9H), 1.05 – 1.00 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 137.9, 135.8, 135.8, 134.7, 129.6, 129.3, 127.6, 127.3, 127.2, 124.7, 74.97,

31.88, 29.53, 29.06, 27.42, 27.03, 23.19, 22.74, 19.37, 14.20, 11.24. Anal Calcd for $C_{27}H_{40}OSi$: C, 79.41; H, 9.79. Found: C, 79.30; H, 9.77.

Epoxides (MF2749). Kinetic resolution: 61.3% yield (*trans* and *cis* mixture) colorless oil; 87.0% ee (*trans*): IR (NaCl): 1964, 1890, 1823, 12472, 1112 cm^{-1}; (*trans*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.60 (m, 4H), 7.45 – 7.30 (m, 6H), 3.29 (d, J = 6.0 Hz, 1H), 2.30 (t, J = 6.3 Hz, 1H), 1.35 – 1.23 (m, 13H), 1.16 (d, J = 6.0 Hz, 3H), 1.06 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.8, 135.7, 134.7, 134.0, 129.6, 127.5, 127.4, 74.18, 64.73, 60.70, 31.78, 29.17, 26.98, 26.59, 22.60, 20.31, 19.07, 14.15, 10.99. 93.0% ee (*cis*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.60 (m, 4H), 7.45 – 7.30 (m, 6H), 3.45 (q, J = 6.6 Hz, 1H), 2.63 (t, J = 6.0 Hz, 1H), 1.35 – 1.23 (m, 13H), 1.08 (s, 9H), 1.00 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 134.6, 133.8, 129.5, 129.4, 127.6, 127.4, 74.93, 64.35, 62.42, 28.52, 28.17, 26.44, 26.38, 19.46, 19.26, 14.12, 11.58. Anal Calcd for $C_{27}H_{40}O_2Si$ (*trans* and *cis* mixture): C, 76.42; H, 9.43. Found: C, 76.60; H, 9.57.

The epoxides were converted to the epoxy-alcohols in order to determine the enantiomeric excess: ^1H NMR (300 MHz, $CDCl_3$) (*trans*): δ 3.45 (dq, J = 6.6, 5.1 Hz, 1H), 2.87 (t, J = 6.6 Hz, 1H), 2.52 (d, J = 5.1 Hz, 1H), 1.22 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H), 1.60 – 1.20 (m, 10H).

(*cis*): ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (q, J = 6.6 Hz, 1H), 3.03 (t, J = 6.6 Hz, 1H), 2.30 (s, 1H), 1.60 – 1.20 (m, 10H), 1.22 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H).

(Table 3.4, Entry 8)

(*E*)-1-Phenyl-2-methyl-3-hydroxy-1-butene (3-68)(MF2715). The alcohol was prepared by the addition of methylmagnesium bromide to α-methyl-*trans*-cinnamaldehyde according to the procedure provided for **3-59** to give the intermediate

alcohol as a light yellow oil (4.87 g, 99.9 %). IR (NaCl) 3346, 1948, 1183, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 5H), 6.49 (s, 1H), 4.34 (q, J = 6.3 Hz, 1H), 2.10 (s, 1H), 1.86 (s, 3H), 1.34 (d, J = 6.3 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$) δ 141.5, 137.5, 128.8, 128.0, 126.2, 124.2, 73.50, 21.76, 13.41.

(*E*)-1-Phenyl-2-methyl-3-(*tert*-butyldiphenylsilyloxy)-1-butene (3-72)(MF2716). The TBS ether was prepared according to the procedure provided for **3-18** to give the product as a colorless oil (1.87 g, 77.0 %). IR (NaCl): 1600, 1472, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.62 (m, 4H), 7.45 – 7.20 (m, 9H), 7.15 – 7.10 (m, 2H), 6.28 (s, 1H), 4.31 (q, J = 6.3 Hz, 1H), 1.83 (d, J = 0.9 Hz, 3H), 1.24 (dd, J = 6.3, 0.9 Hz, 3H), 1.08 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 142.0, 138.0, 128.8, 128.0, 126.0, 123.5, 74.20, 25.94, 23.39, 18.19, 13.45, -4.65, -4.83.

(Table 3.4, Entry 9)

(*E*)-1-Phenyl-2-methyl-3-(*tert*-butyldimethylsilyloxy)-1-butene (3-71)(MF2724). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (1.32 g, 77.4 %). IR (NaCl): 1600, 1472, 1251, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 5H), 6.44 (s, 1H), 4.29 (q, J = 6.3 Hz, 1H), 1.81 (s, 3H), 1.27 (t, J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.71 (s, 3H), 0.45 (3H). ^{13}C (75 MHz, $CDCl_3$) δ 141.1, 137.9, 135.9, 135.8, 134.7, 134.5, 134.0, 129.6, 129.4, 128.8, 127.9, 127.6, 127.4, 126.0, 124.1, 75.03, 27.04, 23.21, 19.38, 13.30.

(Table 3.4, Entry 10)

Ethyl-(*E*)-2,4,4-trimethylpent-2-enoate (3-75)(MF2821). To a solution of isobutyraldehyde (721 mg, 10.0 mmol) in THF (25 mL) was added ethyl-2-triphenylphosphoranepropionate (3.62 g, 10.0 mmol) and the resulting yellow solution was heated to reflux for 20 h. The THF was removed under reduced pressure and the

residue was filtered through a plug of silica gel with 1/1 hexanes/Et_2O to give the product as a colorless oil with 27/1 diastereoselectivity (4.07 g, 87.0 %). ^1H NMR (300 MHz, $CDCl_3$)[64] δ 6.57 (dq, J = 9.6, 1.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.63 (septet of doublets, J = 6.6, 3.0 Hz, 1H), 1.84 (d, J = 1.5 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.6 Hz, 6H).

(*E*)-2,4,4-trimethylpent-2-en-1-ol (3-77)(MF2825). The ester was reduced with 2.0 eq DIBAL according to the procedure provided for **3-13** to give the alcohol as a light yellow oil (720 mg, 35.6 %). ^1H NMR (300 MHz, $CDCl_3$)[51] δ 5.22 (dq, J = 9.3, 1.8 Hz, 1H), 3.97 (s, 2H), 2.54 (septet of doublets, J = 6.9, 2.7 Hz, 1H), 1.67 (d, J = 1.8 Hz, 3H), 1.56 (s, 3H), 0.96 (d, J = 6.9 Hz, 6H).

(*E*)-2,4,4-trimethylpent-2-enal (3-79)(MF2827). The alcohol was oxidized via Swern oxidation according to the procedure provided for **3-78** to give the aldehyde as a colorless oil (520 mg, 76.2 %). ^1H NMR (300 MHz, $CDCl_3$)[51] δ 9.37 (s, 1H), 6.27 (dq, J = 9.9, 1.5 Hz, 1H), 2.83 (septet of doublets, J = 6.6, 2.7 Hz, 1H), 1.75 (d, J = 1.5 Hz, 3H), 1.10 (d, J = 6.6 Hz, 6H).

(*E*)-3,5,5-trimethylhex-3-en-2-ol (3-81)(MF2829). The alcohol was prepared by the addition of methylmagnesium bromide to aldehyde **3-79** according to the procedure provided for **3-59** to give the product as a light yellow oil (378 mg, 64.1 %). The crude alcohol was taken directly to the next step.

(*E*)-3,5,5-trimethyl-2-(*tert*-butyldiphenylsilyloxy)-3-hexene (3-83)(MF2830). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (595 mg, 83.2 %). IR (NaCl): 1590, 1472, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 4H), 7.70 – 7.62 (m, 6H), 6.96 (d, J = 9.0 Hz, 1H);

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[64] Lee, V.J.; Branfman, A.R.; Herrin, T.R.; Rinehart, K.L. *J. Am. Chem. Soc.* **1978**, *100*, 4225.

4.15 (q, J = 6.3 Hz, 1H), 2.12 (d of septets, J = 9.0, 7.2 Hz, 1H), 1.62 (d, J = 1.2 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.05 (s, 9H), 0.89 (d, J = 7.2 Hz, 3H), 0.85 (d, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 135.8, 134.8, 134.7, 134.3, 132.2, 129.3, 127.3, 127.2, 74.94, 27.05, 26.63, 23.19, 22.88, 19.39, 11.12.

(Table 3.4, Entry 11)

Ethyl-(*E*)-4,6-dimethylhept-4-en-3-one (3-76)(MF2810). A suspension of Na (1.3 g) in toluene was heated until the sodium melted, then the sodium was broken into small pieces with vigorouos stirring. The solution was then cooled and the toluene decanted. Ethanol (0.2 mL) in ethyl acetate (20 mL) was then added and the flask was quickly cooled to 0 °C. The aldehyde was then added over 2 h via syringe pump, being careful to keep the internal temperature below 5 °C. After the addition was complete, the reaction was stirred for and additional 1 h at 0 °C, then it was quenched by the addition of glacial acetic acid (4.2 mL) and extracted with Et_2O. The combined ether extracts were washed with 6 N HCl (10 mL), water (10 mL), and brine(10 mL), dried (Na_2SO_4), and the ethyl propionate was removed under high vacuum. This gave the pure *E* isomer that was taken directly to the next step.

(*E*)-4,6-Trimethylhept-2-en-1-ol (3-78)(MF2813). The ester was reduced with 2.0 eq DIBAL according to the procedure provided for **3-13** to give the alcohol as a light yellow oil (1.60 g, 94.6 %). IR (NaCl): 3334, 1465, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (d, J = 1.2 Hz, 1H), 3.93 (d, J = 1.2 Hz, 2H), 1.77 (s, 3H), 1.51 (s, 1H), 1.12 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 136.4, 133.1, 70.69, 32.15, 30.87, 14.67.

(*E*)-4,6-Trimethylhept-2-enal (3-80)(MF2815). To a solution of oxalyl chloride (2.38 g, 18.7 mmol) in distilled CH_2Cl_2 (90 mL) at –78 °C was added freshly distilled DMSO (1.95 g, 25.0 mmol). The solution was stirred at –78 °C for 15 m, then alcohol **3-78** (1.60 mg, 12.5 mmol) was added as a solution in distilled CH_2Cl_2 (10 mL). The solution was

stirred for 1h at –78 °C and then distilled NEt_3 (8.70 mL, 62.5 mmol) was added. After 1 h at –78 °C H_2O (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL), and the combined organics were washed with brine (1 x 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel (10/1 hexanes/Et_2O) to give the aldehyde as a light yellow oil (1.52 mg, 76.2 %). IR (NaCl): 1758, 1693, 1634, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 6.41 (q, J = 1.2 Hz, 1H), 1.87 (d, J = 1.2 Hz, 3H), 1.24 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 196.4, 164.5, 137.3, 34.11, 29.77, 9.76.

(*E*)-5,7-Trimethyloct-3-ene-2-ol (3-82)(MF2818). The alcohol was prepared by addition of methylmagnesium bromide to aldehyde **3-80** according to the procedure provided for **3-59** to give the product as a light yellow oil (441 mg, 64.0 %). IR (NaCl): 3348, 1630, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (septet, J = 1.2 Hz, 1H), 4.07 (dqd, J = 6.6, 3.0, 1.2 Hz, 1H), 1.69 (d, J = 1.2 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 137.0, 135.3, 74.93, 31.95, 30.44, 21.60, 12.07.

(*E*)-5,7-Trimethyl-2-(*tert*-butyldiphenylsilyloxy)-3-hexene (3-84)(MF2819). The TBDPS ether was prepared according to the procedure provided for **3-7** to give the product as a colorless oil (1.87 g, 77.0 %). ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 4H), 7.42 – 7.28 (m, 6H), 5.12 (s, 1H), 4.06 (q, J = 6.3 Hz, 1H), 1.71 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.03 (s, 9H), 1.01 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 136.6, 135.9, 135.7, 134.7, 134.3, 129.6, 129.3, 129.2, 127.7, 127.3, 76.39, 31.86, 30.80, 27.03, 26.61, 23.24, 19.35, 11.95.

Absolute Configuration Determination

Preparation of optically pure (*R*)-allylic alcohols via Sharpless kinetic resolution: To a suspension of 4 Å molecular sieves (30 % of alcohol by weight) in CH_2Cl_2 was added L-

(+)-diethyltartrate (60 mol%) and the solution was cooled to –20 °C with an ice/NaCl mixture. The $Ti(Oi\text{-}Pr)_4$ (50 mol%) was added and the mixture was stirred for 30m, the t-BuOOH was added (60 mol%, 6.8 M in CH_2Cl_2). The reaction was stirred at this temperature for 3 – 5 h, at which time the reaction is quenched with H_2O and the reaction was stirred for 20 – 30 m with warming to room temperature. To this homogeneous mixture was added 30% NaOH saturated with NaCl and the mixture was stirred vigorously for 1 h. A small amount of MeOH is added (about 0.1% of the total volume), the layers were separated, and the aqueous layer is extracted with CH_2Cl_2. The combined organics were then dried. In the case of **3-63**, the olefin and epoxide were separable by column chromatography, however, in the case of **3-70** the alcohol was protected as the TBDPS ether before purification. The crude alcohol showed >99% ee be chiral GC (Chiraldex OD).

The optically pure olefins were epoxidized using identical conditions as the kinetic resolution:

(*R*)-3-70 reaction with **1-28**: 56% conversion, 48% yield, >20/1 dr

(*R*)-3-70 reaction with **ent 1-28**: 28% conversion, 23% yield, 16/1 dr

(*E*)-1-Phenyl-3-(*tert*-butyldiphenylsiloxy)-1-butene (3-63) reaction with **1-28**: 100% conversion, 86% yield, >20/1dr

(*R*)-3-63 reaction with **ent 1-28**: 46% conversion, 19% yield, 1.6/1 dr

CHAPTER FOUR

A MILD AND EFFICIENT EPOXIDATION OF OLEFINS USING IN SITU GENERATED DIMETHYLDIOXIRANE AT HIGH pH

4.A. INTRODUCTION

Epoxides are important synthetic intermediates,[1] and epoxidation of olefins provides a powerful strategy for their construction.[2] Dioxiranes, either isolated or generated *in situ*, (Scheme 4.1) are extremely versatile epoxidation reagents. [3,4,5] The

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[1] For reviews see: (a) Gorzynski Smith, J. *Synthesis*, **1984**, 629. (b) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885.

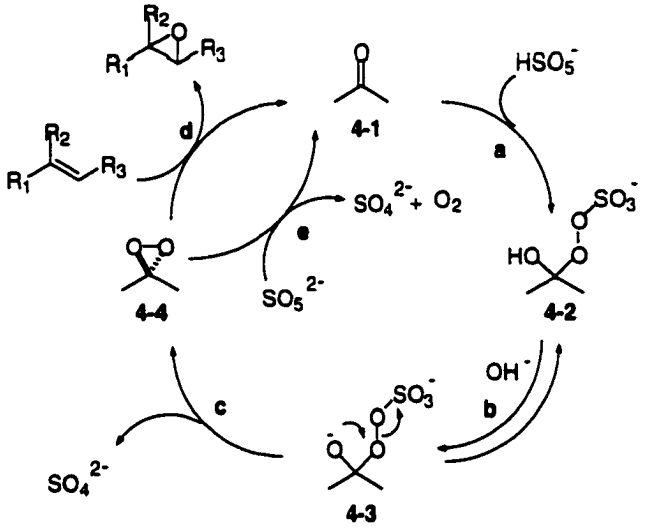
[2] For some recent leading references on epoxidation see: (a) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310. (b) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905. (c) Rudolph, J.; Reddy, K.L.; Chiang, J.P.; Sharpless, K.B. *J. Am. Chem. Soc.* **1997**, *119*, 6189. (d) Coperet, C.; Adolfsson, H.; Sharpless, K.B. *Chem. Commun.* **1997**, 1565. (e) Yudin, A.K. Sharpless, K.B. *J. Am. Chem. Soc.* **1997**, *119*, 11536. (f) Nakajima, M.; Sasaki, Y.; Iwamoto, H.; Hashimoto, S-i. *Tetrahedron Lett.* **1998**, *39*, 87. (g) Murray, R.W.; Iyanar, K. *J. Org. Chem.* **1998**, *63*, 1730. (h) Ueno, S.; Yamaguchi, K.; Yoshida, K.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **1998**, 295. (i) James, A.P.; Johnstone, R.A.W.; McCarron, M.; Sankey, J.P.; Trenbirth, B. *Chem. Commun.* **1998**, 429.

[3] 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) Clennan, E.L. *Trends in Organic Chemistry*, **1995**, *5*, 231-252. (e) Adam, W.; Smerz, A.K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581.

[4] Murray, R.W.; Singh, S. *Org. Synth.* **1996**, *74*, 91.

[5] 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,

reaction is rapid, mild, safe, and a variety of efficient protocols for this type of epoxidation have been developed. Due to the concern for the autodecomposition of Oxone at high pH, the reaction pH for most of the epoxidations mediated by *in situ* generated dioxiranes have generally been controlled at 7 to 8[5] with few exceptions.[5f]



Scheme 4.1

During our studies on chiral ketone mediated asymmetric epoxidations,[6] we found that the catalytic efficiency for certain chiral ketones was highly pH dependent and that

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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) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577. (g) Yang, D.; Wong, M.K.; Yip, Y.C. *J. Org. Chem.* **1995**, *60*, 3887 and references cited therein. (h) Denmark, S.E.; Forbes, D.C.; Hays, D.S.; DePue, J.S.; Wilde, R.G. *J. Org. Chem.* **1995**, *60*, 1391 and references cited therein. . (i) Denmark, S.E.; Wu, Z.; Crudden, C.M.; Matsuhashi H. *J. Org. Chem.* **1997**, *62*, 8288. (j) Boehlow, T.R.; Buxton, P.C.; Grocock, E.L.; Marples, B.A.; Waddington, V.L. *Tetrahedron Lett.* **1998**, *39*, 1839. (k) Denmark, S.E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (l)Yang, D.; Yip, Y.C.; Jiao, G.S.; Wong, M.K.*J. Org. Chem.* **1998**, *63*, 8952. (m) Yang, D.; Yip, Y.C.; Tang, M.W.; Wong, M.K.; Cheung, K.K. *J. Org. Chem.* **1998**, *63*, 9888.

[6] (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) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (e) Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. (f) Cao, G-A.; Wang, Z-X.; Tu, Y.; Shi. Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (f) Zhu, Y.; Tu, Y.; Hongwu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (g) Wang, Z.-X.; Cao, G.;A.; Shi, Y. *J. Org. Chem.* **1999**, *7646*. (h)Warren, J.D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675.

high pH was actually beneficial in these cases.[6b,c] In a subsequent comparison study, we also found that the epoxidation of β-methylstyrene mediated by acetone displayed a similar behavior under the reaction conditions (homogenous organic solvent/water system)(Figure 4.1).[6c]

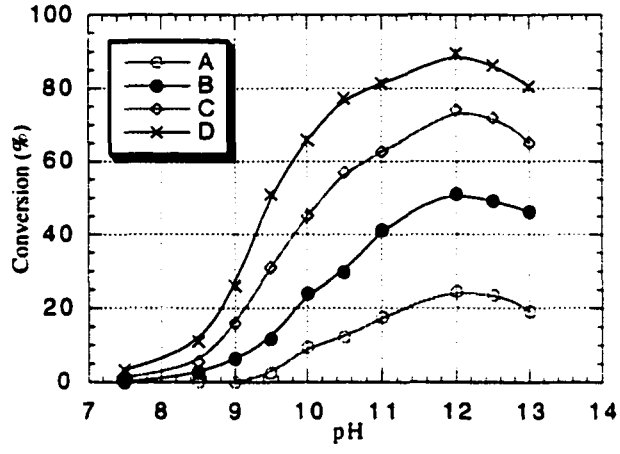


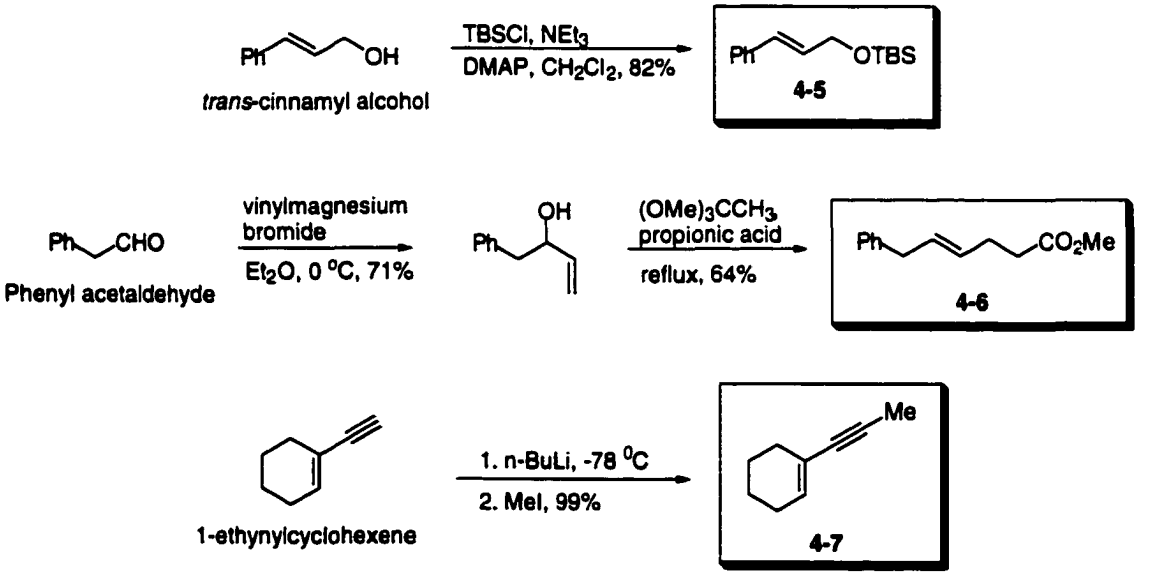
Figure 4.1. Plot of the conversion of *trans*-β-methylstyrene against pH using acetone (3 eq.) as catalyst in H_2O-CH_3CN (1 : 1.5, V/V). Samples were taken at different reaction times for the determination of conversion, 0.5 h (**A**), 1.0 h (**B**), 1.5 h (**C**), 2.0 h (**D**).

In this case, the substrate conversion increased from 3% to 90% within the same reaction time when the apparent pH changed from 7.5 to 12. The enhanced epoxidation efficiency of acetone at higher pH could be due to the fact that the high pH favored the formation of oxy-anion intermediate **4-3**, and led to more efficient generation of dimethyldioxirane (the step from **4-3** to **4-4** could be the rate-determining step). Considering that the basic reaction conditions would also be very attractive for the synthesis of acid-sensitive

epoxides,[7] we thought that this acetone mediated epoxidation at high pH could provide a valuable epoxidation procedure. We therefore decided to undertake a survey of various olefins to ascertain the generality of the reaction.

4.B. RESULTS AND DISCUSSION

Most of the olefins studied were commercially available. However, three of them needed to be prepared (Scheme 4.2). Olefin **4-5** was prepared by simple protection of *trans*-cinnamyl alcohol as the TBS ether in good yield.[8] *Trans* olefin **4-6** was prepared from phenyl acetaldehyde by addition of vinylmagnesium bromide followed by Johnson-Claisen reaction[9] with trimethyl orthoacetate, also in good yield. Finally, enyne **4-7** was prepared by methylation of the commercially available 1-ethynylcyclohexene.



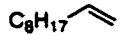
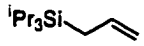
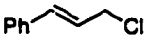
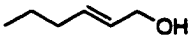
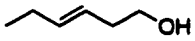
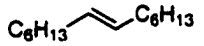
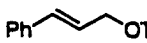
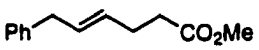
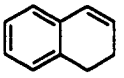
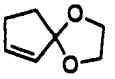
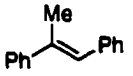
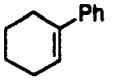
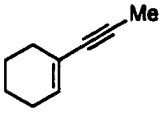
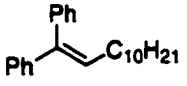
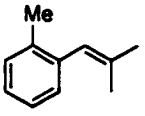
Scheme 4.2

[7] For great success and discussion on this topic see: refs 2c-e.

[8] Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

[9] Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.-T.; Faulkner, D.J.; Petersen, M.R. *J. Am. Chem. Soc* **1970**, *92*, 741.

Table 4.1. Epoxidation of Olefins with *in situ* Generated Dimethyldioxirane at High pH[a]

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

[a] For detail reaction conditions see experimental section. [b] Epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization.

The results of the epoxidation mediated by acetone are shown in Table 4.1. The epoxidation was carried out at apparent pH 10.5-11.5 (Precise control of pH was unnecessary in most cases). As shown in Table 4.1, the epoxidation method appears to be relatively general and effective with substrates containing terminal, *trans*, *cis*, and trisubstituted olefins. Furthermore, a wide variety of functional groups were compatible with the basic reaction conditions; acetylenes, allyl silanes, allyl chlorides, alcohols, esters, ketals, and TBS ethers were all unaffected by the reaction. The conversions of many substrates were greater than 95% as judged by the ^{1}H NMR spectra of the crude reaction mixtures. Side oxidations were also minimal, as only a trace (<5%) of allylic oxidation was seen in the reaction of allylic alcohols (Table 4.1, Entries 5 & 6). Substrates containing hydroxy groups were also epoxidized in good yield even in the absence of acetone. In the case of olefins without hydroxy groups, acetone was required for the epoxidation (for a detailed study on this topic see ref. 6e). The epoxidations of electron-deficient olefins were not efficient under the current reaction conditions. For example, only 21% conversion was obtained for ethyl *trans*-cinnamates. The low efficiency could be due to the fact that the dimethyldioxirane generated was converted back to acetone by Oxone via pathway **e** (Scheme 4.1), as the epoxidation was slower when the electron-deficient olefins were used as substrates.

The olefin reactivity and solubility are two important factors affecting the epoxidation. Upon screening solvent systems, we found that CH_3CN-dimethoxymethane (2:1) produced the best combination of dioxirane reactivity and substrate solubility although other solvents such as alcohols, dioxane, DME, dimethoxymethane, DMF, and CH_3CN were also good for many substrates. For less reactive substrates, the epoxidation could be enhanced by adding Oxone over longer periods of time (4 h). For substrates which were less soluble in the reaction system (such as entries 8, 12, & 18 in Table 4.1),

the epoxidation could be boosted by using more organic solvent. The experimental procedure presented provides the most general procedure possible. In many cases, less Oxone is needed to achieve complete conversion. The reactions presented in Table 1 were run on a small scale (1 mmol). To further illustrate the usefulness of this epoxidation, the epoxidations of two selected olefins (*trans*-stilbene and 1-phenylcyclohexene) were carried out on a multigram scale (see experimental section). In each case the epoxidation also worked well.

4.C. CONCLUSIONS

In conclusion, the above epoxidation utilizing the *in situ* generated dimethyldioxirane at high pH is highly efficient. The method is exceedingly mild and can be used to prepare acid labile epoxides. In addition, this procedure is easy to carry out and will provide a highly attractive epoxidation method since it is safe and economical. The ability to epoxidize and isolate acid sensitive epoxides is particularly attractive and should find wide use in these situations.

2.D. EXPERIMENTAL

Preparation of Starting Materials

***trans*-3-(*tert*-Butyldimethylsilyloxy)-1-phenylpropene (YT062).** To a solution of *trans*-cinnamyl alcohol (6.70 g, 50.0 mmol) and *tert*-butyldimethylsilyl chloride (7.56 g, 50 mmol) in CH_2Cl_2 (150 mL) was added NEt_3 (7.25 g, 100 mmol) and 4-dimethylaminopyridine (50 mg). The reaction was stirred overnight, quenched with H_2O (50 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (2 X 100 mL). The combined organics were washed with brine (1 X 100 mL) and dried (Na_2SO_4).

The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (10/1 hexanes/Et_2O) to give the silyl ether as a colorless oil (10.17 g, 82.0%). ^1H NMR (300 MHz, $CDCl_3$) [6c] δ 7.36 – 7.10 (m, 5H), 6.54 (dt, J = 15.9, 1.8, 1H), 6.23 (dt, J = 15.9, 5.1 Hz, 1H), 4.3 (dd, J = 5.1, 1.8 Hz, 1H), 0.89 (s, 9H), 0.062 (s, 6H).

***trans*-Methyl-6-phenylhex-4-enoate (4-6)(YT750).** To a solution of phenylacetaldehyde (6.0 g, 50 mmol) in Et_2O (100 mL) at 0 °C was added vinylmagnesium bromide (70 ml, 70 mmol, 1.0 M in Et_2O) and the solution was stirred with gradual warming to room temperature for 4 h. The reaction was quenched with saturated NH_4Cl (50 mL), the layers were separated , and the aqueous layer was extracted with Et_2O (2 X 100 mL). The combined organics were washed with brine (1 X 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (3/1 hexanes/Et_2O) to give the allylic alcohol as a colorless oil (5.28 g, 71.3%). The crude material was taken to the next step without characterization.

To a mixture of the above alcohol (5.28 g, 35.7 mmol) and trimethyl orthoacetate (35 mL) was added propionic acid (0.60 g, 8.1 mmol) and the solution was heated to reflux for 7 h. at which time it was cooled, partitioned between H_2O (50 mL) and Et_2O (50 mL), the layers separated, and the aqueous layer extracted with Et_2O (2 X 50 mL). The combined organics were washed with brine (1 X 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting light yellow oil was purified by flash column chromatography (5/1 hexanes/Et_2O) to give the *trans* olefin as a colorless oil (4.63 g, 63.7%). ^1H NMR (300 MHz, $CDCl_3$)[6c] δ 7.35 – 7.13 (m, 5H), 5.67 (dt, J = 15.3, 6.6 Hz, 1H), 5.54 (dt, J = 15.3, 6.0 Hz, 1H), 3.68 (s, 3H), 3.36 (d, J = 6.6 Hz, 1H), 2.47 – 2.34 (m, 4H).

1-(1'-Propynyl)cyclohexene (4-7). To a solution of 1-ethynylcyclohexene (4.25 g, 40 mmol) in dry THF (80 mL) at –78 °C under nitrogen was added n-BuLi (17.6 mL, 44 mmol, 2.5 M in hexanes) dropwise. The reaction mixture was warmed to 0 °C over 3 h and iodomethane (6.25 g, 44 mmol) was then added dropwise. After stirring overnight, the reaction mixture was quenched with H_2O (50 mL), the layers were separated, and the aqueous layer was extracted with hexanes (2 X 30 mL). The combined organic layers were washed with H_2O (1 X 50 mL) and brine (1 X 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the product as a colorless liquid (4.80 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$)[6g] δ 5.99 (br s, 1H), 2.10 – 2.03 (m, 4H), 1.93 (s, 3H), 1.64 – 1.53 (m, 4H).

General epoxidation procedure for Table 4.1: To a mixture of the olefin (1 mmol) and tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol) in CH_3CN-dimethoxymethane (2:1) (4-8 ml), acetone (2.2 mL, 30 mmol), and 0.1 M solution of K_2CO_3 (2 mL) was added Oxone (1.84 g, 3 mmol in 8 mL 4 x 10^{-4} M EDTA solution) and K_2CO_3 (1.84 g, 13.3 mmol in 8 mL H_2O) separately either by syringe pump or addition funnel over the indicated time. After completing the addition of Oxone, the reaction mixture was extracted with hexanes or methylene chloride (3 x 25 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Upon removal of solvent under reduced pressure the crude product was purified by flash column chromatography with silica gel (buffered with 1 % Et_3N) as the stationary phase.

1-Decene oxide (Table 4.1, Entry 1)(MF1138). Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 2.91 (dddd, J = 6.6, 3.9, 2.7, 1.5 Hz, 1H), 2.75 (dd, J = 5.4, 3.9 Hz, 1H), 2.46

(dd, J = 5.4, 2.7 Hz, 1H), 1.60 – 1.35 (m, 4H), 1.35 – 1.20 (m, 10H), 0.89 (t, J = 7.2 Hz, 3H).

(Triisopropylsilyl)propene oxide (Table 4.1, Entry 2)(MF1122). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 2.81 (dddd, J = 9.0, 4.5, 4.2, 3.0 Hz, 1H), 2.81 (ddd, J = 4.9, 4.2, 1.2 Hz, 1H), 2.48 (dd, J = 4.9, 3.0 Hz, 1H), 1.30 (dd, J = 14.3, 4.5 Hz, 1H), 1.07 (m, 3H), 1.06 (d, J = 2.7 Hz, 18H).

α-Methylstyrene oxide (Table 4.1, Entry 3)(MF1127). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.40 – 7.25 (m, 5H), 2.98 (d, J = 5.4 Hz, 1H), 2.81 (dq, J = 5.4, 0.7 Hz, 1H), 1.72 (d, J = 0.7 Hz, 3H).

2-(Chloromethyl)-3-phenyloxirane (Table 4.1, Entry 4)(MF1016). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6a] δ 7.35 – 7.15 (m, 1H), 3.77 (d, J = 2.1 Hz, 1H), 3.66 (dd, J = 12.0, 5.1 Hz, 1H), 3.22 (ddd, J = 5.7, 5.1, 2.1 Hz, 1H).

2-(Hydroxymethyl)-3-phenyloxirane (Table 4.1, Entry 5)(MF1017). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[10] δ 7.40 – 7.35 (m, 5H), 4.06 (ddd, J = 12.9, 5.4, 2.4 Hz, 1H), 3.94 (d, J = 2.4 Hz, 1H), 3.80 (ddd, J = 12.9, 7.8, 3.9 Hz, 1H), 3.24 (dt, J = 3.9, 2.4 Hz, 1H), 1.92 (dd, J = 7.8, 5.4 Hz, 1H).

2-(Hydroxymethyl)-3-propyloxirane (Table 4.1, Entry 6)(MF1018, 1038). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[11] δ 3.91 (d, J = 12.6, 2.4 Hz, 1H), 3.61 (dt, J = 12.6, 5.1

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[10] Melloni, P.; Della, T.A.; Lazzari, E.; Mazzani, G.; Meroni, M.; *Tetrahedron* **1985**, *41*, 1393.
[11] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

Hz, 1H), 2.98 (dd, J = 5.1, 2.4 Hz, 1H), 2.93 (dt, J = 4.5, 2.4 Hz, 1H), 2.38 (br s, 1H), 1.60 –1.40 (m,4H), 0.97 (t, J = 7.2 Hz, 3H).

***trans*-2-[2-(hydroxyethyl)]-3-ethyloxirane (Table 4.1, Entry 7)(MF1020).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[12] δ 3.79 (t, J = 6.0 Hz, 2H), 2.88 (ddd, J = 6.6, 3.9, 2.1 Hz, 1H), 2.80 (dt, J = 5.7, 2.1, Hz, 1H), 2.10 (br s, 1H), 2.03 – 1.93 (m, 1H), 1.75 – 1.65 (m, 1H), 1.63 – 1.55 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H).

2,3-Dihexyloxirane (Table 4.1, Entry 8). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[12] δ 2.66 (m, 2H), 1.60 – 1.20 (m, 20H), 0.89 (t, J = 6.9 Hz, 6H).

2-[(*tert*-Butyldimethylsilyloxy)methyl]-3-phenyloxirane (Table 4.1, Entry 9). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6a] δ 7.38 – 7.20 (m, 5H), 3.97 (dd, J = 12.0, 3.0 Hz, 1H), 3.84 (dd, J = 12.0, 4.5 Hz, 1H), 3.14 (ddd, J = 4.5, 3.0, 2.4 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).

2-Benzyl-3-[2-(methoxycarbonyl)ethyl]oxirane (Table 4.1, Entry 10)(MF1039). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.40 – 7.15 (m, 5H), 3.65 (s, 3H), 3.00 – 2.80 (m, 4H), 2.41 (dd, J = 7.8, 7.2 Hz, 2H), 1.97 (dqd, J = 14.4, 7.5, 4.8 Hz, 1H), 1.78 (dq, J = 14.4, 6.9 Hz, 1H).

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[12] Rossiter, B.E.; Sharpless, K.B. *J. Org. Chem.* **1984**, *49*, 3707.

***trans*-β-Methylstyrene oxide (Table 4.1, Entry 11)(MF1128).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[13] δ 7.45 – 7.20 (m, 5H), 3.57 (d, J = 2.1 Hz, 1H), 3.03 (dq, J = 5.1, 2.1Hz, 1H), 1.44 (d, J = 5.1 Hz, 3H).

***trans*-Stilbene oxide (Table 4.1, Entry 12)(MF1032).** Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$)[14] δ 7.50 – 7.30 (m, 10H), 3.98 (s, 2H).

***cis*-2-[2-(hydroxyethyl)]-3-ethyloxirane (Table 4.1, Entry 13)(MF1106).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[12] δ 3.83 (d, J = 5.4 Hz, 2H), 3.11 (dtd, J = 8.1, 4.2, 1.2 Hz, 1H), 2.93 (td, J = 6.9, 4.2 Hz, 1H), 2.65 (br s, 1H), 1.95 – 1.83 (m, 1H), 1.73 – 1.61 (m, 1H), 1.63 – 1.50 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H).

3,4-Dihydronaphthalene oxide (Table 4.1, Entry 14)(MF1123). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.40 (dd, J = 6.9, 1.8 Hz, 1H), 7.30 – 7.15 (m, 2H), 7.09 (d, J = 7.2 Hz, 1H), 3.85 (d, J = 4.2 Hz, 1H), 3.73 (ddd, J = 4.2, 3.0, 0.6 Hz, 1H), 2.78 (ddd, J = 15.6, 14.7, 6.6 Hz, 1H), 2.55 (dd, J = 15.6, 5.7 Hz, 1H), 2.42 (dddd, J = 14.4, 6.6, 3.0, 1.8 Hz, 1H), 1.77 (ddd, J = 14.7, 14.4, 5.7 Hz, 1H).

3,3-Ethylidenedioxycyclopentene oxide (Table 4.1, Entry 15)(MF1117). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[15] δ 4.20 – 3.90 (m, 4H), 3.52 (d, J = 2.7 Hz, 1H), 3.26 (d, J = 2.7 Hz, 1H), 2.20 – 2.05 (m, 1H), 1.90 – 1.60 (m, 3H).

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[13] Witkop, B.; Foltz, C.M. *J. Am. Chem. Soc.* **1957**, *79*, 197.
[14] Imuta, M.; Ziffer, H.J. *J. Org. Chem.* **1979**, *44*, 2505.
[15] Vankar, Y.D.; Chaudhuri, N.C.; Rao, C.T. *Tetrahedron Lett.* **1987**, *28*, 551.

2-Methyl-2,3-diphenyloxirane (Table 4.1, Entry 16)(MF1021). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.48 – 7.28 (m, 10H), 3.97 (s, 1H), 1.47 (s, 3H).

1-Phenylcyclohexene oxide (Table 4.1, Entry 17)(MF1041). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.40 – 7.20 (m, 5H), 3.10 (br s, 1H), 2.29 (ddd, J = 15.0, 8.4, 5.1 Hz, 1H), 2.12 (dt, J = 15.0, 5.1 Hz, 1H), 2.0 – 1.95 (m, 2H), 1.65 – 1.25 (m, 4H).

1-(1'-Propynyl)cyclohexene oxide[16] (Table 4.1, Entry 18). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (br s, 1H), 2.10 (dt, J = 15.1, 6.0, Hz, 1H), 2.00 – 1.85 (m, 3H), 1.82 (s, 3H), 1.44 – 1.16 (m, 4H).

3-Decyl-2,2-diphenyloxirane[6c] (Table 4.1, Entry 19)(MF950). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 10H), 3.38 (dd, J = 6.6, 4.8 Hz, 1H), 1.50 – 1.17 (m, 18H), 0.87 (t, J = 6.6 Hz, 3H).

(Table 4.1, Entry 20) (MF1107). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$)[6c] δ 7.30 –7.10 (m, 3H), 3.83 (s, 1H), 2.31 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H).

Large Scale Epoxidation Procedures

***trans*-Stilbene Oxide**: To a 5 L three-necked flask equipped with a mechanical stirrer was added *trans* -stilbene (18.02 g, 100 mmol), CH_3CN-dimethoxymethane (1.17 L, 2/1 v/v), 0.1 M aqueous K_2CO_3 (330 mL), acetone (220 mL, 3 mol), and

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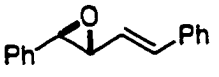
[16] Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron*, **1991**, *47*, 1677.

tetrabutylammonium hydrogen sulfate (1.5 g). The pH was adjusted to 10.5 by the dropwise addition of glacial acetic acid. Oxone (92.2 g, 150 mmol) in 330 mL 4 x10^{-4} M EDTA and K_2CO_3 (92.2 g, 667 mmol) in 330 mL H_2O were added separately via addition funnels over 2h. The reaction mixture was extracted with hexanes (3 x 1.5 L), washed with brine (1 x 1L), dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel buffered with 1 % Et_3N) (hexanes) to yield *trans*-stilbene oxide as a white solid (17.00 g, 86.7 %).

1-Phenylcyclohexene Oxide: To a 5 L three-necked flask equipped with a mechanical stirrer was added 1-phenylcyclohexene (15.82 g, 100 mmol), CH_3CN-dimethoxymethane (400 mL, 2/1 v/v), 0.1 M aqueous K_2CO_3 (200 mL), acetone (220 mL, 3 mol), and tetrabutylammonium hydrogen sulfate (1.5 g). The pH was adjusted to 10.5 by the dropwise addition of glacial acetic acid. Oxone (184 g, 300 mmol) in 660 mL 4 x 10^{-4} M EDTA and K_2CO_3 (184 g, 1.33 mol) in 660 mL H_2O were added separately via addition funnels over 2h. The reaction mixture was extracted with hexanes (3 x 1.5 L), washed with brine (1 x 1L), dried (Na_2SO_4), concentrated, and filtered through a bed of silica gel (buffered with 1 % Et_3N) (hexane/ether, 10/1 v/v) to yield 1-phenylcyclohexene oxide as a colorless oil (14.48 g, 83.1 %).

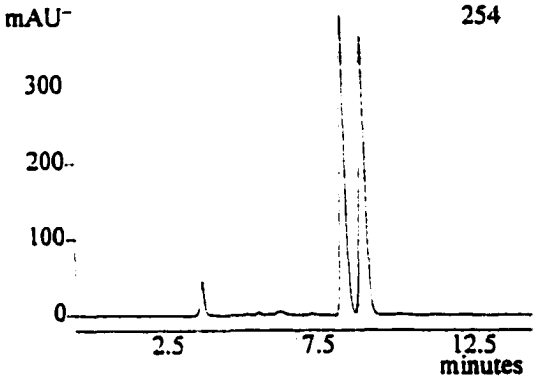
Supplementary Material

(Table 2.1, Entry 1)



HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (90/10)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



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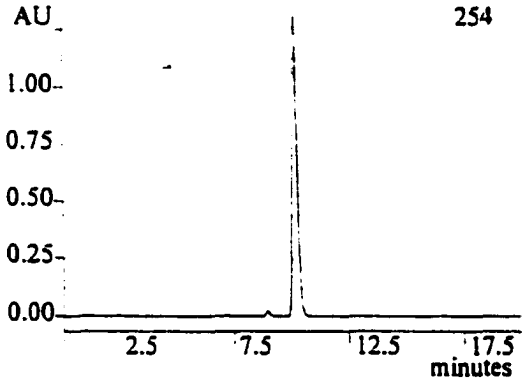
Optically Active



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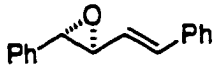
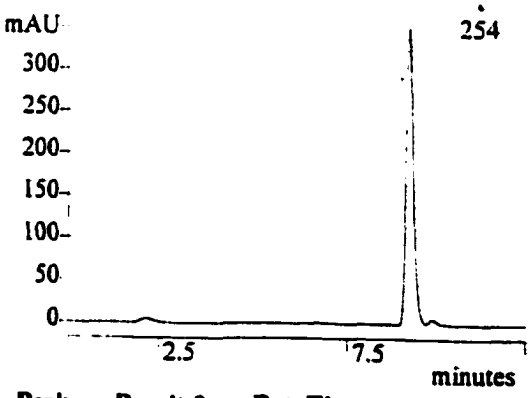
(Table 2.1, Entry 2)



Optically Active



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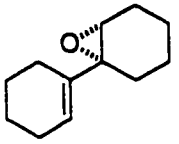
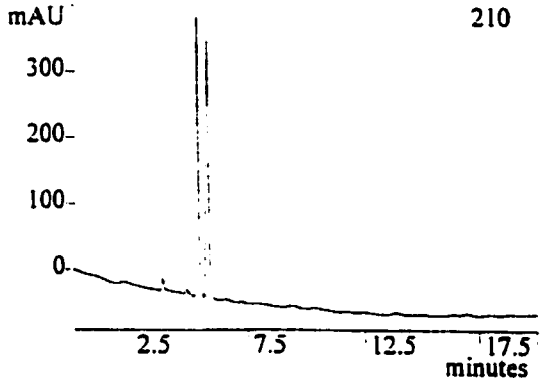
(Table 2.1, Entry 3)



HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (95/5)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



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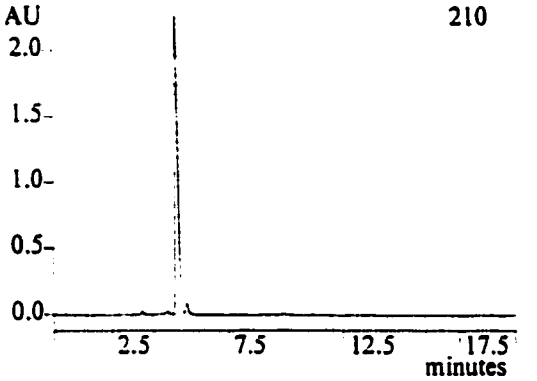
Optically Active



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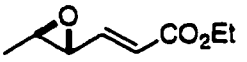
(Table 2.1, Entry 4)



HPLC Conditions
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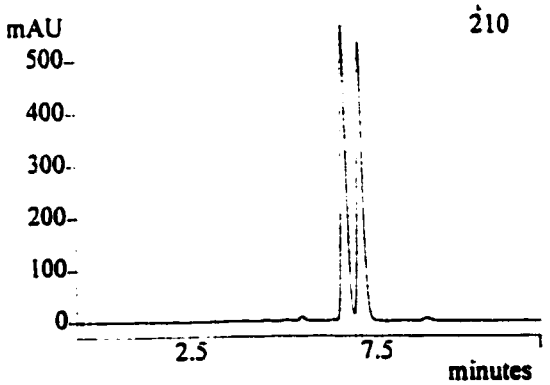
Eluent: Hexane/IPA (90/10)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



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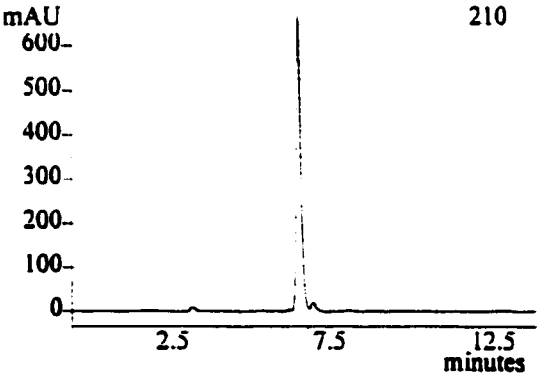
Optically Active



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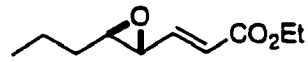
(Table 2.1, Entry 5)



HPLC Conditions
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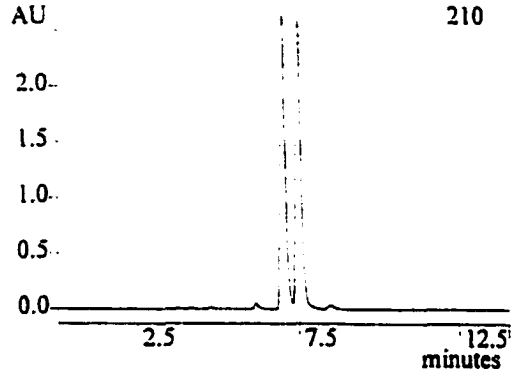
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



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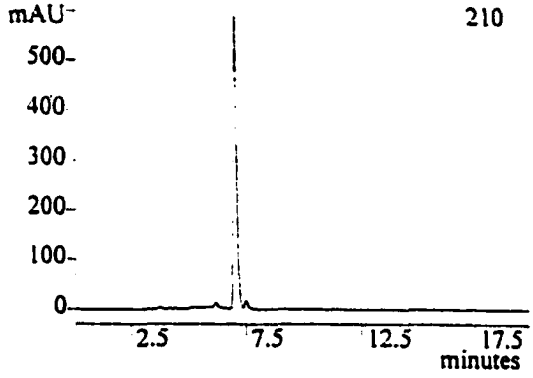
Optically Active



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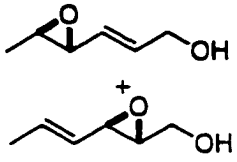
	100.0000		**3323609**

(Table 2.1, Entry 6)



HPLC Conditions
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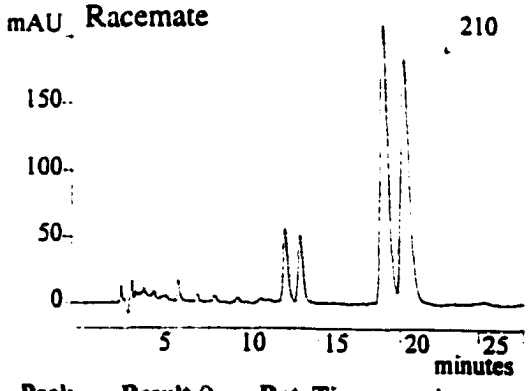
Detection: UV 210 nm

Racemate



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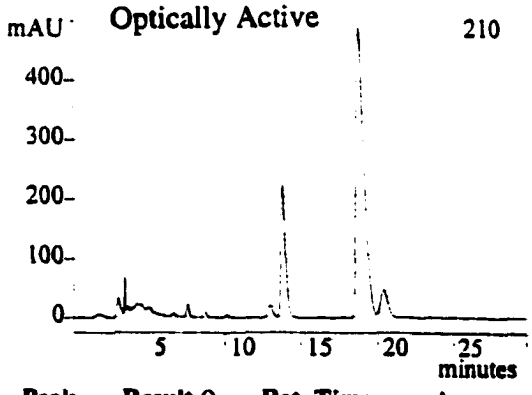
	100.0000		**8281399**

Optically Active



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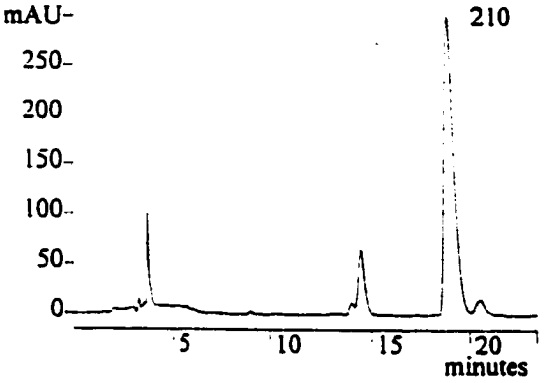
4	5.2188	20.342	706995
	100.0001		**13547133**

(Table 2.1, Entry 7)

HPLC Conditions

Column:	Chiralcel OD
Eluent:	Hexane/IPA (98/2)
Flow Rate:	0.8 mL/min
Detection:	UV 210 nm

Optically Active



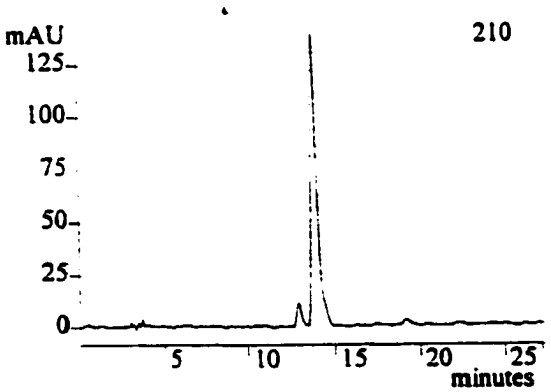
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	96.4347	18.889	5515820
2	3.5653	20.471	203929
	100.0000		**5719749**

(Table 2.1, Entry 7)

HPLC Conditions

Column:	Chiralcel OD
Eluent:	Hexane/IPA (98/2)
Flow Rate:	0.8 mL/min
Detection:	UV 210 nm

Optically Active



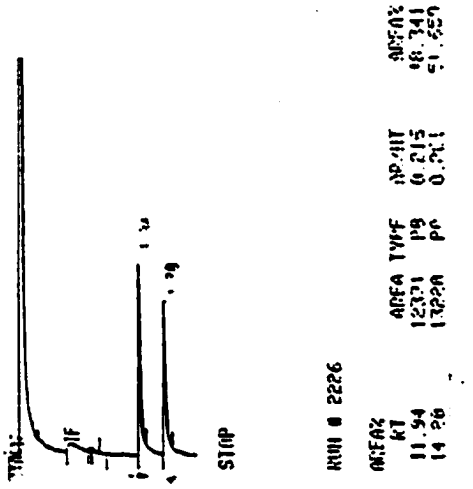
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	6.3093	12.966	113669
2	93.6907	13.882	1687930
	100.0000		**1801599**

(Table 2.1, Entry 8)

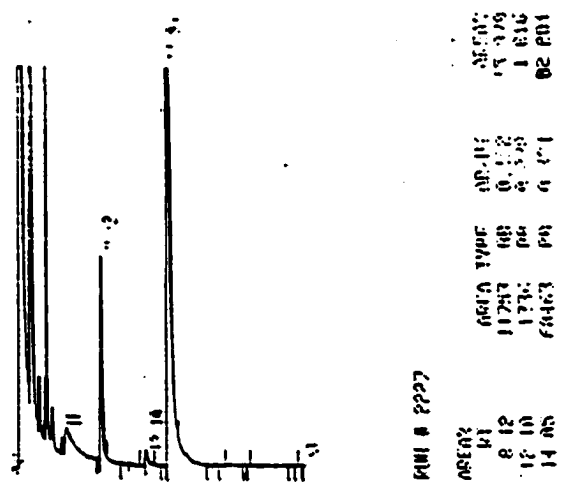
GC Conditions

Column:	Chiraldex G-TA
Oven:	85 C
Carrier:	Helium, head pressure: 260 kPa
Injection:	250 C
Detection:	FID 250 C

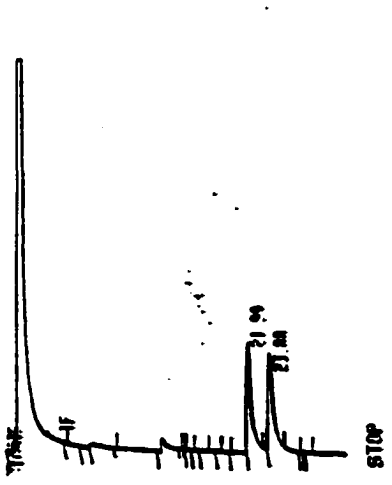
Racemate



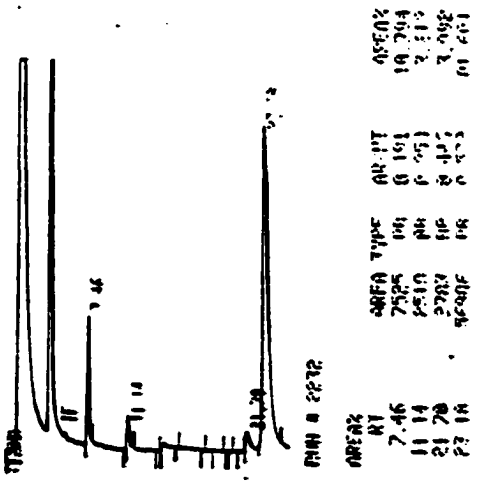
Optically Active



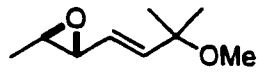
Racemate



Optically Active



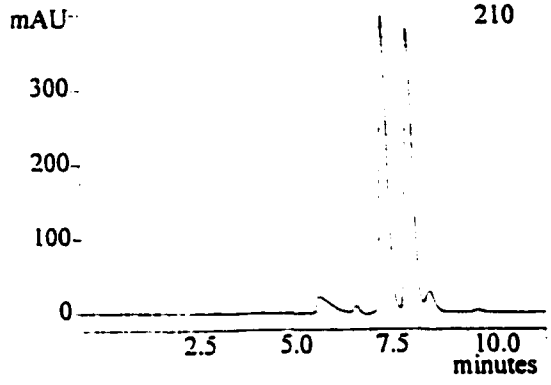
(Table 2.1, Entry 9)



HPLC Conditions

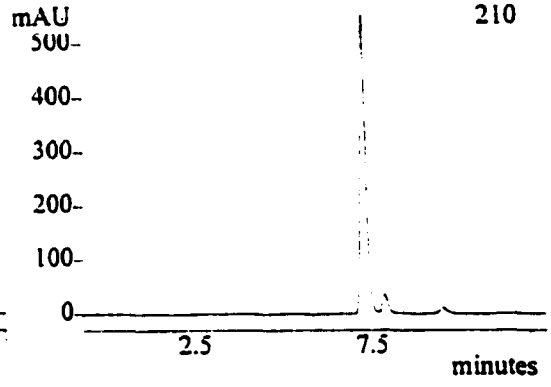
Column: Chiralcel OD
Eluent: Hexane/IPA (96/4)
Flow Rate: 0.5 mL/min
Detection: UV 210 nm

Racemate



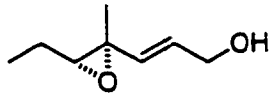
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.4341	7.872	2768099
2	50.5659	8.517	2831472
	100.0000		5599571

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	92.1854	7.860	3318647
2	5.4594	8.460	196536
3	2.3552	10.102	84788
	100.0000		3599971

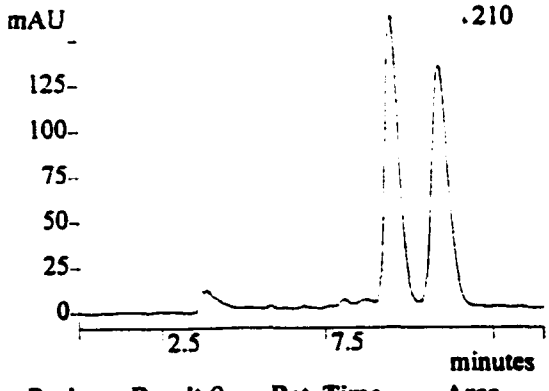
(Table 2.1, Entry10)



HPLC Conditions

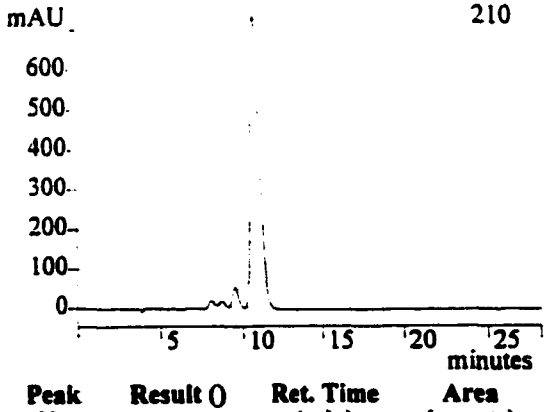
Column: Chiralcel OB
Eluent: Hexane/IPA (90/10)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm

Racemate



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.8486	9.529	2378886
2	50.1514	10.940	2393333
	100.0000		4772219

Optically Active



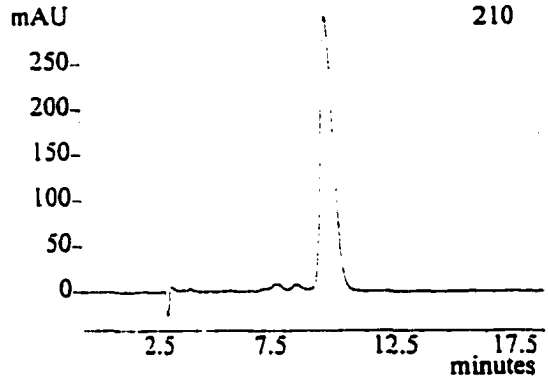
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	5.1551	9.521	806145
2	94.8449	10.724	14831561
	100.0000		15637706

(Table 2.1, Entry 11)

HPLC Conditions

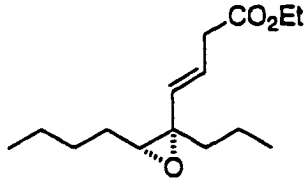
Column:	Chiralcel OB
Eluent:	Hexane/IPA (90/10)
Flow Rate:	1.0 mL/min
Detection:	UV 210 nm

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.0845	9.568	126211
2	97.9155	10.928	5928407
	100.0000		**6054618**

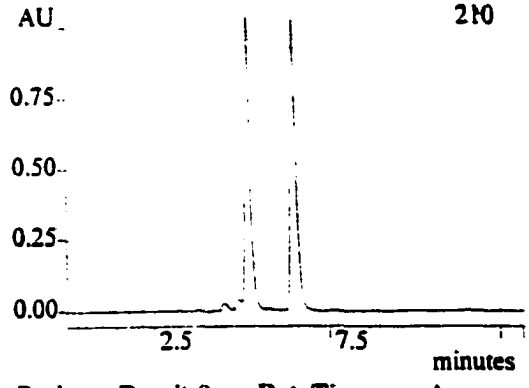
(Table 2.1, Entry 12)



HPLC Conditions

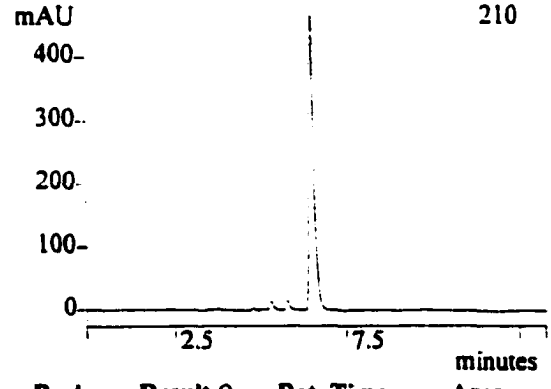
Column:	Chiralcel OD
Eluent:	Hexane/IPA (97/3)
Flow Rate:	0.8 mL/min
Detection:	UV 210 nm

Racemate



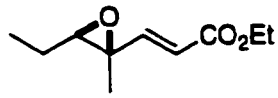
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.4405	5.192	5924552
2	49.5595	6.490	5821068
	100.0000		**11745620**

Optically Active



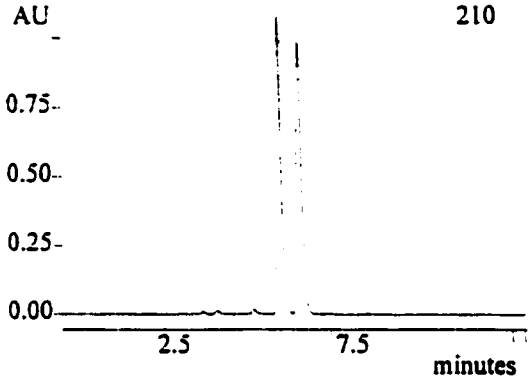
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.3669	5.283	59825
2	2.6449	5.769	66852
3	94.9881	6.516	2400867
	99.9999		**2527544**

(Table 2.1, Entry 13)



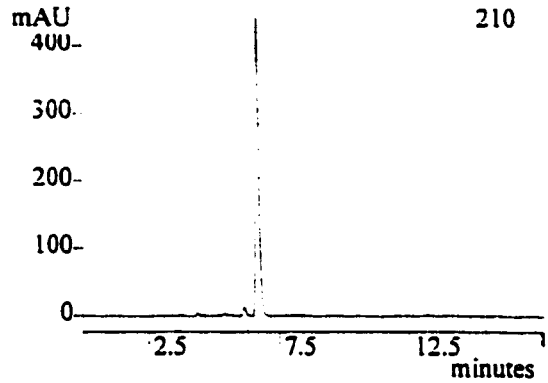
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (97/3)
Flow Rate: 0.9 mL/min
Detection: UV 210 nm

Racemate



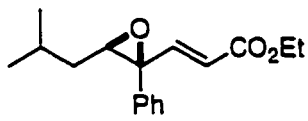
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.3540	6.087	5122262
2	49.6460	6.635	5050248
	100.0000		**10172510**

Optically Active



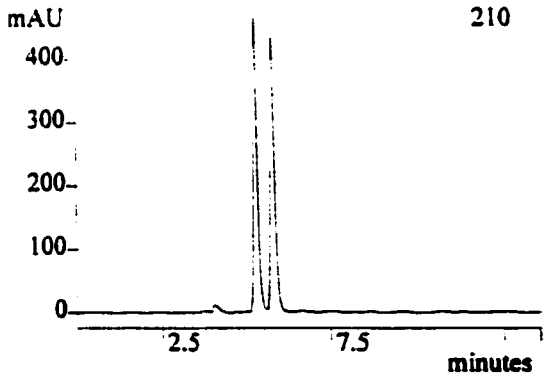
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.6821	6.118	61053
2	97.3179	6.635	2215226
	100.0000		**2276279**

(Table 2.1, Entry 14)



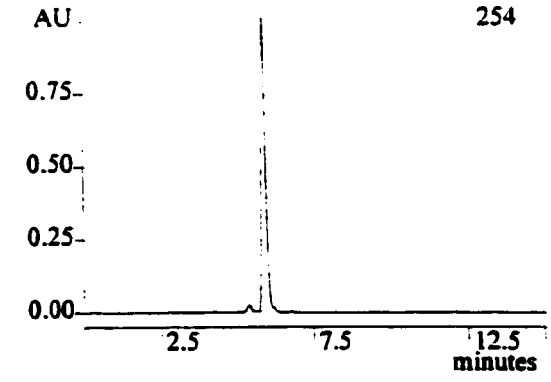
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (96/4)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



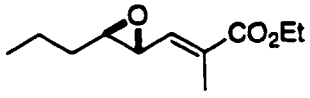
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.5467	5.328	2062374
2	50.4533	5.832	2100109
	100.0000		**4162483**

Optically Active



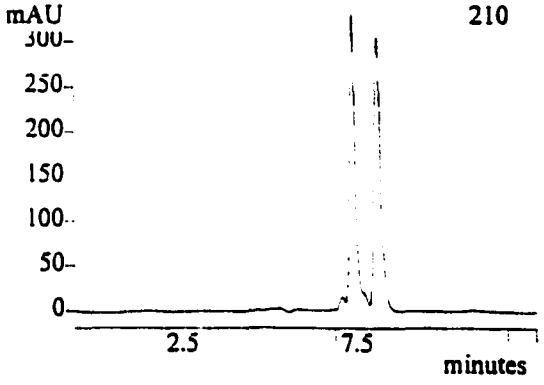
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.5336	5.334	132278
2	97.4664	5.841	5088695
	100.0000		**5220973**

(Table 2.1, Entry 15)



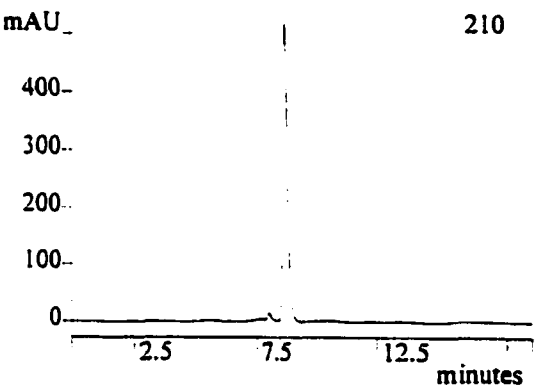
HPLC Conditions
Column: Chiralcel OB
Eluent: Hexane/IPA (97/3)
Flow Rate: 0.6 mL/min
Detection: UV 210 nm

Racemate



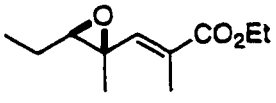
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.5370	8.000	2178501
2	49.4630	8.725	2132201
	100.0000		4310702

Optically Active



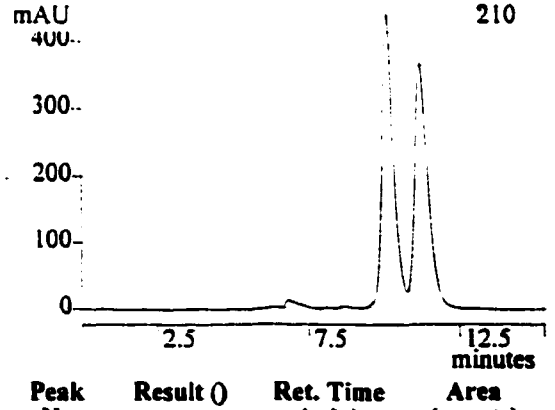
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.8785	8.012	108092
2	97.1215	8.731	3647046
	100.0000		3755138

(Table 2.1, Entry 16)



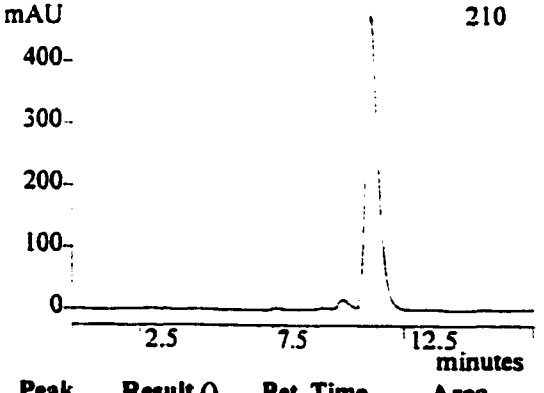
HPLC Conditions
Column: Chiralcel OB
Eluent: Hexane/IPA (97/3)
Flow Rate: 0.5 mL/min
Detection: UV 210 nm

Racemate



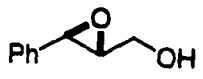
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.6417	10.116	6291861
2	49.3583	11.223	6132397
	100.0000		12424258

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.7717	10.217	225588
2	97.2283	11.275	7913465
	100.0000		8139053

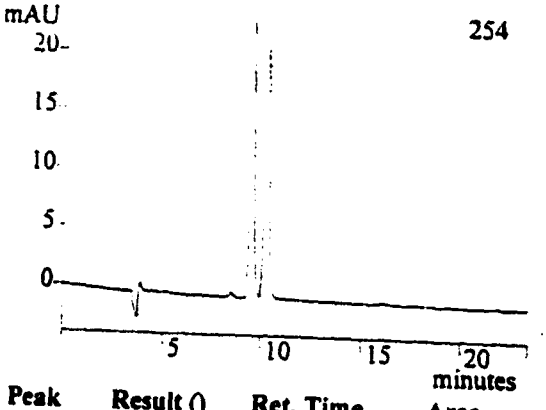
Absolute Configuration Determination



Racemate

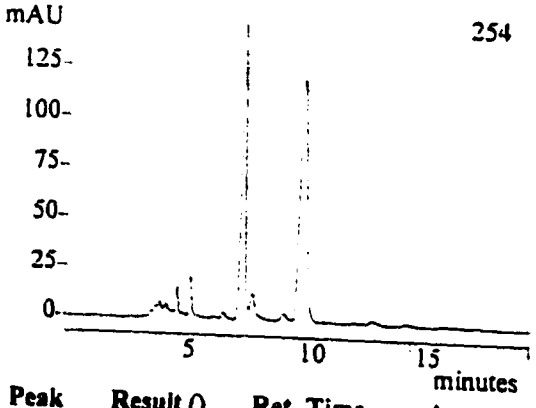
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (80/20)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

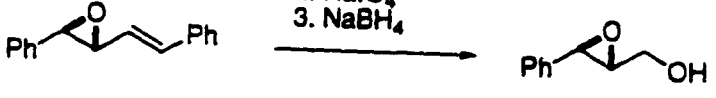


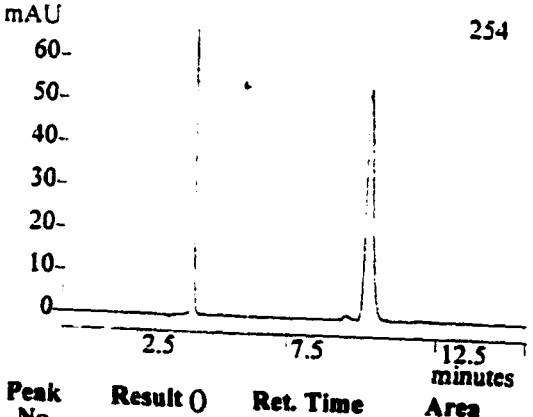
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.0835	9.443	179790
2	49.9165	10.208	179191
	100.0000		358981

Authentic Sample



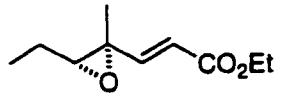
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	2.5198	9.524	34001
2	97.4802	10.251	1315389
	100.0000		1349390





Peak No	Result ()	Ret. Time (min)	Area (counts)
1	1.4808	9.469	6882
2	98.5192	10.165	457869
	100.0000		464751

Absolute Configuration Determination

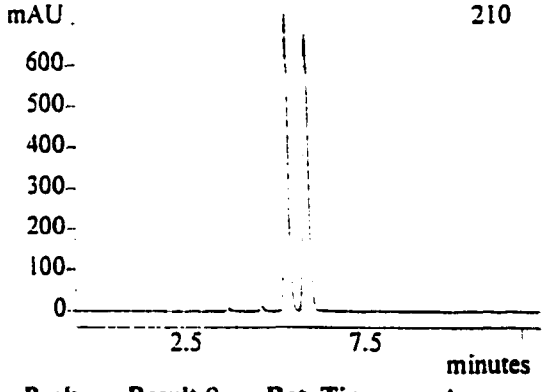


Racemate

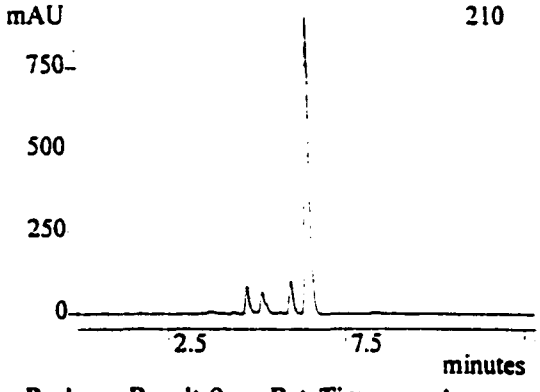
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (96/4)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Optically Active

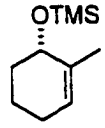


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.1966	5.936	3300973
2	49.8034	6.465	3275118
	100.0000		**6576091**



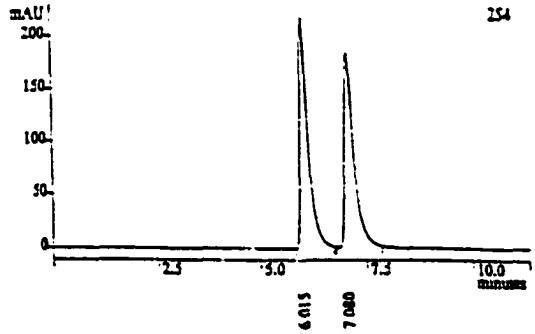
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	9.4471	5.898	465146
2	90.5529	6.415	4458523
	100.0000		**4923669**

(Table 3.1, Entry 1)



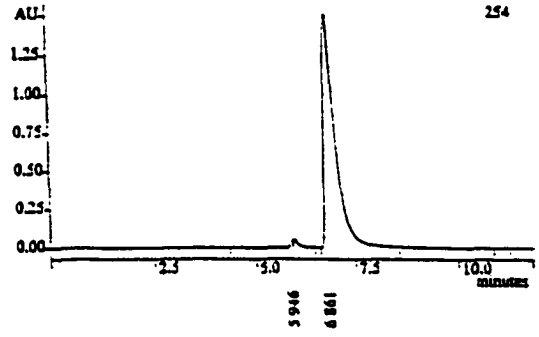
Racemate

HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

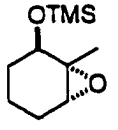


Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		50.4652	6.015	1493430
2		49.5348	7.080	1465899
	Totals	100.0000		2959329

Optically Active

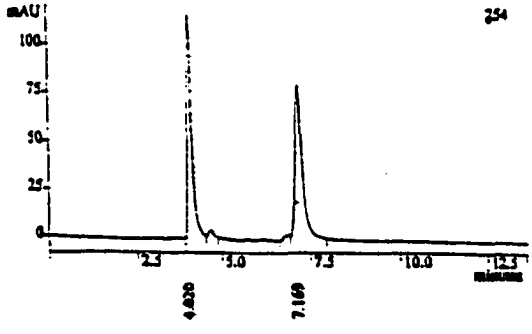


Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		2.2347	5.946	353102
2		97.7653	6.861	15447903
	Totals	100.0000		15801005



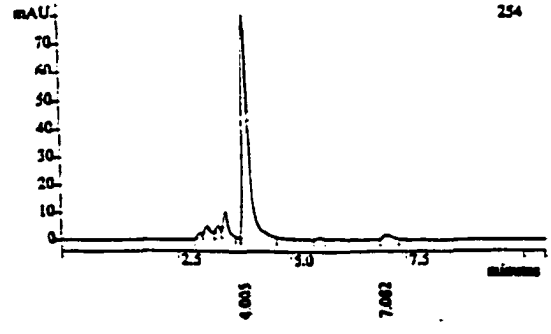
Racemate

HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm



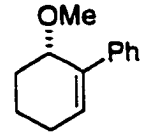
Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		50.2387	4.020	634138
2		49.7614	7.169	628113
	Totals	100.0001		1262251

Optically Active



Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		97.6288	4.005	408029
2		2.3712	7.082	9910
	Totals	100.0000		417939

(Table 3.1, Entry 2)

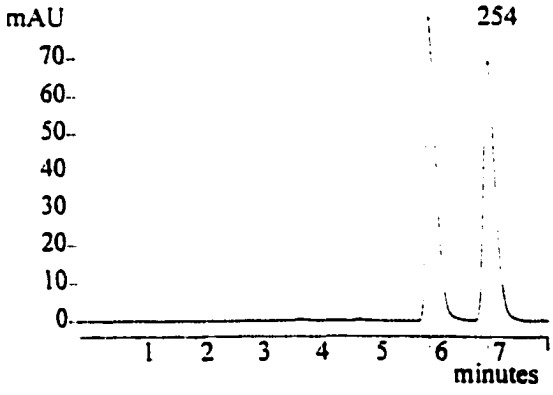


Racemate

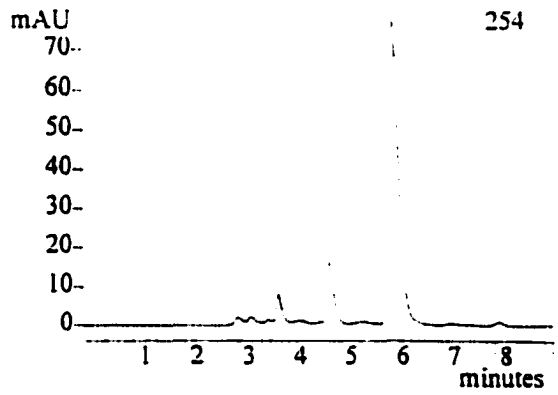
HPLC Conditions

Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

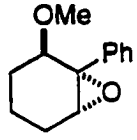
Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.7724	6.043	493708
2	50.2276	7.045	498223
	100.0000		**991931**



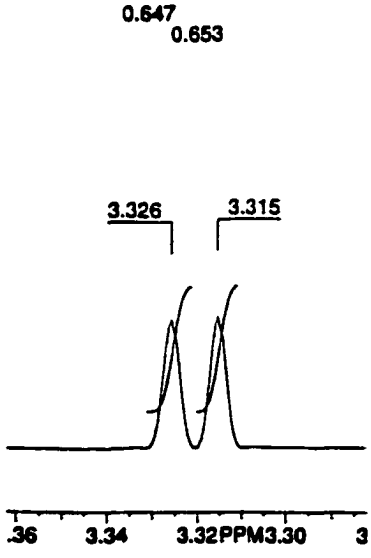
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	99.3507	6.043	537249
2	0.6493	7.164	3511
	100.0000		**540760**

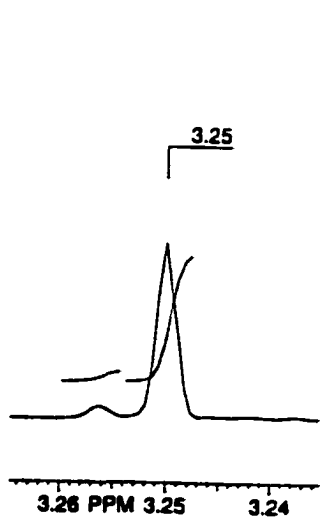


Racemate

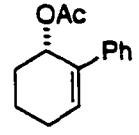
Chiral shift NMR was done with $Eu(hfc)_3$ as chiral shift agent

Optically Active





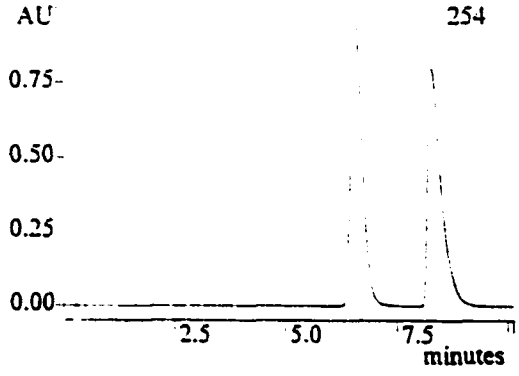
(Table 3.1, Entry 3)



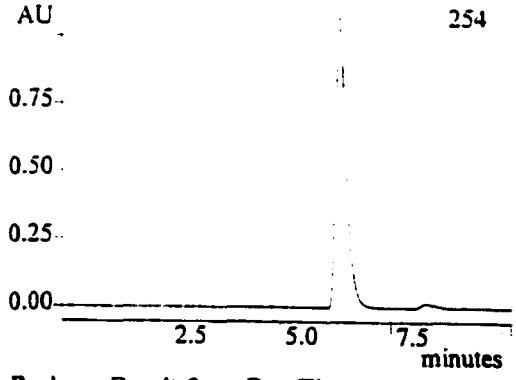
Racemate

HPLC Conditions
Column: Chiralcel OJ
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

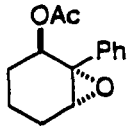
Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.8160	6.609	8972730
2	50.1840	8.308	9039023
	100.0000		18011752



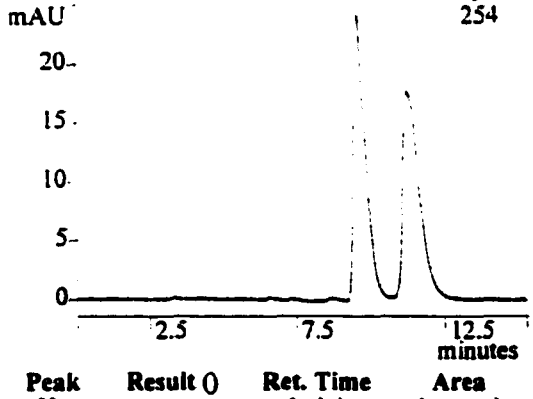
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	98.0170	6.307	9351594
2	1.9830	8.264	189190
	100.0000		9540784



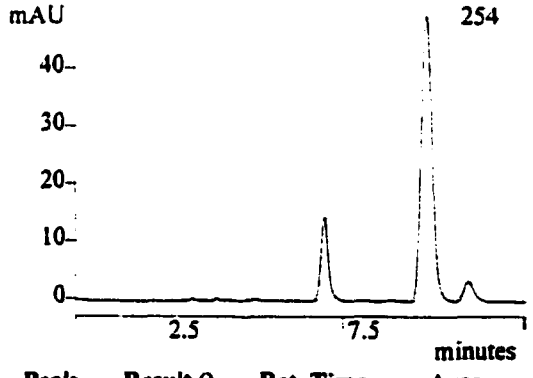
Racemate

HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Optically Active

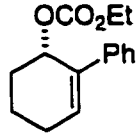


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.4429	9.601	330046
2	50.5571	11.287	337484
	100.0000		667530



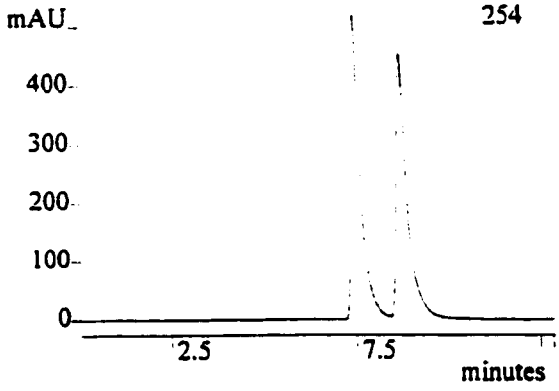
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	94.1846	9.854	531596
2	5.8154	10.960	32824
	100.0000		564420

(Table 3.1, Entry 4)



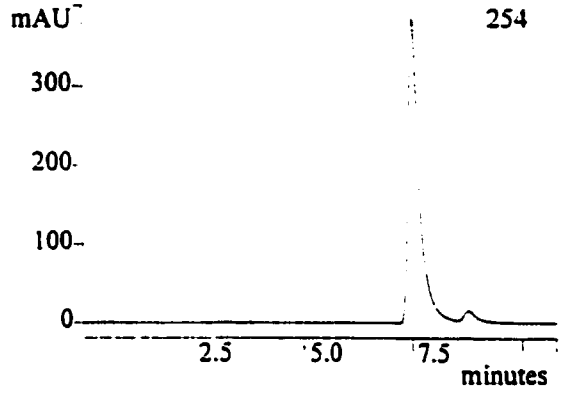
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate

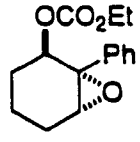


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.3053	7.492	4792079
2	49.6947	8.729	4733906
	100.0000		9525985

Optically Active

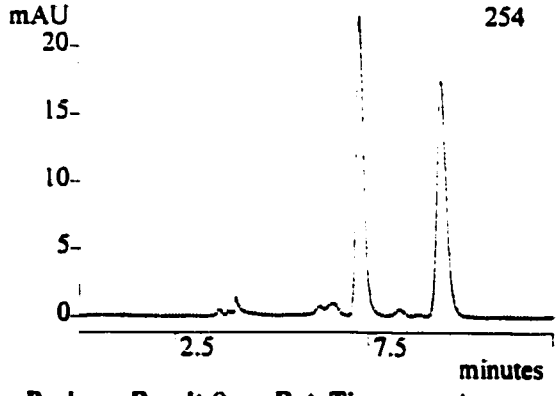


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	96.8428	7.522	3513690
2	3.1572	8.800	114553
	100.0000		3628243



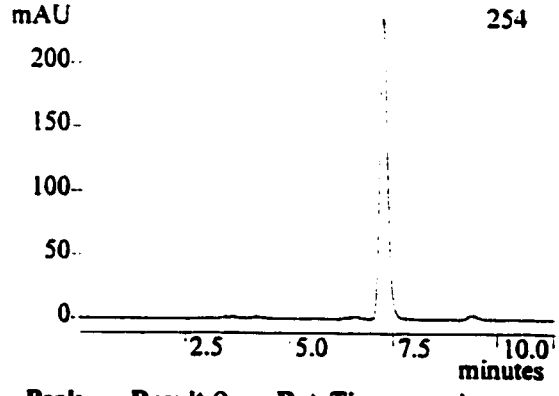
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate



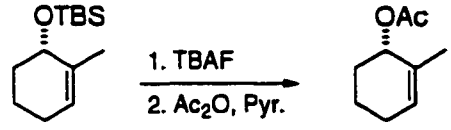
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.4096	7.293	159282
2	49.5904	9.384	156694
	100.0000		315976

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	98.2758	7.285	1562507
2	1.7242	9.387	27413
	100.0000		1589920

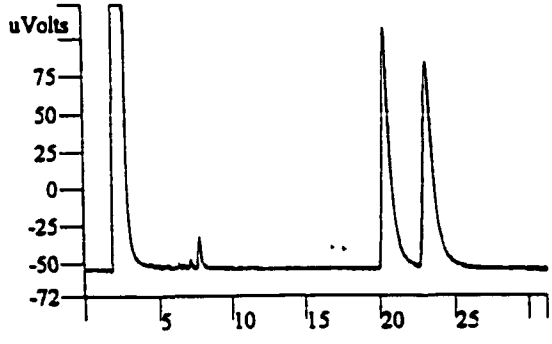
(Table 3.1, Entry 5)



GC Conditions

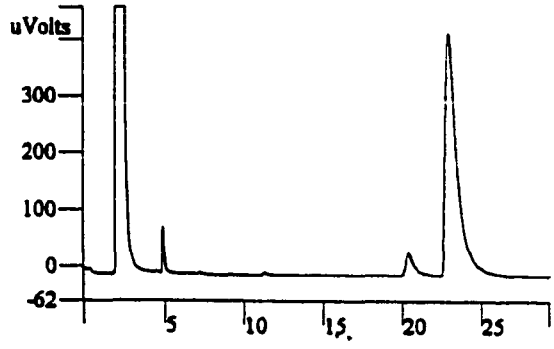
Column: Chiraldex G-TA
Oven: 70 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

Racemate



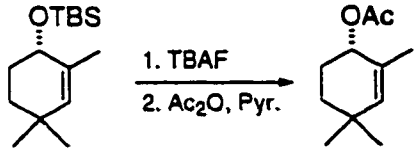
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	50.4913	20.349	6126
2	49.5087	23.142	6007
	100.0000		**12133**

Optically Active



Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	5.6723	20.281	1325
2	94.3277	22.859	22035
	100.0000		**23360**

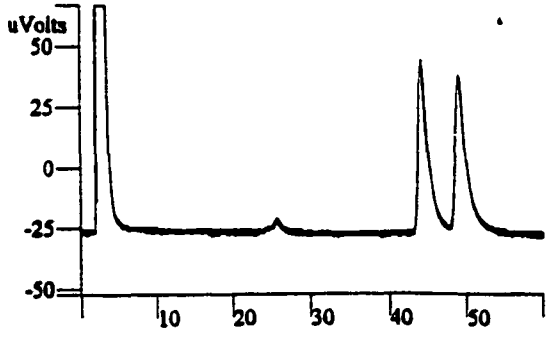
(Table 3.1, Entry 6)



GC Conditions

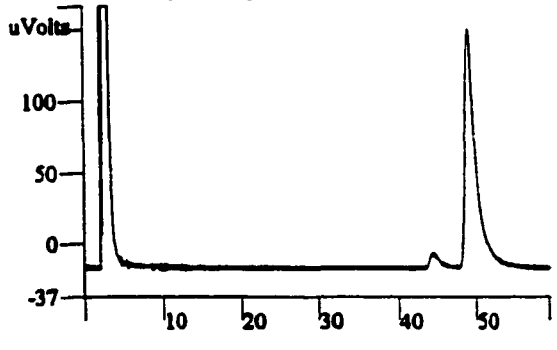
Column: Chiraldex G-TA
Oven: 60 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

Racemate



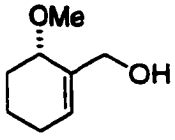
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	49.9014	44.159	6097
2	50.0987	48.984	6121
	100.0001		**12218**

Optically Active



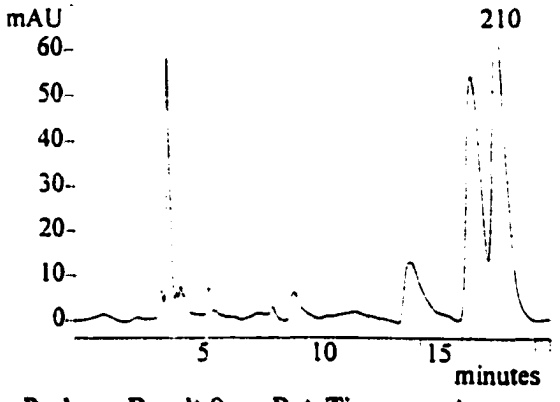
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	5.6959	44.116	1027
2	94.3041	48.903	17010
	100.0000		**18037**

(Table 3.1, Entry 7)



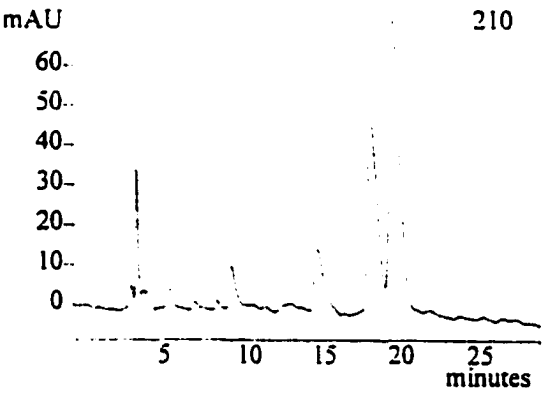
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (97/3)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



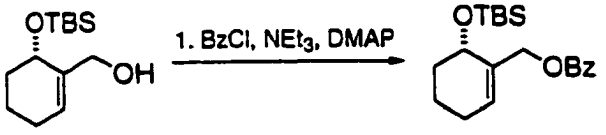
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	45.0504	17.247	1220570
2	54.9496	18.381	1488772
	100.0000		2709342

Optically Active



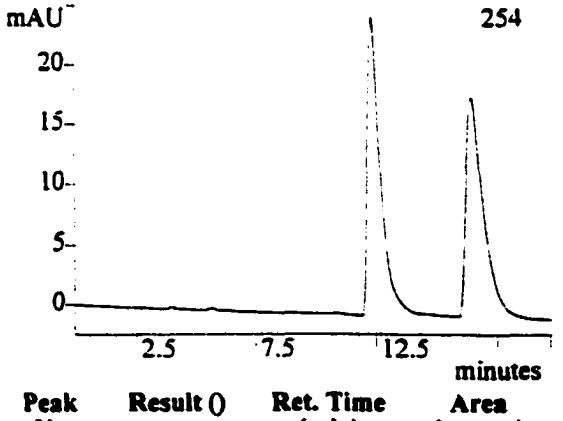
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	38.3111	19.223	1180567
2	61.6889	20.626	1900959
	100.0000		3081526

(Table 3.1, Entry 8)



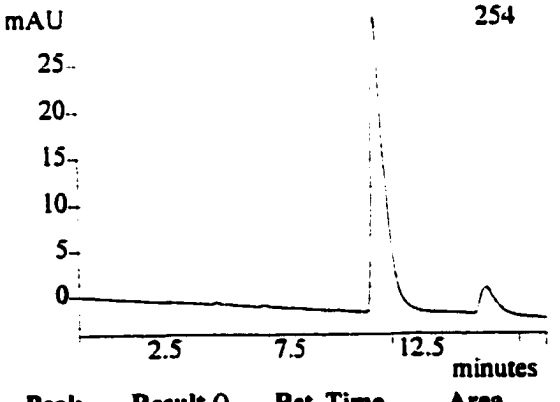
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



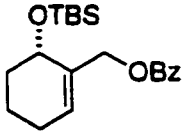
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.3362	12.311	486747
2	49.6638	16.435	480244
	100.0000		966991

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	90.5478	11.898	579532
2	9.4522	16.184	60497
	100.0000		640029

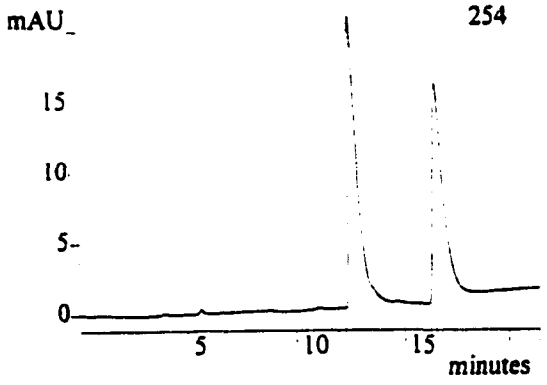
(Table 3.1, Entry 9)



HPLC Conditions

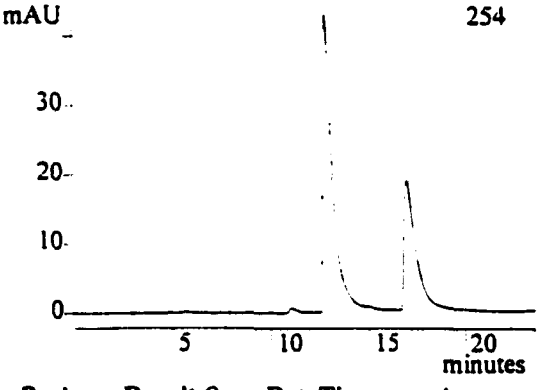
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



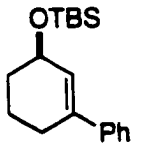
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.6002	12.555	277384
2	50.3998	16.590	281855
	100.0000		**559239**

Optically Active

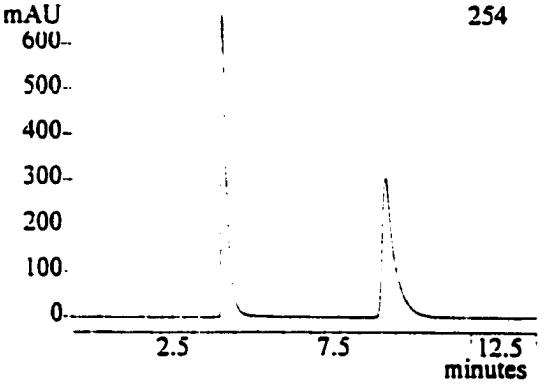


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	65.0983	12.809	727647
2	34.9017	17.058	390120
	100.0000		**1117767**

(Table 3.2, Entry 1)



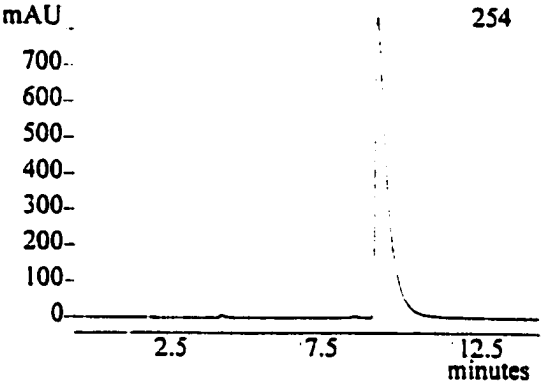
Racemate



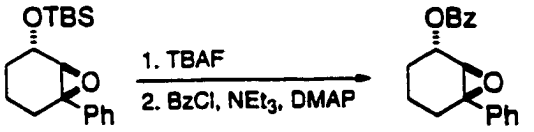
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.7947	4.768	4106284
2	50.2053	9.808	4140147
	100.0000		8246431

HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (99/1)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Optically Active

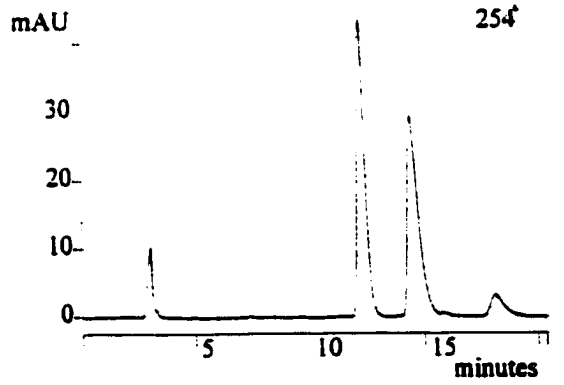


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	0.2957	4.882	34966
2	0.3296	9.258	38968
3	99.3747	10.119	11750304
	100.0000		11824238



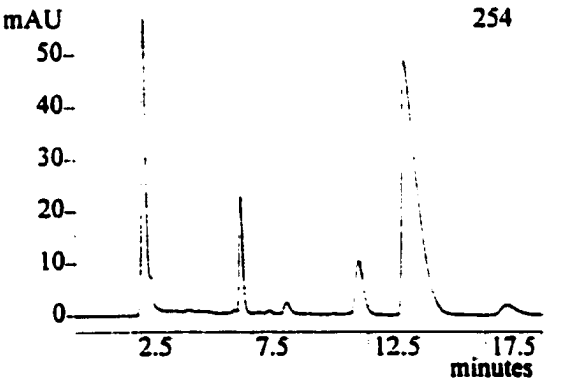
HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate



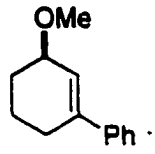
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.3239	12.226	508210
2	49.6761	14.389	501668
	100.0000		1009878

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	9.6894	12.159	116074
2	90.3106	14.141	1081875
	100.0000		1197949

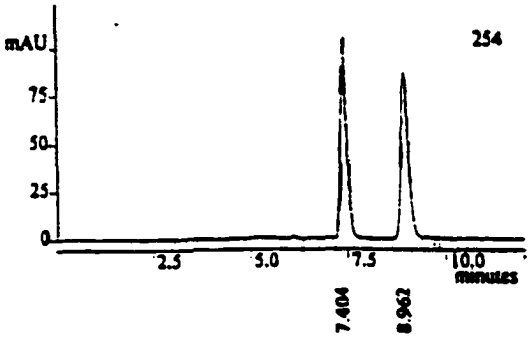
(Table 3.2, Entry 2)



Racemate

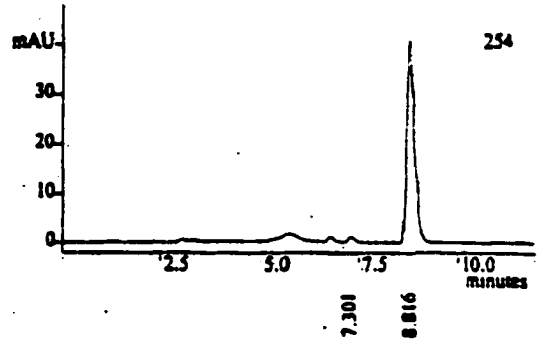
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (97/3)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm



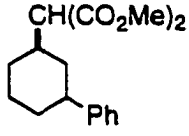
Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		49.6443	7.404	612947
2		50.3557	8.962	621731
	Totals	100.0000		1234678

Optically Active



Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		2.4070	7.301	7025
2		97.5930	8.816	284831
	Totals	100.0000		291856

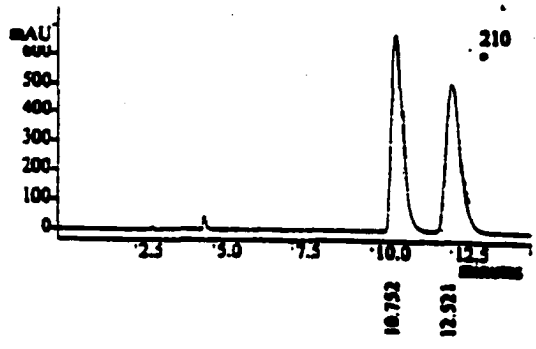
(Table 3.2, Entry 3)



Racemate

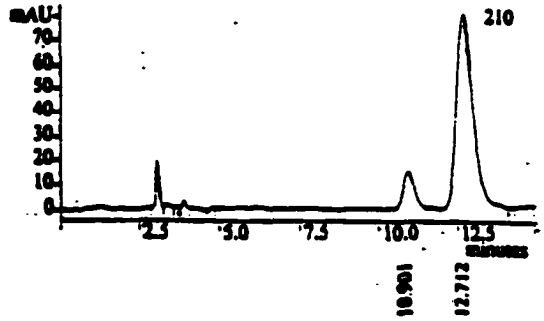
HPLC Conditions

Column: Chiralcel OJ
Eluent: Hexane/IPA (95/5)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm



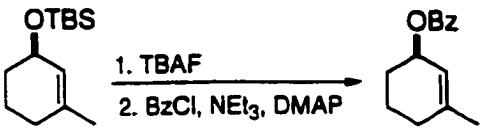
Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		49.6298	10.752	8404820
2		50.3702	12.521	8530217
	Totals	100.0000		16935036

Optically Active



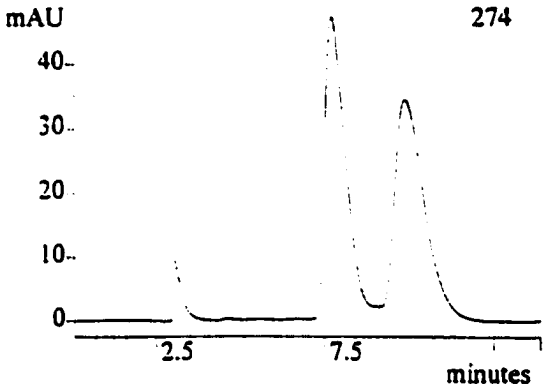
Peak No	Peak Name	Result 0	Ret. Time (min)	Area (counts)
1		9.7032	10.901	172216
2		90.2968	12.712	1602622
	Totals	100.0000		1774838

(Table 3.2, Entry 4)



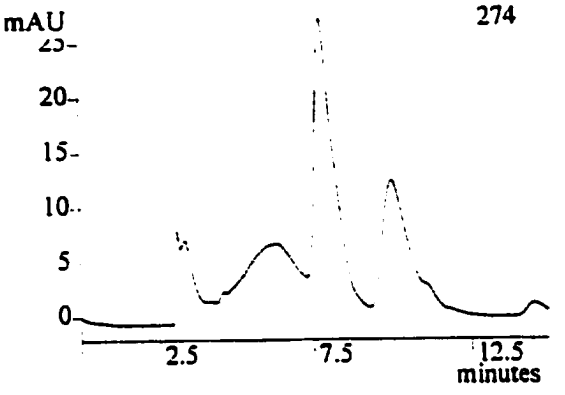
HPLC Conditions
Column: Chiralcel OB
Eluent: Hexane/IPA (99/1)
Flow Rate: 1.0 mL/min
Detection: UV 274 nm

Racemate

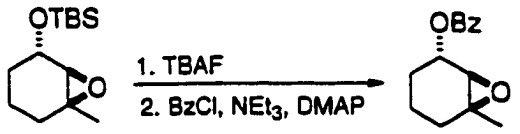


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.7629	7.754	972422
2	50.2371	9.913	981689
	100.0000		1954111

Optically Active

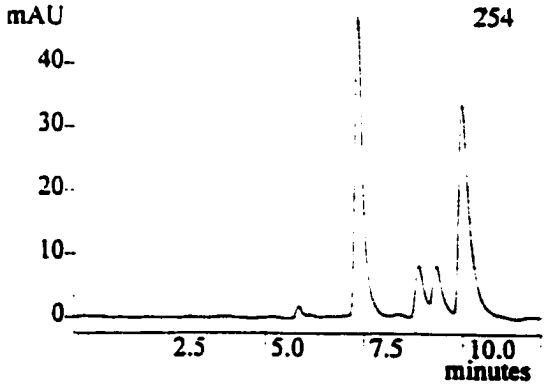


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	65.4661	7.803	484540
2	34.5339	10.014	255599
	100.0000		740139



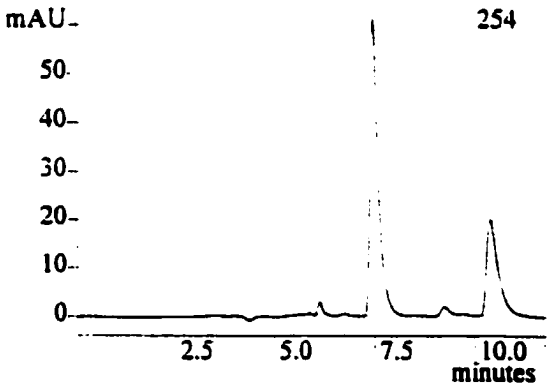
HPLC Conditions
Column: Chiralcel OJ
Eluent: Hexane/IPA (95/5)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm

Racemate



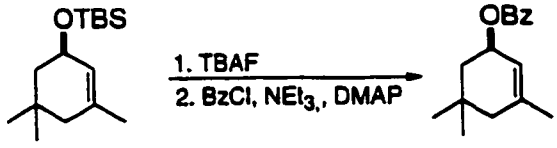
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.5664	7.346	339541
2	49.4336	9.986	331934
	100.0000		671475

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	68.2709	7.473	456320
2	31.7291	10.418	212076
	100.0000		668396

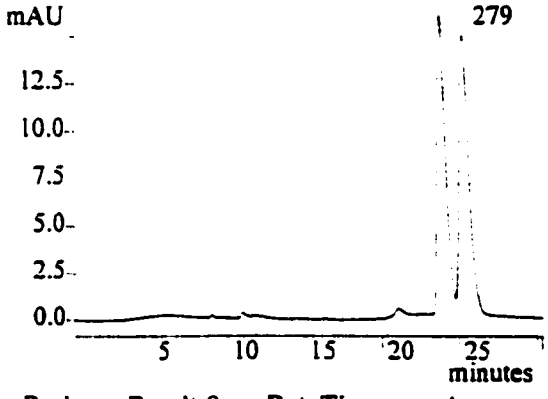
(Table 3.2, Entry 5)



HPLC Conditions

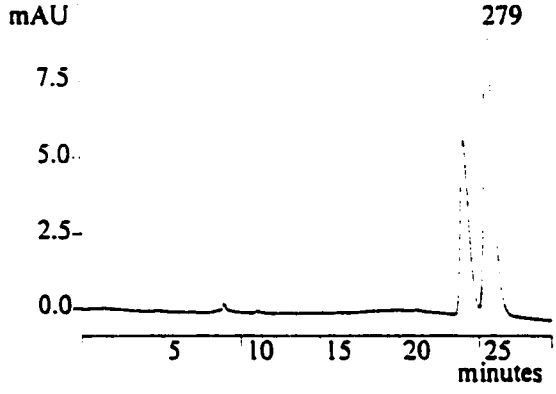
Column: Chiralcel OD
Eluent: Hexane/IPA (100/0)
Flow Rate: 0.5 mL/min
Detection: UV 279 nm

Racemate



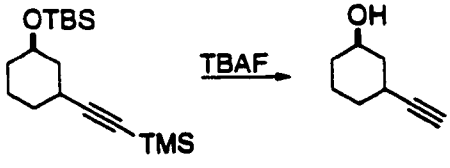
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.9370	23.820	319641
2	50.0630	25.278	320448
	100.0000		640089

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	34.3745	24.096	112983
2	65.6255	25.601	215700
	100.0000		328683

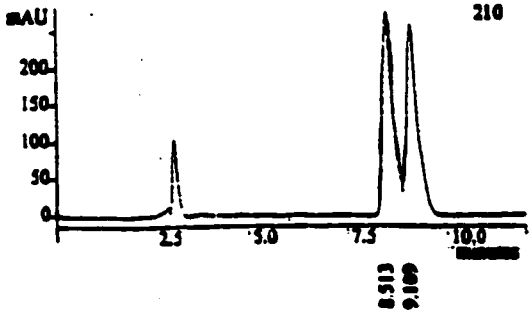
(Table 3.2, Entry 7)



HPLC Conditions

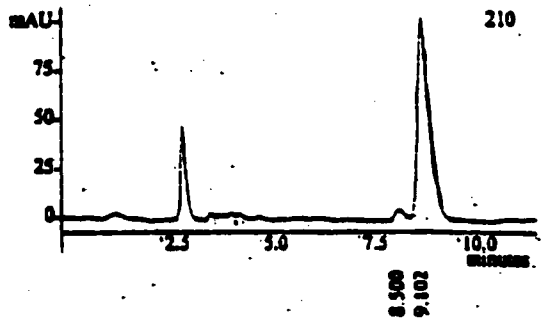
Column: Chiralcel OD
Eluent: Hexane/IPA (99/1)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm

Racemate



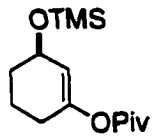
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		48.4809	8.513	2524832
2		51.5191	9.109	2683055
	Totals	100.0000		5207887

Optically Active

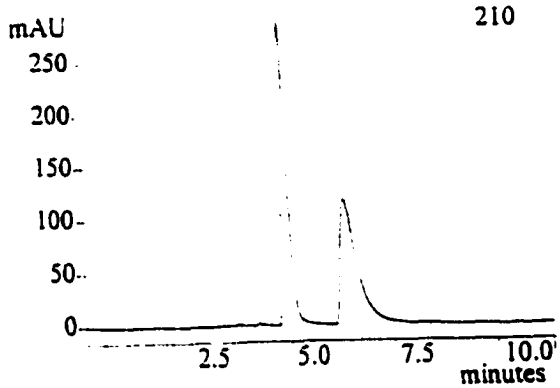


Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		2.1701	8.500	23067
2		97.8299	9.102	1039898
	Totals	100.0000		1062965

(Table 3.2, Entry 8)



Racemate

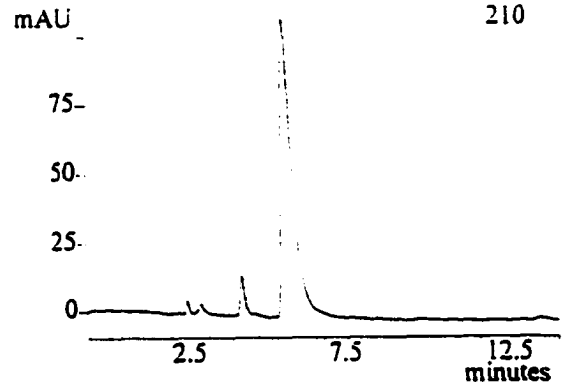


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.9041	4.874	1719692
2	49.0959	6.338	1658607
	100.0000		3378299

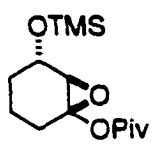
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (100/0)
Flow Rate: 0.5 mL/min
Detection: UV 279 nm

Optically Active

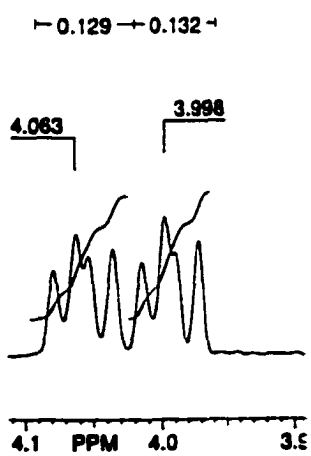


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	4.4154	4.892	68681
2	95.5846	6.276	1486802
	100.0000		1555483

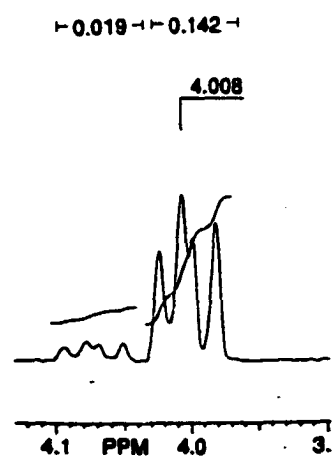


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

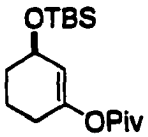
Racemate



Optically Active

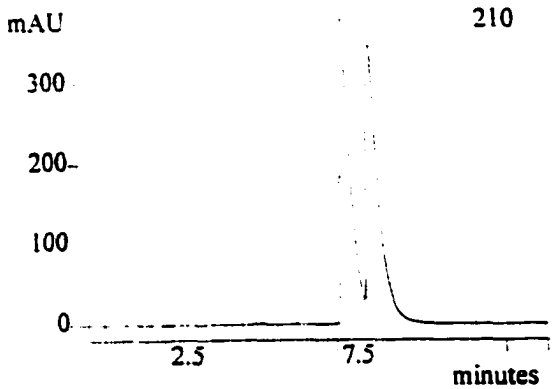


(Table 3.2, Entry 9)



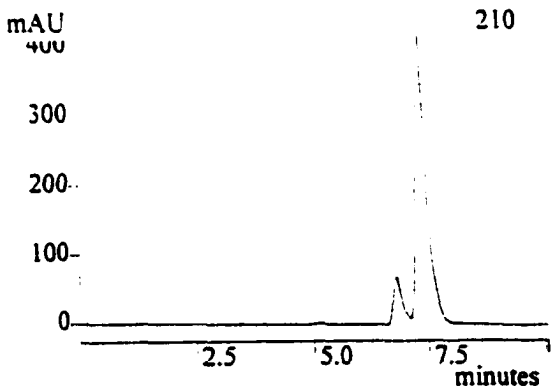
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (99/1)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm

Racemate

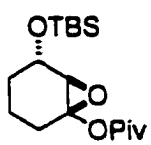


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	48.1025	7.759	4316800
2	51.8975	8.563	4657362
	100.0000		**8974162**

Optically Active

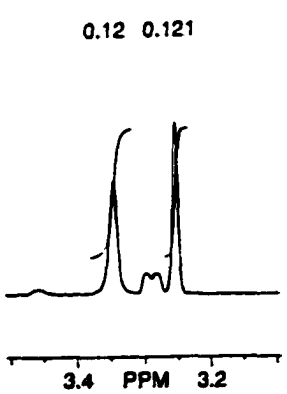


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	11.8661	6.813	489780
2	88.1339	7.330	3637770
	100.0000		**4127550**

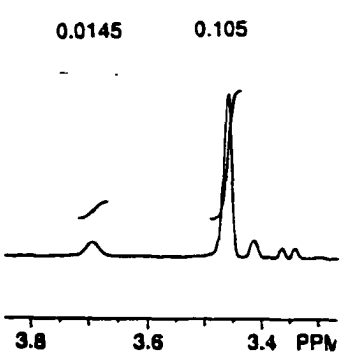


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

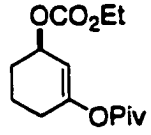
Racemate



Optically Active



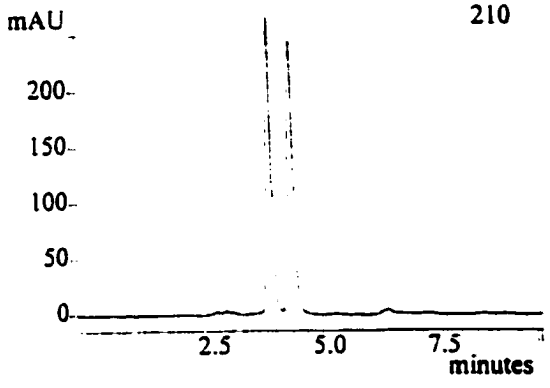
(Table 3.2, Entry 10)



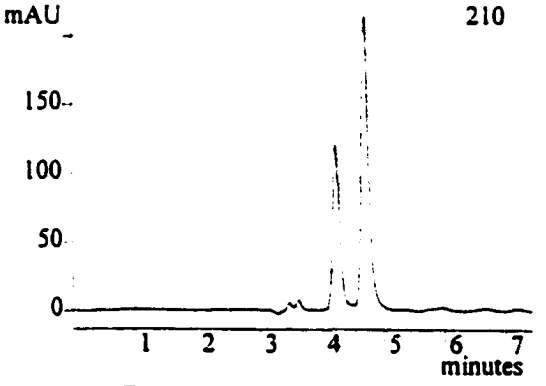
Racemate

HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (96/4)
Flow Rate: 1.0 mL/min
Detection: UV 210 nm

Optically Active

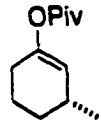


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.3907	4.185	1074505
2	50.6093	4.659	1101016
	100.0000		**2175521**



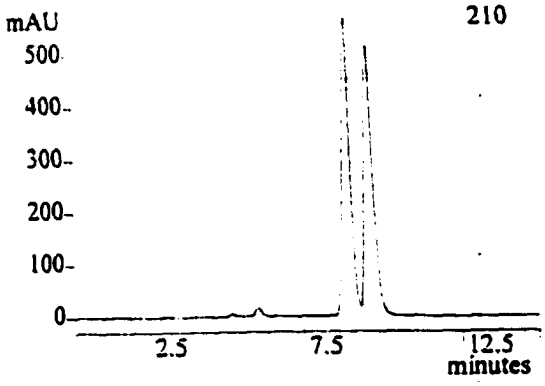
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	32.5476	4.216	476297
2	67.4524	4.686	987091
	100.0000		**1463388**

(Table 3.2, Entry 11)



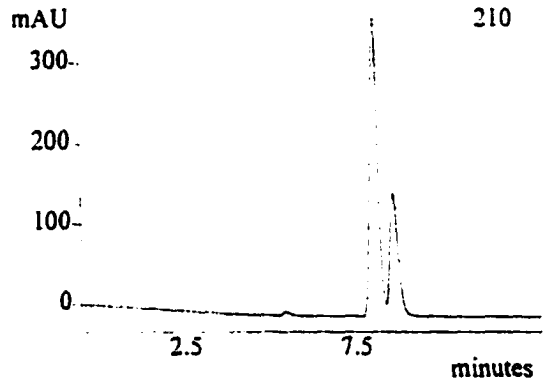
HPLC Conditions
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.6 mL/min
Detection: UV 210 nm

Racemate

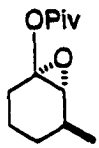


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.5341	8.894	5221258
2	50.4659	9.558	5319470
	100.0000		10540728

Optically Active

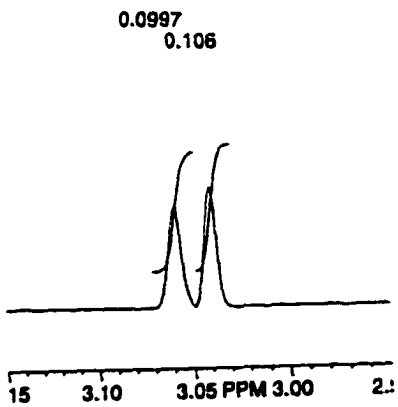


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	68.6138	8.717	3196474
2	31.3862	9.319	1462169
	100.0000		4658643

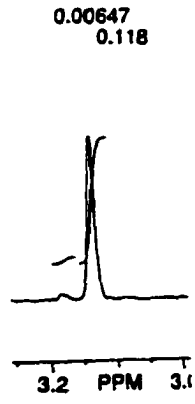


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

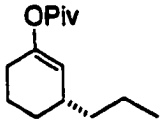
Racemate



Optically Active



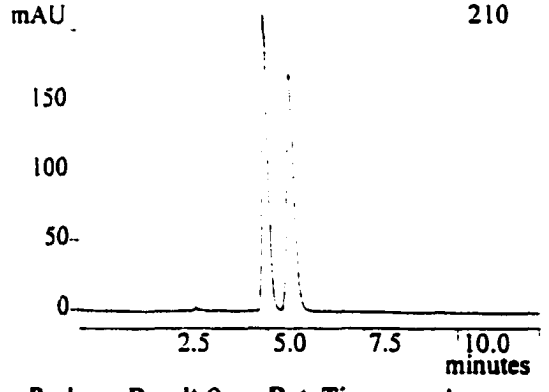
(Table 3.2, Entry 12)



HPLC Conditions

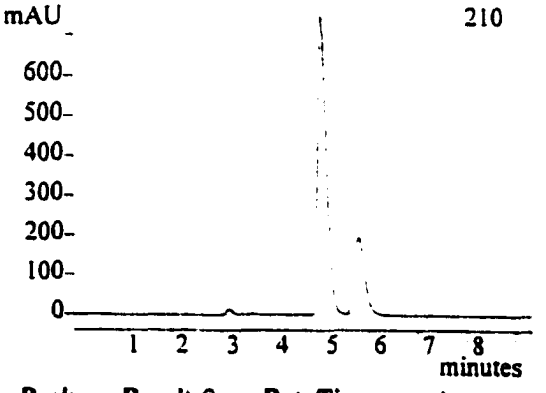
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.6 mL/min
Detection: UV 210 nm

Racemate

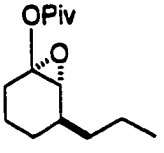


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.9610	4.954	1223102
2	50.0390	5.601	1225011
	100.0000		**2448113**

Optically Active

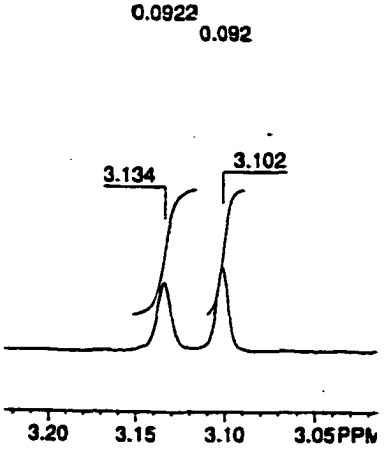


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	75.0966	5.029	4839075
2	24.9034	5.785	1604724
	100.0000		**6443799**

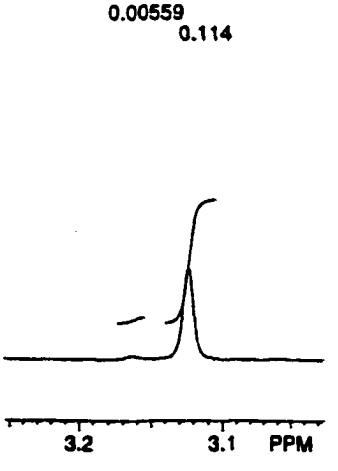


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

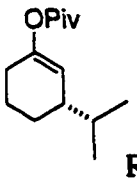
Racemate



Optically Active

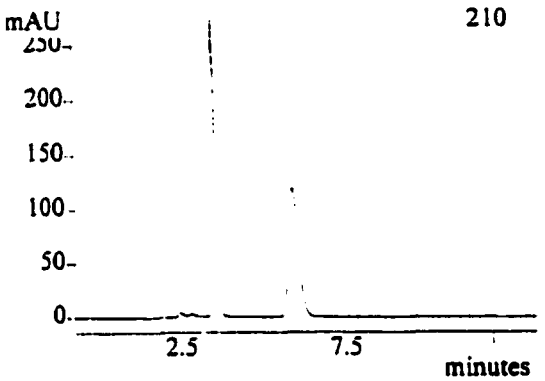


(Table 3.2, Entry 13)



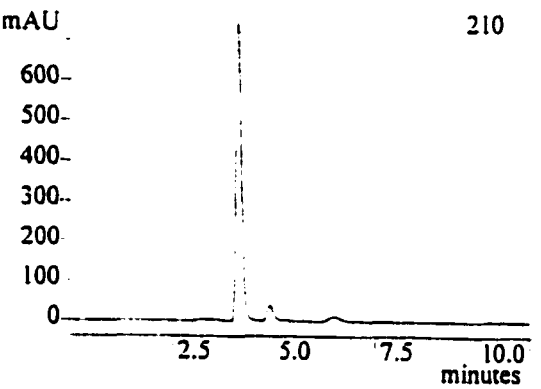
HPLC Conditions
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.6 mL/min
Detection: UV 210 nm

Racemate

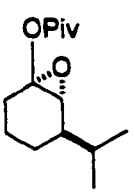


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.9482	4.150	1299535
2	50.0518	6.535	1302228
	100.0000		2601763

Optically Active

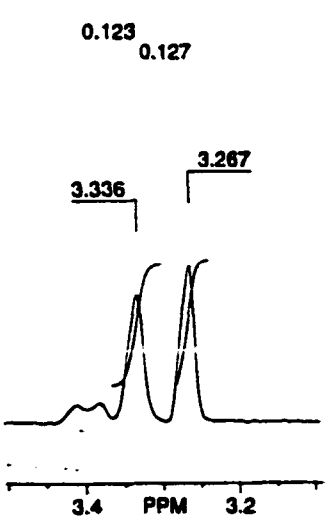


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	96.5710	4.128	3547728
2	3.4290	6.508	125971
	100.0000		3673699

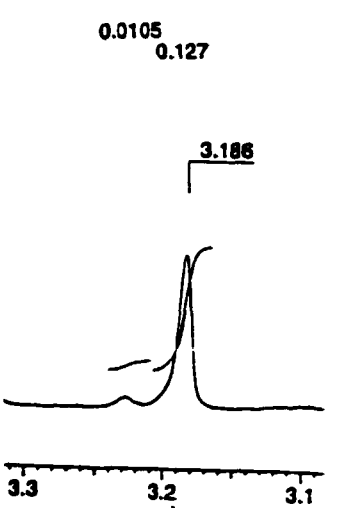


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

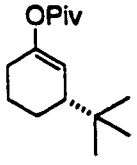
Racemate



Optically Active



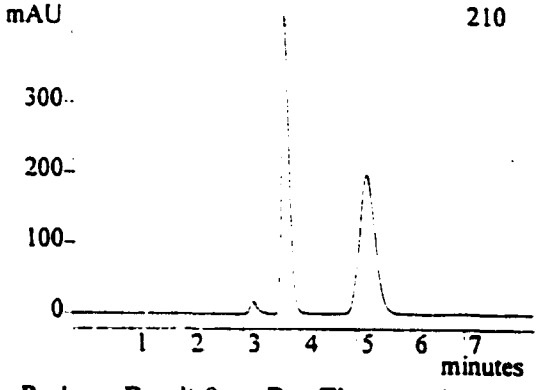
(Table 3.2, Entry 14)



HPLC Conditions

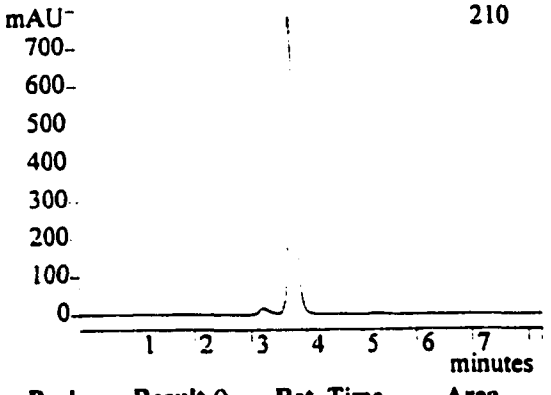
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.6 mL/min
Detection: UV 210 nm

Racemate

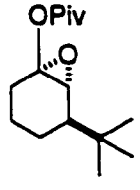


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.6068	3.731	1994673
2	50.3932	5.180	2026291
	100.0000		4020964

Optically Active

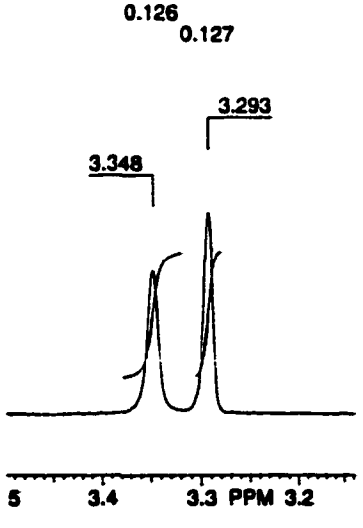


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	99.5510	3.749	3842054
2	0.4490	5.264	17330
	100.0000		3859384

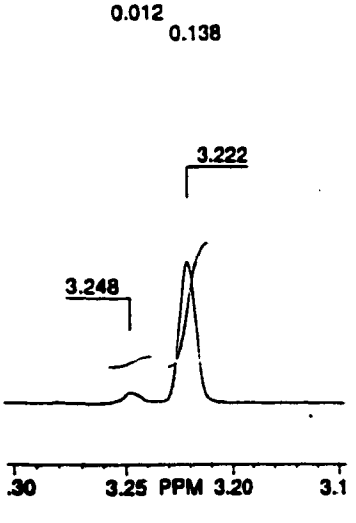


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

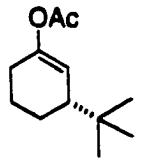
Racemate



Optically Active



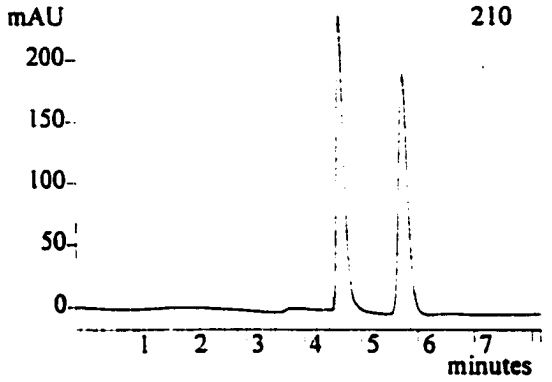
(Table 3.2, Entry 15)



HPLC Conditions

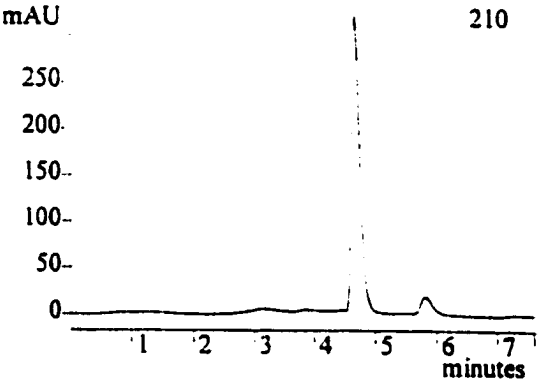
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate

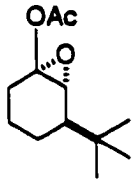


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.7381	4.645	1134932
2	50.2619	5.747	1146885
	100.0000		**2281817**

Optically Active

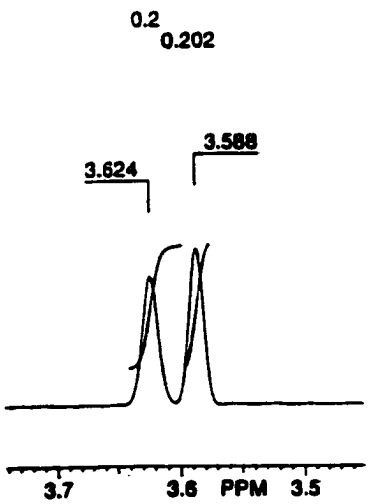


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	92.6265	4.674	1495875
2	7.3735	5.815	119079
	100.0000		**1614954**

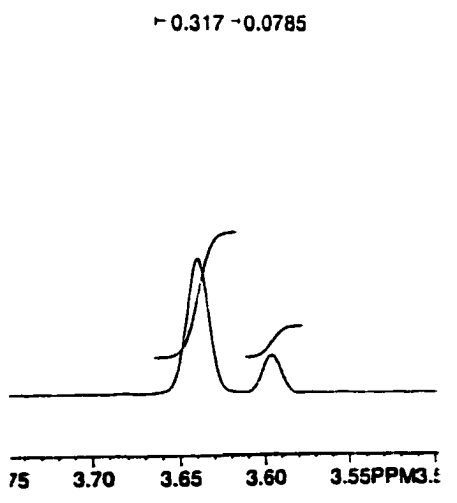


The ee was determined by chiral shift NMR using $Eu(hfc)_3$ as the chiral shift agent

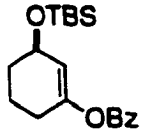
Racemate



Optically Active

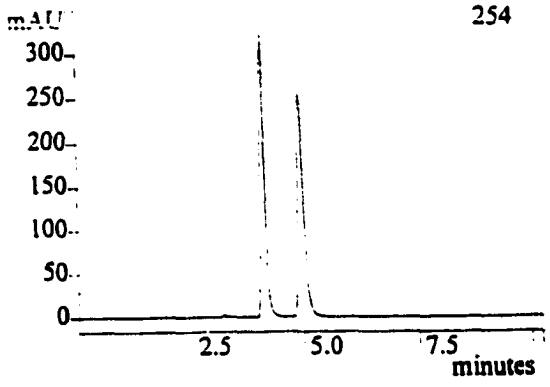


(Table 3.2, Entry 16)



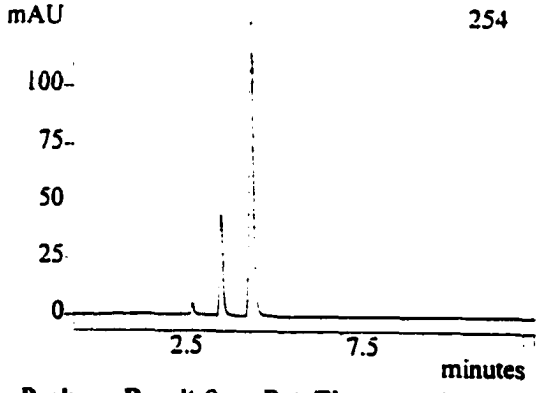
HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate

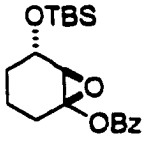


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.7725	4.095	1236334
2	50.2275	4.942	1247635
	100.0000		2483969

Optically Active

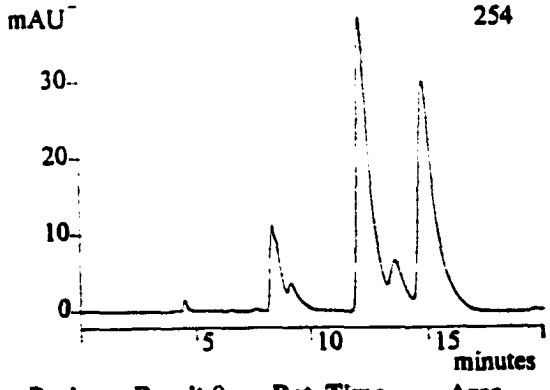


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	21.5063	4.050	160633
2	78.4937	4.911	586278
	100.0000		746911



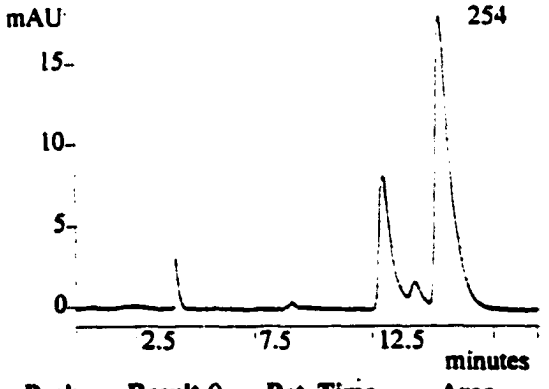
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



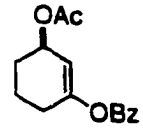
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.7776	12.238	724546
2	49.2224	14.851	702355
	100.0000		1426901

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	25.2763	12.974	128776
2	74.7236	15.368	380698
	99.9999		509474

(Table 3.2, Entry 17)

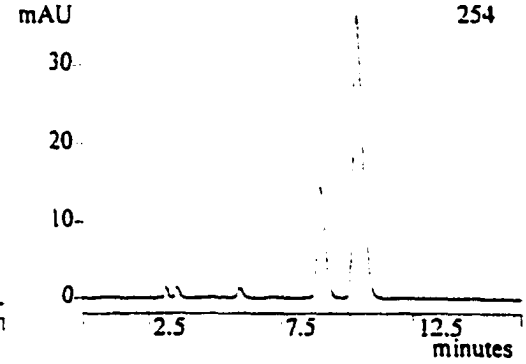


HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (97/3)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

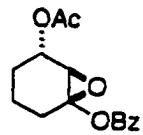
Racemate

Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.0228	8.926	794204
2	49.9772	10.356	793479
	100.0000		1587683

Optically Active

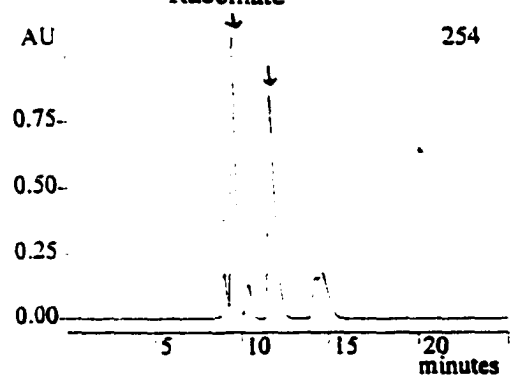


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	24.6732	9.035	154474
2	75.3268	10.448	471608
	100.0000		626082



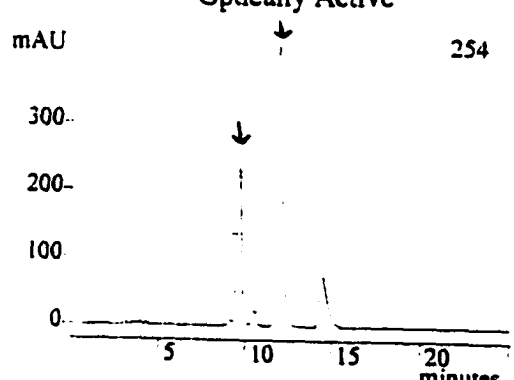
HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (97/3)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate



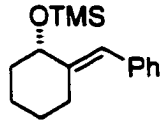
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	4.6755	8.992	1528823
2	35.4694	9.511	11598125
3	4.8187	10.426	1575648
4	39.2389	11.705	12830686
5	4.9028	14.274	1603166
6	10.8948	14.642	3562483
	100.0001		32698932

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	24.6427	9.594	2344616
2	2.2911	10.467	217984
3	60.0240	11.821	5710960
4	13.0422	14.483	1240898
	100.0000		9514458

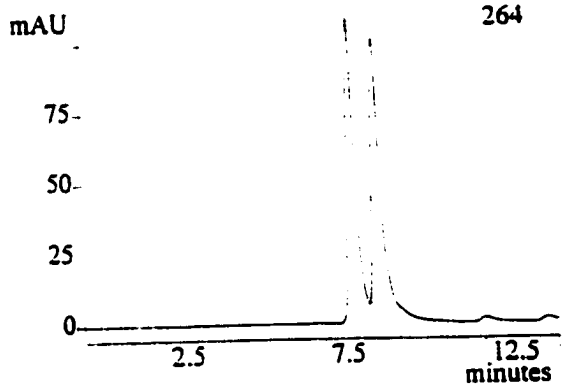
(Table 3.3, Entry 1)



HPLC Conditions

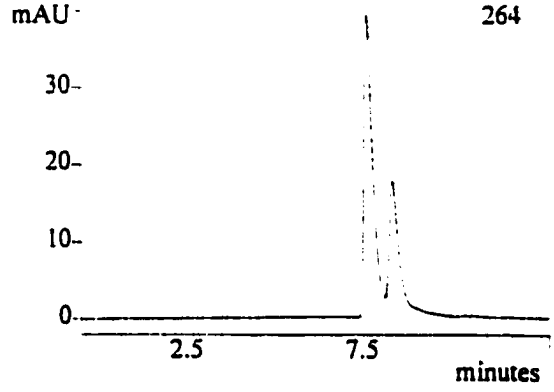
Column: Chiralcel OD
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.5 mL/min
Detection: UV 264 nm

Racemate



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	47.4080	8.355	999805
2	52.5920	9.115	1109134
	100.0000		2108939

Optically Active

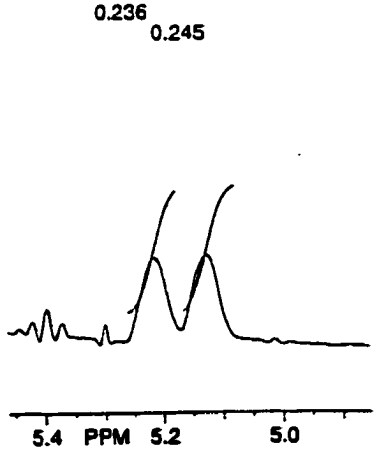


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	70.3396	8.294	329660
2	29.6604	9.024	139009
	100.0000		468669

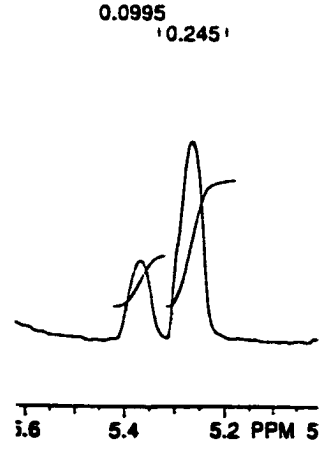
(Table 3.3, Entry 2)

The ee was determined by chiral shift NMR on the alcohol using $Eu(hfc)_3$ as the chiral shift agent

Racemate



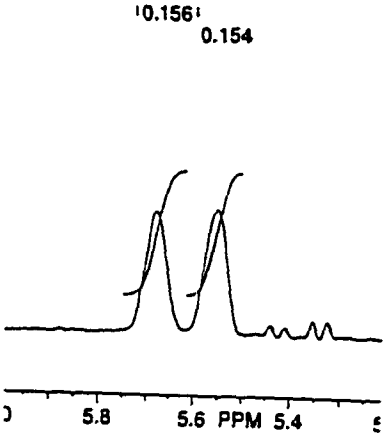
Optically Active



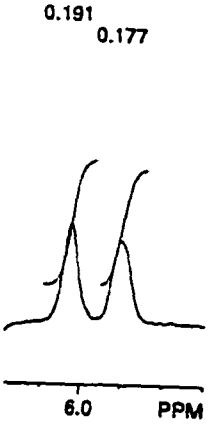
(Table 3.3, Entry 3)

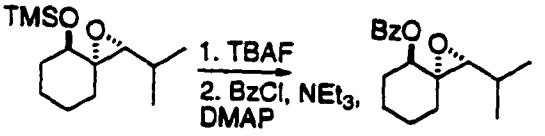
The ee was determined by chiral shift NMR on the alcohol using $Eu(hfc)_3$ as the chiral shift agent

Racemate

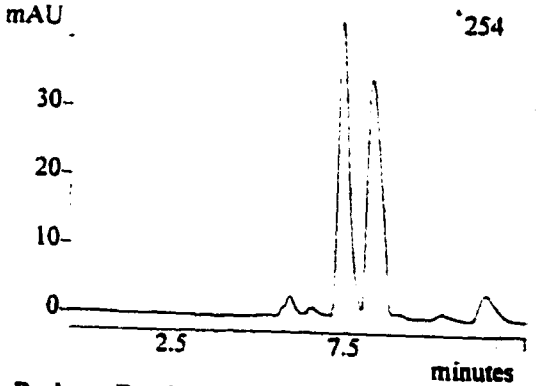


Optically Active





Racemate

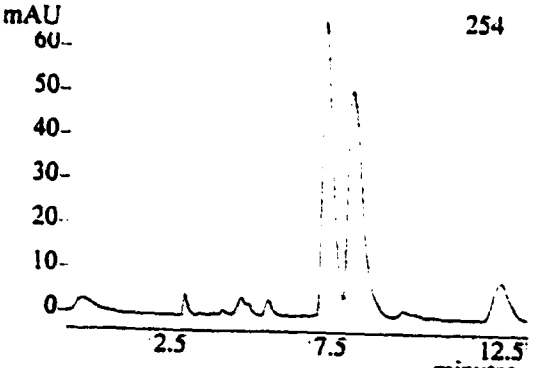


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.3902	7.990	471940
2	49.6098	8.859	464631
	100.0000		936571

HPLC Conditions

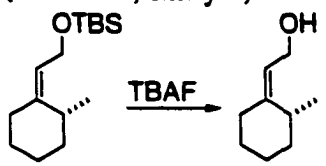
Column: Chiralcel AD
Eluent: Hexane/IPA (98/2)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.0798	7.964	754242
2	50.9202	8.773	782526
	100.0000		1536768

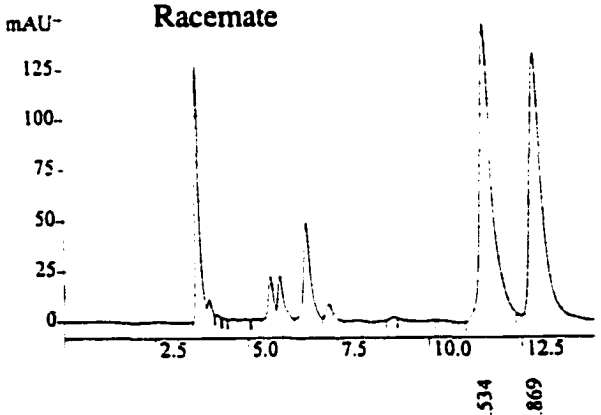
(Table 3.3, Entry 4)



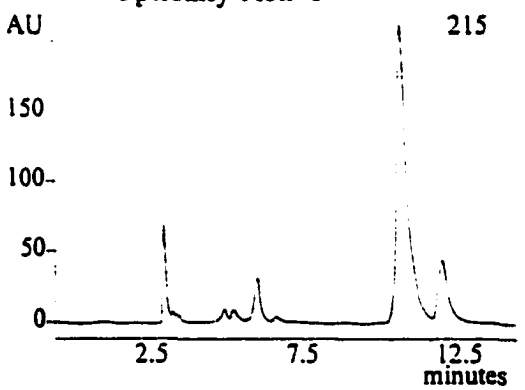
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (97/3)
Flow Rate: 0.8 mL/min
Detection: UV 215 nm

Racemate



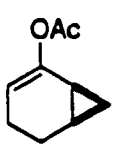
Optically Active



Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		52.1527	11.534	1795713
2		47.8473	12.869	1647469
	Totals	100.0000		3443182

Peak No	Result ()	Ret. Time (min)	Area (counts)
1	82.8826	11.572	2627128
2	17.1174	12.893	542570
	100.0000		3169698

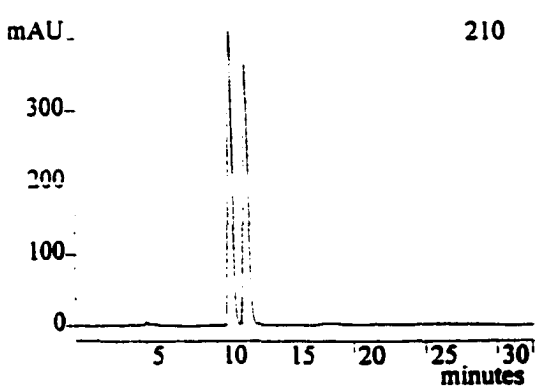
(Table 3.3, Entry 5)



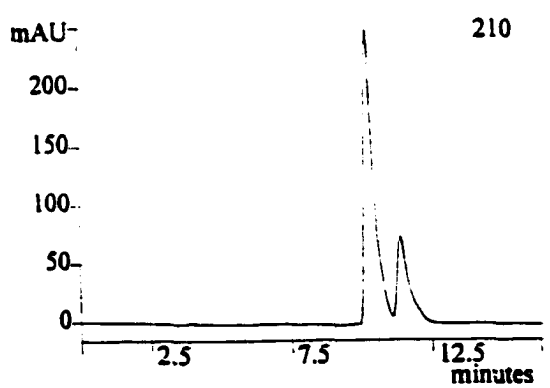
HPLC Conditions

Column: Chiralcel OD
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 210 nm

Racemate



Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.0193	10.937	4984348
2	49.9807	12.085	4980498
	100.0000		9964846

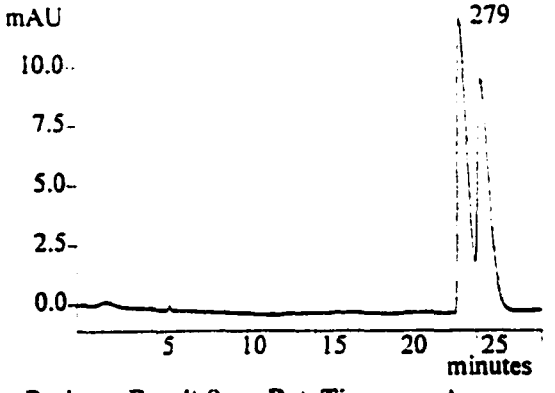
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	74.1720	10.285	3195180
2	25.8280	11.437	1112615
	100.0000		4307795

(Table 3.3, Entry 6)

HPLC Conditions

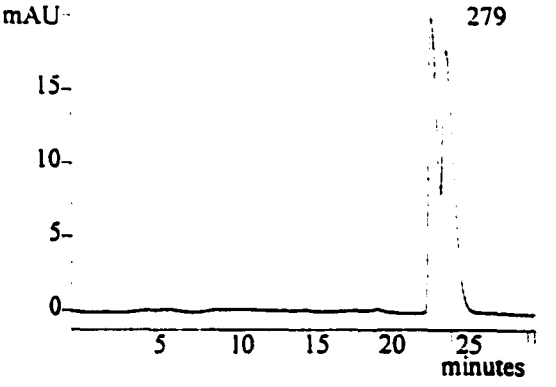
Column: Chiralcel AD
Eluent: Hexane/IPA (97/3)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate

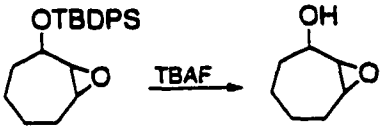


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	51.2789	24.181	260841
2	48.7211	25.431	247830
	100.0000		508671

Optically Active



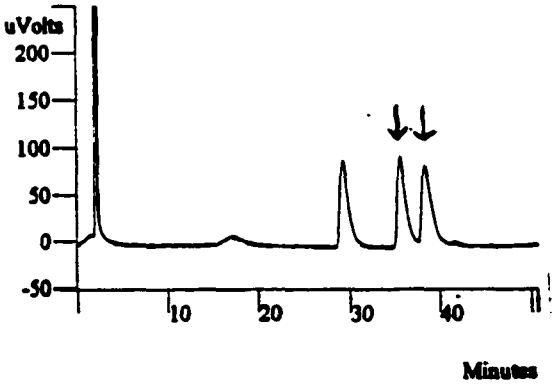
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	48.9648	23.782	407387
2	51.0352	24.764	424613
	100.0000		832000



GC Conditions

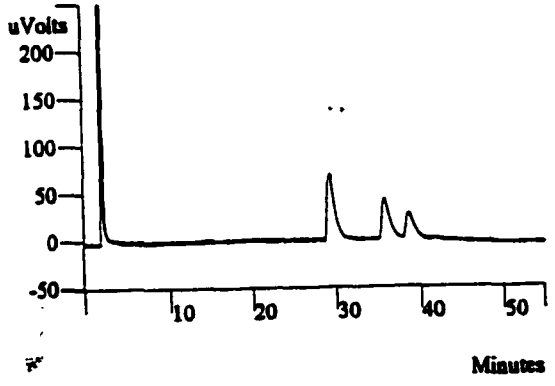
Column: Chiraldex G-TA
Oven: 100 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

Racemate



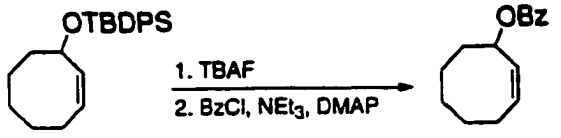
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	49.9360	35.574	6371
2	50.0640	38.329	6387
	100.0000		12758

Optically Active



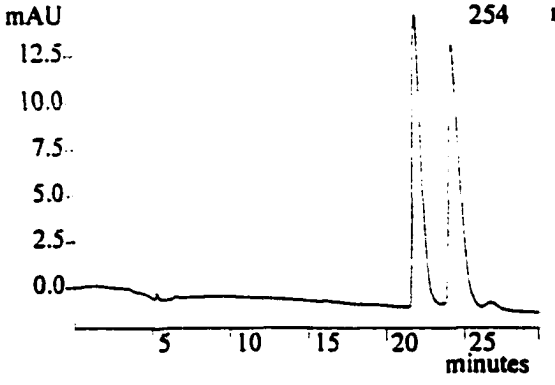
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	60.2573	35.724	2705
2	39.7427	38.559	1784
	100.0000		4489

(Table 3.3, Entry 7)



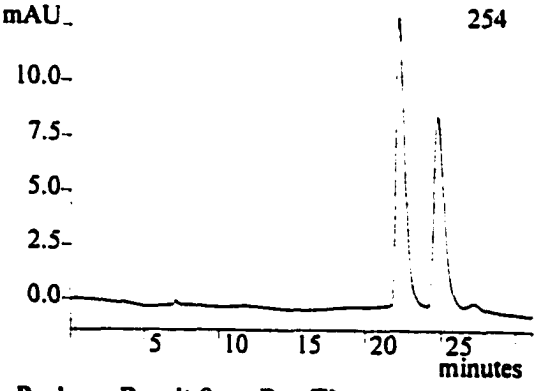
HPLC Conditions
Column: Chiralcel AD
Eluent: Hexane/IPA (97/3)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate



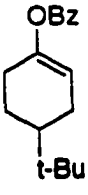
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.2125	21.942	336965
2	50.7875	24.344	347749
	100.0000		684714

Optically Active



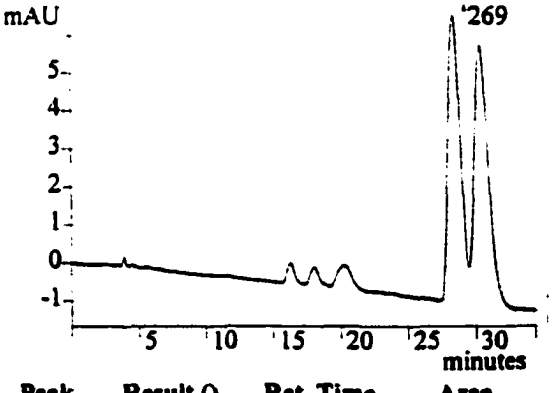
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	57.6051	22.236	281710
2	42.3949	24.759	207326
	100.0000		489036

(Table 3.3, Entry 8)



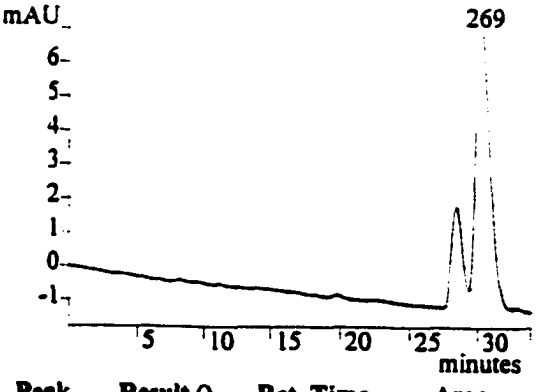
HPLC Conditions
Column: Chiralcel OD
Eluent: Hexane/IPA (100/0)
Flow Rate: 0.85 mL/min
Detection: UV 269 nm

Racemate



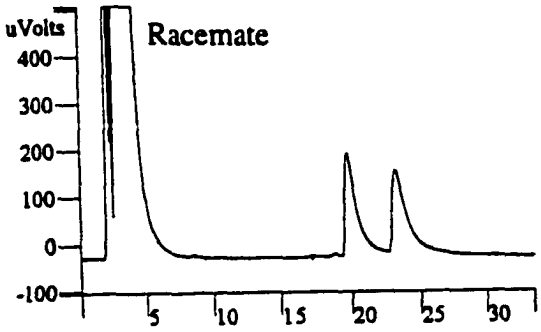
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.6114	28.343	244248
2	50.3886	30.358	248074
	100.0000		492322

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	22.6717	28.423	91476
2	77.3283	30.271	312003
	100.0000		403479

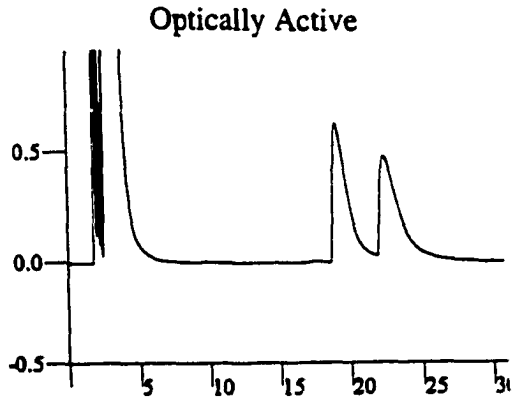
(Table 3.4, Entry 1)



Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	49.0609	19.754	12787
2	50.9391	23.189	13276
	100.0000		**26063**

GC Conditions

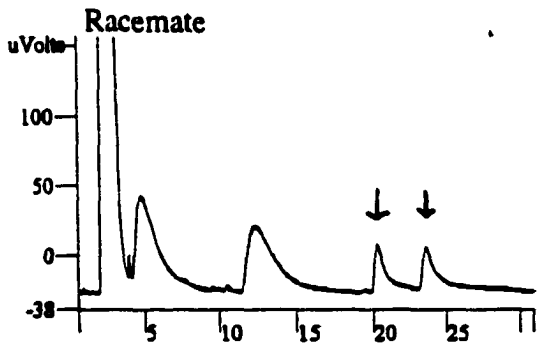
Column: Chiraldex G-TA
Oven: 40 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C



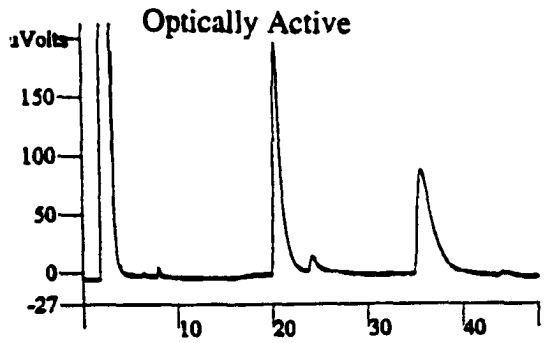
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.6193	18.986	44646
2	50.3807	22.364	45331
	100.0000		**89977**

GC Conditions

Column: Chiraldex G-TA
Oven: 60 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C



Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	51.0239	20.173	1727
2	48.9761	23.468	1658
	100.0000		**3385**

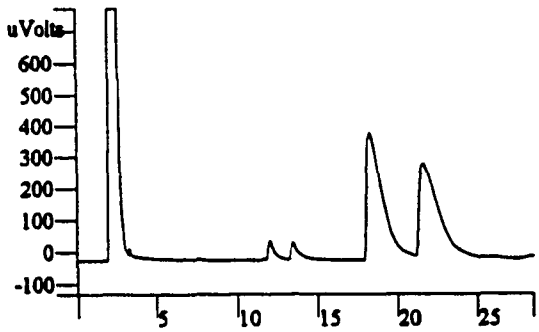


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	91.0007	20.229	11435
2	8.9993	24.154	1131
	100.0000		**12566**

GC Conditions

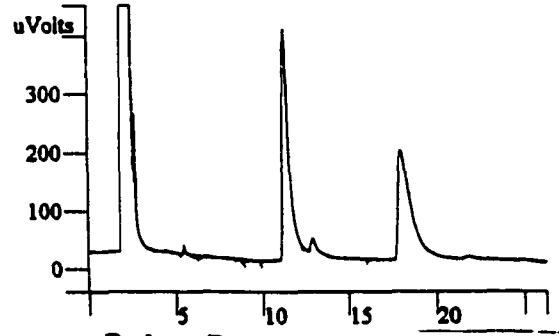
Column: Chiraldex G-TA
Oven: 70 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

Racemate



Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	50.9296	18.313	27493
2	49.0704	21.579	26489
	100.0000		53982

Optically Active



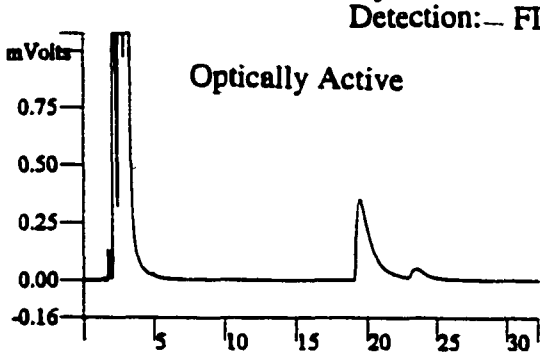
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	50.6604	11.243	11089
2	5.4308	12.851	1189
3	43.3950	17.987	9498
4	0.5138	21.639	112
	100.0000		21888

(Table 3.4, Entry 2)

GC Conditions

Column: Chiraldex G-TA
Oven: 40 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

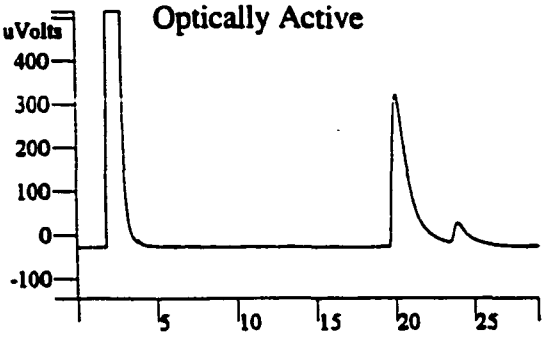
Optically Active



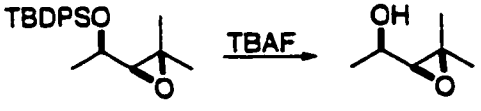
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	86.2465	19.452	25110
2	13.7535	23.296	4004
	100.0000		29114

GC Conditions

Column:	Chiraldex G-TA
Oven:	60 C
Carrier:	Helium, head pressure: 15 psi
Injection:	250 C
Detection:	FID 250 C

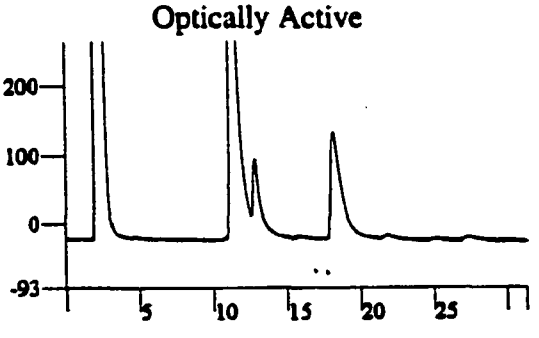


Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	87.1813	19.964	24626
2	12.8187	23.839	3621
	100.0000		**28247**



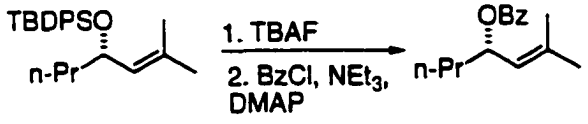
GC Conditions

Column:	Chiraldex G-TA
Oven:	70 C
Carrier:	Helium, head pressure: 15 psi
Injection:	250 C
Detection:	FID 250 C



Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	95.7806	18.067	8168
2	4.2194	21.757	360
	100.0000		**8528**

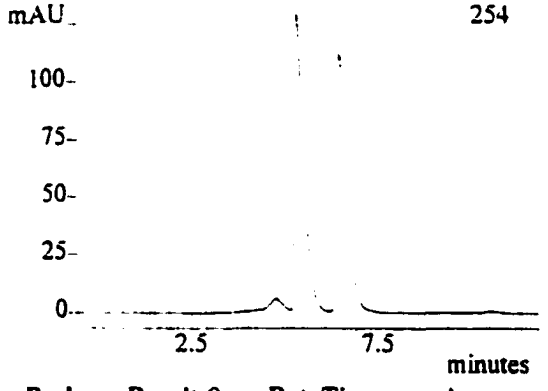
(Table 3.4, Entry 3)



HPLC Conditions

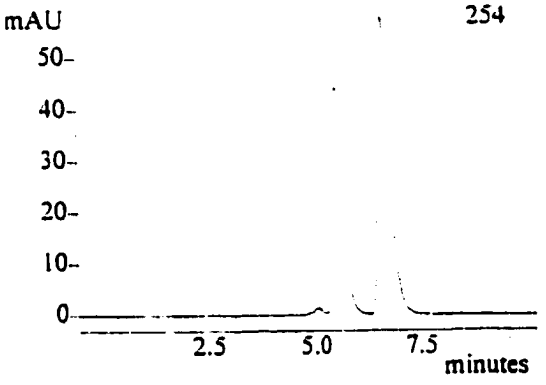
Column: Chiralcel OJ
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.9204	5.993	1156656
2	50.0796	7.117	1160345
	100.0000		**2317001**

Optically Active

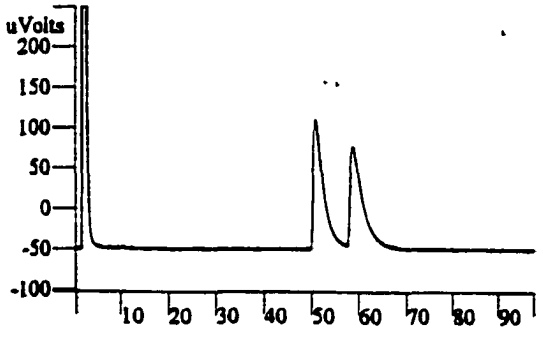


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	39.7122	6.016	390868
2	60.2878	7.139	593383
	100.0000		**984251**

GC Conditions

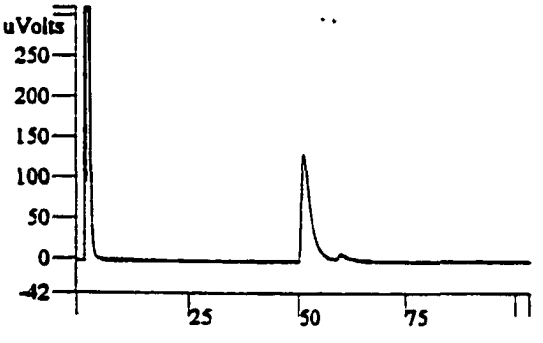
Column: Chiraldex G-TA
Oven: 60 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

Racemate



Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	49.8088	50.684	23402
2	50.1912	58.519	23581
	100.0000		**46983**

Optically Active

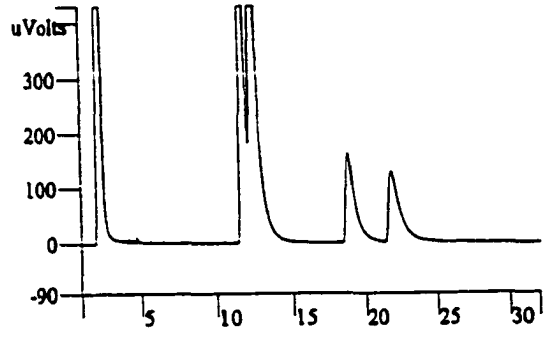


Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	93.4747	50.914	19782
2	6.5253	59.504	1381
	100.0000		**21163**

GC Conditions

Column: Chiraldex G-TA
Oven: 85 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C

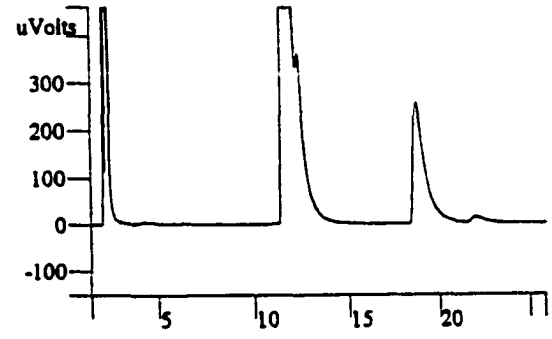
Racemate



Minutes

Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	50.4577	18.764	6918
2	49.5423	21.801	6793
	100.0000		**13711**

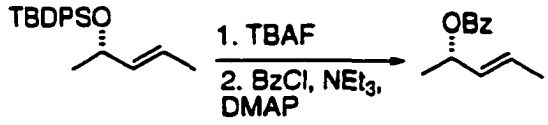
Optically Active



Minutes

Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	95.7799	18.646	11845
2	4.2201	21.904	522
	100.0000		**12367**

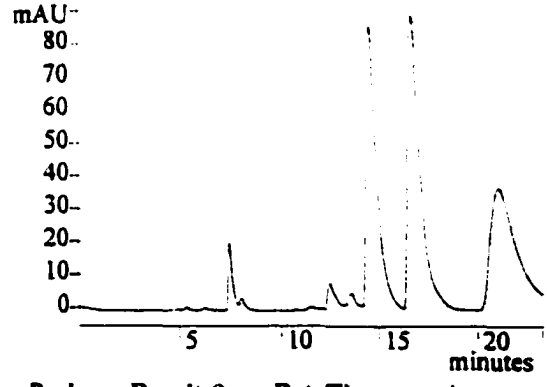
(Table 3.4, Entry 5)



HPLC Conditions

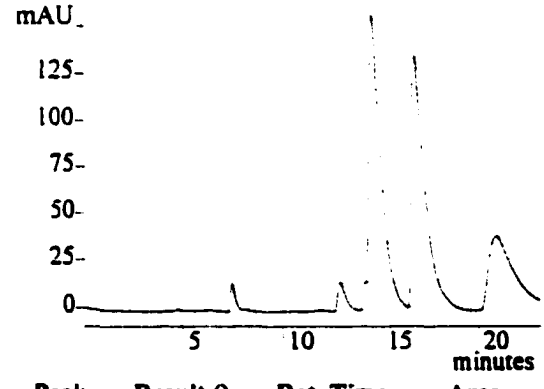
Column: Chiralcel OD
Eluent: Hexane/IPA (99/1)
Flow Rate: 0.7 mL/min
Detection: UV 254 nm

Racemate

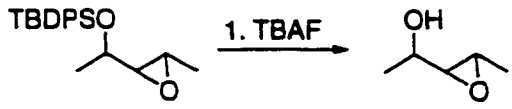


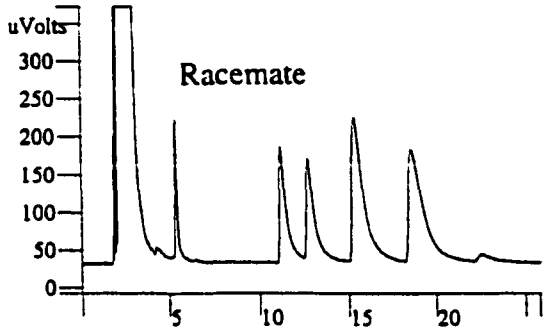
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	45.4157	14.530	1708524
2	54.5843	16.659	2053443
	100.0000		**3761967**

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	50.7808	14.546	3519907
2	49.2192	16.771	3411666
	100.0000		**6931573**

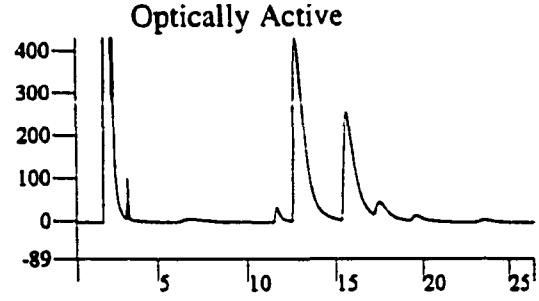




Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	14.0111	11.154	3376
2	15.0299	12.688	3622
3	34.3644	15.289	8281
4	36.5947	18.647	8818
	100.0001		**24097**

GC Conditions

Column: Chiraldex G-TA
Oven: 60 C
Carrier: Helium, head pressure: 15 psi
Injection: 250 C
Detection: FID 250 C



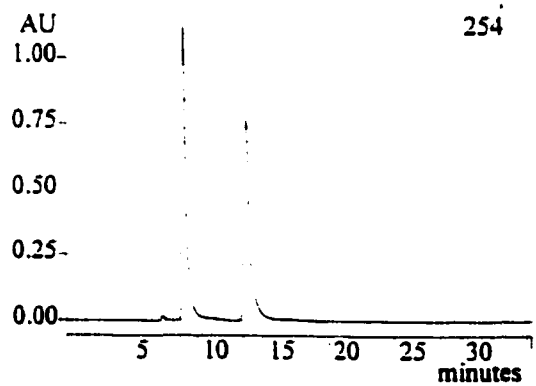
Peak No	Result ()	Ret Time (min)	Peak Area (counts)
1	2.2539	11.637	665
2	61.0773	12.761	18031
3	35.0063	15.691	10334
4	1.6625	19.549	491
	100.0000		**29521**

(Table 3.4, Entry 6)

HPLC Conditions

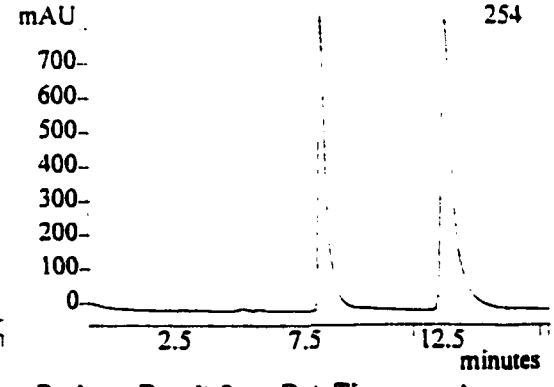
Column: Chiralcel OD
Eluent: Hexane/IPA (90/10)
Flow Rate: 1.0 mL/min
Detection: UV 254 nm

Racemate

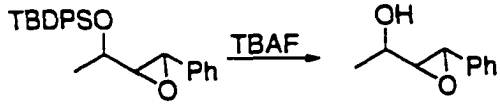


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	49.6888	9.021	12664835
2	50.3112	13.745	12823458
	100.0000		**25488292**

Optically Active



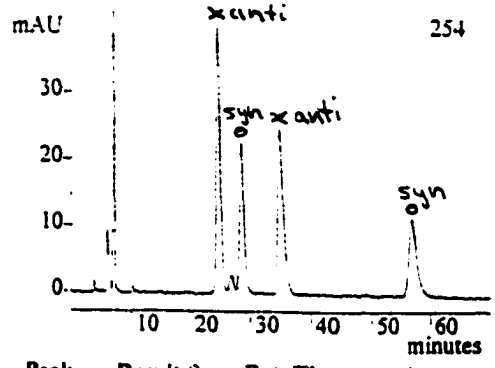
Peak No	Result ()	Ret. Time (min)	Area (counts)
1	39.6514	9.012	9391959
2	60.3486	13.802	14294384
	100.0000		**23686344**



HPLC Conditions

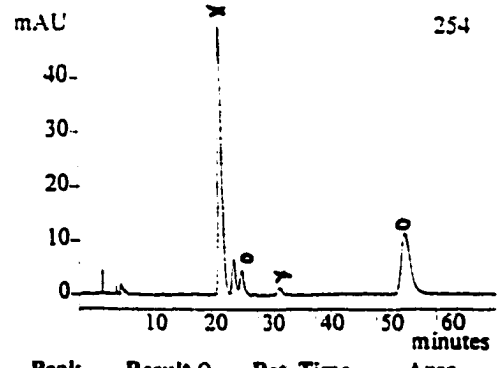
Column: Chiralcel AD
Eluent: Hexane/IPA (98/2)
Flow Rate: 0.8 mL/min
Detection: UV 254 nm

Racemate



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	30.7895	24.719	909972
2	20.5677	28.489	607871
3	28.6606	34.831	847054
4	19.9822	56.763	590565
	100.0000		2955462

Optically Active

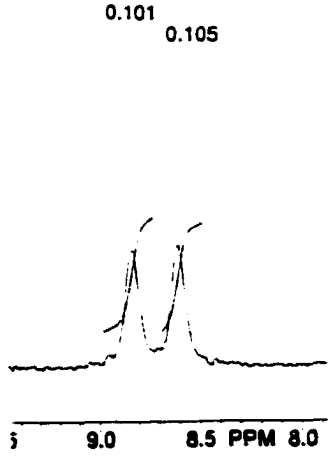


Peak No	Result ()	Ret. Time (min)	Area (counts)
1	55.7268	23.580	1127350
2	7.0745	25.990	143117
3	5.6964	27.358	115238
4	2.0168	33.785	40799
5	29.4855	54.879	596491
	100.0000		2022995

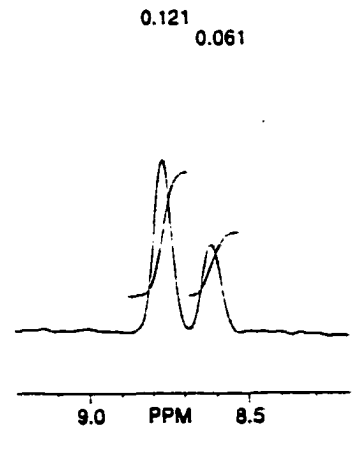
(Table 3.4, Entry 7)

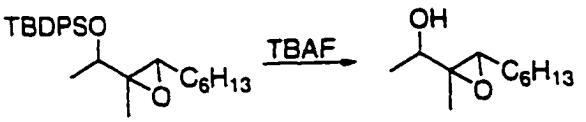
The ee was determined by chiral shift NMR of the alcohol using $Eu(hfc)_3$ as the chiral shift agent

Racemate



Optically Active

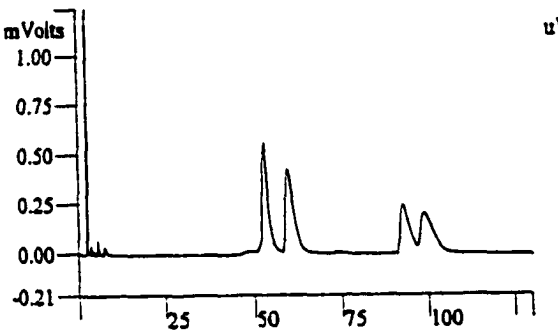




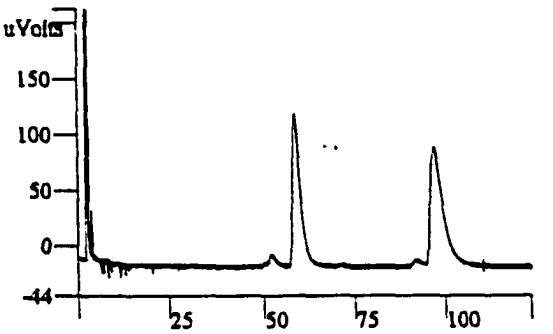
GC Conditions

Column:	Chiraldex G-TA
Oven:	90 C
Carrier:	Helium, head pressure: 15 psi
Injection:	250 C
Detection:	FID 250 C

Racemate



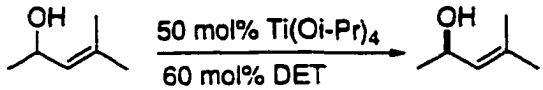
Optically Active



Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	28.8445	52.478	68105
2	27.9488	59.232	65991
3	20.2579	92.601	47831
4	22.9487	98.764	54185
	99.9999		**236112**

Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	2.9451	51.722	1428
2	42.3349	58.211	20520
3	1.9417	91.336	941
4	52.7783	96.878	25582
	100.0000		**48471**

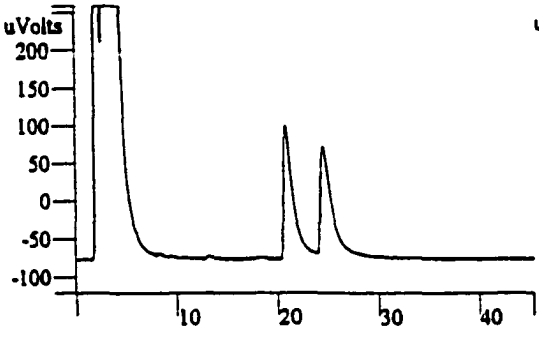
Preparation of (*R*) allylic alcohol derivatives



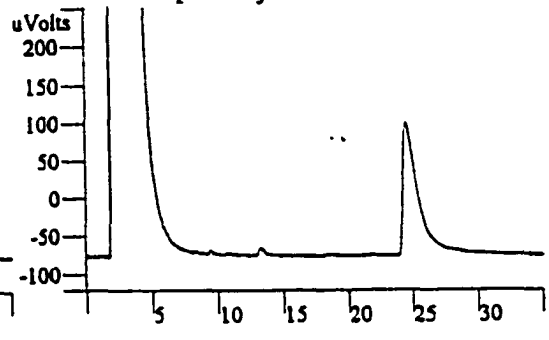
GC Conditions

Column:	Chiraldex G-TA
Oven:	40 C
Carrier:	Helium, head pressure: 15 psi
Injection:	250 C
Detection:	FID 250 C

Racemate

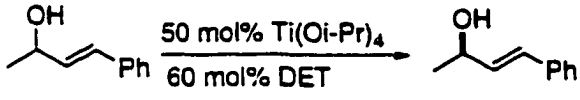


Optically Active



Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	48.8632	20.819	11189
2	51.1368	24.397	11709
	100.0000		**22898**

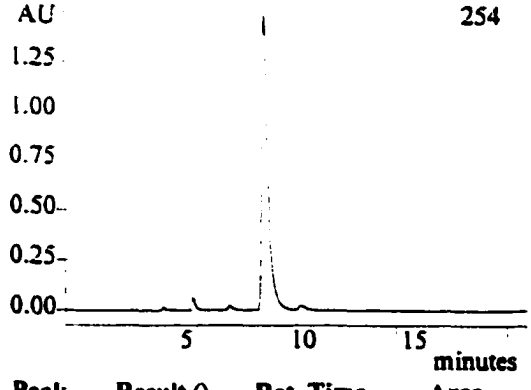
Peak No	Result ()	Ret Time (min)	Minutes Peak Area (counts)
1	100.0000	24.501	14844
	100.0000		**14844**



HPLC Conditions

Column:	Chiralcel OD
Eluent:	Hexane/IPA (90/10)
Flow Rate:	1.0 mL/min
Detection:	UV 254 nm

Optically Active



Peak No	Result ()	Ret. Time (min)	Area (counts)
1	100.0000	9.063	15033719
	100.0000		**15033719**